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Eerika Keskitalo

ASSESSMENT OF PROGNOSIS IN ASBESTOSIS

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ASSESSMENT OF PROGNOSIS IN ASBESTOSIS

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Abstract

Asbestosis is a common differential diagnostic dilemma in diagnostics of interstitial lung diseases (ILDs). Previous research on prognosis-associated factors in asbestosis has been sparse. Nowadays, pharmacological treatment of ILDs is evolving, and information of prognostic factors in asbestosis is thus important.

We investigated clinical features, lung function parameters and bronchoalveolar lavage (BAL) fluid findings as well as their association with survival in asbestosis patients treated in Oulu University Hospital during the years 1996–2015.

We observed that a high percentage of neutrophils (6.5%) was a typical BAL cell count in asbestosis patients. Smoking and BAL asbestos bodies (ABs) were associated with BAL cell profile. Non-smoking asbestosis patients had a high percentage of lymphocytes in BAL (25%). A high number of BAL ABs and low lymphocyte, high neutrophil and high eosinophil differential counts were associated with shortened patient survival.

Decreased diffusion capacity (DLCO) (65%) and restriction in spirometry were common changes in lung functions at the time of diagnosis of asbestosis. Risk predicting models, i.e., gender, age and physiologic variables (GAP) and composite physiologic index (CPI), in addition to DLCO, were useful in predicting survival in asbestosis. The median estimated survival in GAP stage I, II and III was 171, 50 and 21 months, respectively.

Asbestosis patients had several comorbidities. Almost all of the patients had pleural plaques (96%). The next most common comorbidities were coronary artery disease (67%) and chronic obstructive pulmonary disease (54%). Relatively common were also malignant diseases (36%). Median survival of the patients was about ten years (125 months) after the asbestosis diagnosis and the patients were on average 79 years at the time of death. The most common underlying cause of death was asbestosis/lung fibrosis (36%) and the most common immediate cause of death was pneumonia (38%). Coronary artery disease and lung cancer were both common causes of death (24% and 10%, respectively), and they both related to mortality in adjusted analyses.

The information of the clinical features of asbestosis observed in our study could be utilised in differential diagnostics of ILDs. Several novel factors were observed which may be useful in evaluating the prognosis of asbestosis patients.

Keywords: asbestosis, bronchoalveolar lavage, cause of death, comorbidity, diffusing capacity, interstitial lung disease, spirometry, survival

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Tiivistelmä

Asbestoosi on yleinen interstitiaalisten keuhkosairauksien erotusdiagnostiikassa huomioitava sairaus. Tutkimustieto asbestoosin ennusteeseen vaikuttavista tekijöistä on ollut vähäistä. Interstitiaalisten keuhkosairauksien lääkehoito kehittyy, minkä vuoksi tieto ennusteeseen vaikuttavista tekijöistä on tärkeää.

Tutkimme sairastuneiden ominaisuuksia, keuhkojen toimintakokeiden ja keuhkohuuhtelunestenäytteiden (BAL) tuloksia sekä niiden vaikutusta ennusteeseen asbestoosipotilailla, joita oli hoidettu Oulun yliopistollisessa sairaalassa vuosina 1996–2015.

Havaitsimme, että asbestoosipotilailla oli BAL:ssa suuri neutrofiilien osuus (6,5 %). Tupakointi ja BAL:n asbestikappaleiden määrä olivat yhteydessä BAL-soluerittelylöydökseen. Tupakoimattomilla asbestoosipotilailla oli BAL:ssa suuri lymfosyyttien osuus (25 %). Suuri asbestikappaleiden lukumäärä, pieni lymfosyyttien, suuri neutrofiilien ja suuri eosinofiilien osuus olivat yhteydessä lyhyempään elinaikaan.

Keuhkojen toimintakokeissa alentunut diffuusiokapasiteetti (65 %) ja spirometrian restriktio olivat tyypillisiä löydöksiä. Riskinarviomallit GAP (gender, age and physiologic variables) ja CPI (composite physiologic index) olivat diffuusiokapasiteetin lisäksi toimivia asbestoosipotilaiden ennusteen arvioimisessa. Keskimääräinen elinaika GAP-luokissa I, II ja III oli 171, 50 ja 21 kuukautta.

Asbestoosipotilailla oli tyypillisesti useita liitännäissairauksia. Lähes kaikilla potilailla havaittiin pleuraplakkeja (96 %). Sepelvaltimotauti (67 %) ja keuhkoahtaumatauti (54 %) olivat seuraavaksi yleisimmät liitännäissairaudet. Suhteellisen yleisiä liitännäissairauksia olivat myös syöpätaudit (36 %). Mediaanielinaika oli noin kymmenen vuotta (125 kuukautta) asbestoosidiagnoosin ajankohdan jälkeen ja potilaat olivat kuollessaan keskimäärin 79-vuotiaita. Yleisin peruskuolinsyy oli asbestoosi (36 %) ja yleisin välitön kuolinsyy keuhkokuume (38 %). Sepelvaltimotauti ja keuhkosyöpä olivat yleisiä kuolinsyitä (24 % ja 10 %), ja molemmat olivat yhteydessä kuolleisuuteen.

Tutkimuksessa saatiin asbestoosin kliinisistä löydöksistä uutta tietoa, jota voidaan hyödyntää esimerkiksi interstitiaalisten keuhkosairauksien erotusdiagnostiikassa. Lisäksi tutkittiin ensimmäistä kertaa useiden kliinisten piirteiden yhteyttä asbestoosin ennusteeseen, ja havaitsimme niiden olevan toimivia tekijöitä ennusteen arvioinnissa.

Asiasanat: asbestoosi, diffuusiokapasiteetti, elinaika, interstitiaalinen keuhkosairaus, keuhkohuuhtelunäyte, kuolinsyy, liitännäissairaus, spirometria

To my family

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Abbreviations

AB	asbestos body
AE	acute exacerbation
ATS	American Thoracic Society
BAL	bronchoalveolar lavage
CHP	chronic hypersensitivity pneumonitis
COPD	chronic obstructive pulmonary disease
CPI	composite physiologic index
CT	computed tomography
DLCO	diffusion capacity for carbon monoxide
DLCO/VA	diffusion capacity for carbon monoxide per unit of lung volume
ERS	European Respiratory Society
FEV1	forced expiratory volume in one second
FVC	forced vital capacity
GAP	gender, age and physiologic variables
HRCT	high-resolution computed tomography
ICD	International Classification of Diseases
ILD	interstitial lung disease
ILO	International Labour Organization classification
IPF	idiopathic pulmonary fibrosis
MGG	May-Grünwald-Giemsa
PAPA	Papanicolaou
PFT	pulmonary function test
PPF	progressive pulmonary fibrosis
RA-ILD	rheumatoid arthritis-associated interstitial lung disease
WHO	World Health Organization

List of original publications

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals:

I Keskitalo, E., Varis, L., Bloigu, R., & Kaarteenaho, R. (2019). Bronchoalveolar cell differential count and the number of asbestos bodies correlate with survival in patients with asbestosis. *Occupational and Environmental Medicine, 76,* 765–771. https://doi.org/10.1136/oemed-2018-105606

II Keskitalo, E., Salonen, J., Vähänikkilä, H., & Kaarteenaho, R. (2021). Survival of patients with asbestosis can be assessed by risk-predicting models. *Occupational and Environmental Medicine, 78,* 516–521. https://doi.org/10.1136/oemed-2020-106819

III Keskitalo, E., Salonen, J., Nurmi, H., Vähänikkilä, H., & Kaarteenaho, R. (2023). Comorbidities and causes of death of patients with asbestosis. *Journal of Occupational and Environmental Medicine, 65,* 349–353. https://doi.org/10.1097/JOM.0000000000002777

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1 Introduction

Asbestosis is a fibrotic lung disease caused by past exposure to asbestos (Tossavainen, 1997). It can be classified as an interstitial lung disease (ILD), pneumoconiosis and asbestos-related disease (Cullinan & Reid, 2013; Tossavainen, 1997; Wijsenbeek et al., 2022). Several countries have banned the use of asbestos; in Finland, the use of asbestos was banned in 1994 (Government Decree on the Prohibition of Manufacture, Import, Trade and Use of Asbestos 3 §; International Ban Asbestos Secretariat, 2022). However, asbestos is still produced and used in many countries globally (Stayner et al., 2013; United States Geological Survey, 2022). Asbestosis and other asbestos-related diseases have a long latency period, i.e., time since exposure to clinical evidence of disease, which is generally more than twenty years in asbestosis (Guidotti et al., 2004; Tossavainen, 1997). Thus, new cases of asbestosis are still found in Finland, although the incidence has been decreasing (Koskela et al., 2022). In contrast, globally the number of asbestosis cases has still been increasing (Shi et al., 2020; Yang et al., 2020).

The first reports of asbestosis were published in the early 20th century while asbestosis research was most active at the end of the 20th century (Cooke, 1924, 1927; Murray, 1990). On the contrary, rather few publications of asbestosis have been published after the turn of the millennium during the past two decades.

In addition to asbestosis, other asbestos-related diseases also include malignant diseases, benign pleural diseases and retroperitoneal fibrosis (Tossavainen, 1997; Wolff et al., 2015). Previously it was observed that asbestosis patients were at increased risk of getting cancer (Karjalainen et al., 1999; Oksa et al., 1997). However, the most common comorbid diseases of asbestosis patients have not previously been widely investigated.

ILDs include more than 200 different diseases, including both acute and chronic diseases (Wijsenbeek et al., 2022). In ILDs, inflammation and/or fibrosis occur mainly in the lung interstitium, that is, the area between pulmonary alveoli and capillaries (Wijsenbeek et al., 2022). Differential diagnosis of ILDs is often challenging and even though asbestosis is nowadays relatively rare in Finland, it is a relevant differential diagnostic dilemma in clinical practice (Koskela et al., 2022). For this reason, it is important to have knowledge of both the common features of ILDs and the characteristic features of certain ILD, such as asbestosis. For example, bronchoalveolar lavage (BAL) and pulmonary function test (PFT) results are usually taken into consideration in diagnostics of ILDs. In previous publications on

BAL results of asbestosis patients, cohorts have been small, and smoking has mostly been left out of account.

Previously, prognostic factors have been recognised in many other ILDs, such as risk predicting models, gender, age and physiologic variables (GAP) and composite physiologic index (CPI) (Ley et al., 2012; Wells et al., 2003). In contrast, the knowledge of factors associated with survival in asbestosis has been sparse. Asbestosis patients have usually lived for several years after the diagnosis, even though, to our knowledge, previous studies have not reported average survival time in cohorts of asbestosis patients (Cookson et al., 1985; Huuskonen, 1978). However, asbestosis may also progress rapidly and moreover, patients may suffer from acute exacerbation (AE) of the disease, which has been observed to be related to poor prognosis in asbestosis patients (Barnikel et al., 2019; Salonen et al., 2020b).

Treatment of asbestosis has previously been symptomatic. Until recently, no pharmacological treatment was able to affect the course of disease in asbestosis. New medications have entered clinical use in the treatment of ILDs. Since 2022, an antifibrotic drug that may slow progression of disease, namely nintedanib, has been eligible for Kela reimbursement also for asbestosis patients with progressive pulmonary fibrosis in Finland (Flaherty et al., 2019; The Social Insurance Institution of Finland (Kela), n.d.). Therefore, research information of factors affecting prognosis is currently important, given that the options for pharmacological treatment are evolving.

In this study, we investigated the disease course and prognosis of asbestosis from a similar point of view as other ILDs. Our aim was to determine clinical features as well as prognostic factors including BAL, PFTs, risk-predicting models and comorbid diseases in a relatively large group of asbestosis patients.

2 Review of the literature

2.1 Asbestos

Asbestos is an umbrella term for a group of silicate minerals which have specific features such as poor heat conduction and high tensile strength and which have thus been of commercial value (World Health Organization, 2014). Asbestos has been used, for example, in building materials, especially insulation materials, and in products such as paints and brake discs, thus, exposure to asbestos is a risk in occupations related to asbestos products, construction, shipyards and vehicle repair (Finnish Institute of Occupational Health, n.d.; Oksa & Nynäs, 2019).

The two main categories of asbestos are serpentine and amphibole (Virta, 2006). Chrysotile, i.e., white asbestos, is worldwide the most common type of asbestos and it is only type of serpentine asbestos (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012; Virta, 2006). The form of large chrysotile fibres is usually curved as they split into smaller parts in the lungs (Roggli et al., 2010). Chrysotile dissolves due to the effect of acids, for example, after the fibre has been phagocytised by macrophages (Roggli et al., 2010). The group of amphibole asbestos includes crocidolite, i.e., blue asbestos, amosite, i.e., brown asbestos, actinolite, anthophyllite, and tremolite (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012). Amphibole fibres tolerate chemicals better than chrysotile and do not break down in the lungs (Roggli et al., 2010).

2.1.1 Global use of asbestos

The peak in the worldwide use of asbestos was in the 1980s (Virta, 2006). Asbestos use is currently banned in more than 60 countries (International Ban Asbestos Secretariat, 2022). The use of asbestos was banned in many European countries in the 1990s and 2000s, and currently, all European Union countries have banned the use of all kinds of asbestos (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012; World Health Organization, 2014).

Despite the known carcinogenicity of asbestos, however, it is still used in many countries (Straif et al., 2009; Virta, 2006). Most developed countries have banned the use of asbestos but, for example, the United States has not completely banned its use (Stayner et al., 2013; United States Geological Survey, 2022). The countries

which currently produce the vast majority of world asbestos are Russia, Kazakhstan, China and Brazil (United States Geological Survey, 2022). According to the estimations of the World Health Organisation (WHO), globally, about 125 million people are still exposed to asbestos at work (World Health Organization, 2014).

2.1.2 The use of asbestos in Finland

The use of asbestos was at its highest level in Finland in the 1960s and 1970s and decreased rapidly in the 1980s (Huuskonen et al., 1995). A total of 300,000 tons of asbestos has been used in Finland since the 1920s (Finnish Institute of Occupational Health, n.d.). Most of the asbestos used was chrysotile (175,000 tons) and anthophyllite (120,000 tons); in addition, minor amounts of crocidolite and amosite (a total of 5,000 tons) were also used (Ministry of Labour, 1989). The Paakkila asbestos mine, where anthophyllite asbestos was mined, operated until 1975, and thus, amphibole asbestos had been used exceptionally commonly in Finland compared to other countries (Ministry of Labour, 1989). Chrysotile, crocidolite and amosite were imported to Finland from abroad (Ministry of Labour, 1989). Most of the asbestos used still remains in Finnish buildings (Finnish Institute of Occupational Health, n.d.). In 1987–1992, the Finnish Institute of Occupational health arranged the Asbestos Programme, the main goals of which were to reduce exposure to asbestos as much as possible, to evaluate the number of asbestos-exposed subjects and identify these individuals, to evaluate asbestos-induced health risks, and to improve diagnostics of asbestos-related diseases (Huuskonen et al., 1995) The import and manufacture, and the use and sale of asbestos and asbestos-containing products was banned in Finland in 1993 and 1994, respectively (Government Decree on the Prohibition of Manufacture, Import, Trade and Use of Asbestos 3 §).

When bound to building materials, asbestos is not usually a health hazard whereas in demolition work, fibres are released into the air (Ministry of Labour, 1989). Thus, exposure to asbestos is still possible in Finland during demolition of buildings if the protective equipment and actions are insufficient (Ylioinas et al., 2012). Organising asbestos demolition work is regulated by Finnish legislation (Act on Certain Requirements Concerning Asbestos Removal Work 1–17 §; Government Decree on the Safety of Asbestos Work 1–18 §). Exposure to asbestos can still also occur in mining because asbestos occurs in the Finnish bedrock (Kähkönen et al., 2019).

2.2 History of asbestosis

Asbestosis is pulmonary fibrosis caused by asbestos. It develops after significant exposure and long latency, i.e., time since first exposure to clinical evidence of disease (Tossavainen, 1997). Asbestosis is generally defined as a slowly progressive disease with restrictive ventilatory function and decreased diffusion capacity (DLCO) (Alfonso et al., 2005; Algranti et al., 2001; Bégin et al., 1983; Cookson et al., 1986).

The first reports of asbestosis cases were published in Great Britain in 1906 and 1924 (Cooke, 1924, 1927; Murray, 1990). Cooke (1924) described a 33-year-old female asbestos factory worker, who had started asbestos work already at the age of 13, and whose pulmonary fibrosis was diagnosed by both x-ray plate and autopsy. A similar patient case was reported already in 1906 (Cooke, 1927; Murray, 1990). Three articles on the topic of asbestosis were published in the British Medical Journal in 1927 (Cooke, 1927; Mcdonald, 1927; Oliver, 1927). Cooke (1927) reported clinical features of the previously described asbestosis case (Cooke, 1924), Mcdonald (1927) described histological features focusing on foreign bodies, which he estimated to contain asbestos, and Oliver (1927) presented clinical features of asbestosis including dyspnoea, cough and the presence of basal crepitation in lung auscultation. Soon after these publications, many case reports of asbestosis were published, which also included publications of asbestosis with lung cancer since the 1930s (Lynch & Smith, 1935). The first Finnish studies on asbestosis were published in 1946 and 1947; they reported histological and radiological features (Noro, 1946; Wegelius, 1947). Wegelius (1947) investigated 126 asbestosis patients and observed that most of the cases had mild fibrosis in chest radiograph, although disease progression was seen in some patients during a short two-year follow-up period (Wegelius, 1947).

Knowledge about asbestosis increased from the middle of the 20th century onwards. Sander (1955) reported that asbestosis developed slowly after years of asbestos exposure, the disease was preventable, and changes in chest x-ray occurred earlier in lower lobes (Sander, 1955). Sander (1955), however, supposed that asbestos-induced fibrosis would not progress after exposure has ceased. In a review article published in 1966, Elmes described that symptoms may begin even years after asbestos exposure has stopped, and with a latency period as long as 20 to 30 years (Elmes, 1966). Typical symptoms such as dyspnoea and cough as well as physical findings such as restricted chest movement, basal rales and finger clubbing in severe asbestosis were described (Elmes, 1966). Moreover, PFTs of asbestos

workers, i.e., decreased vital capacity (VC) without obstruction, decreased total lung volume, decreased DLCO and low pulmonary compliance, were also displayed (Elmes, 1966). In the 1950s, Sander reported that an association between asbestosis and lung cancer was uncertain (Sander, 1955), while in a review article of the American College of Chest Physicians in 1964, it was noted that there were more published studies in which an association between asbestosis and lung cancer was observed than studies without an association, and that the diagnostic criteria of asbestosis were variable (Liddle, 1964).

The number of publications on asbestosis increased since the mid-20th century until the 1980s. In 1978, two publications of large Finnish asbestosis cohorts were published in which clinical, physiological and radiological features, survival and mortality of patients were reported (Huuskonen, 1978; Zitting et al., 1978). International consensus criteria for diagnosis of asbestosis, namely the Helsinki criteria, were first published in 1997 and updated in 2014 (Tossavainen, 1997; Wolff et al., 2015).

2.3 Other asbestos-related diseases

2.3.1 Malignant diseases

Asbestos is known to cause both benign and malignant diseases (Tossavainen, 1997; Wolff et al., 2015). Asbestos causes mesothelioma and lung, laryngeal and ovarian cancers (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012; Ngo et al., 2022).

The strongest evidence of malignancies caused by asbestos exposure has been shown in lung cancer and mesothelioma (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012). Lung cancer is the third most common cancer in both men and women and the most common cause of cancer death in Finland (Pitkäniemi et al., 2022). The risk of lung cancer increases with increasing cumulative asbestos exposure (Brims et al., 2020; Tossavainen, 1997). The latent period is typically estimated to be 20 to 30 years (Suojalehto et al., 2019). Smoking further increases the risk of lung cancer also in asbestos-exposed patients (Brims et al., 2020; Markowitz et al., 2013). In addition, diagnosis of asbestosis, but not pleural plaques, was associated with increased risk of lung cancer (Brims et al., 2020; Markowitz et al., 2013).

Asbestos is the principal cause of mesothelioma (Tossavainen, 1997). Even low asbestos exposure can cause mesothelioma (Suojalehto et al., 2019; Tossavainen, 1997). In an Australian register study of about 6,000 mesothelioma cases, almost all the cases had an established previous asbestos exposure since 88% of the patients had a history of past exposure, and in the cases with no known asbestos exposure history, 81% had nonetheless more than 200,000 asbestos fibres/g of dry lung tissue (Leigh et al., 2002). Of the cases, 93% were pleural mesotheliomas while 6.5% were peritoneal (Leigh et al., 2002). In Finland, about 100 new mesothelioma cases have been diagnosed annually in recent years; in 2021, there were 100 new mesothelioma cases (Finnish Cancer Registry, n.d.). The latent period for mesotheliomas is typically about 30 to 40 years (Tossavainen, 1997). The prognosis of survival is weak. In the previous Finnish studies the median survival time was 9.7 months in pleural and 4 months in peritoneal mesothelioma (Laaksonen et al., 2019; Salo et al., 2017).

In a review article by the International Agency for Research on Cancer by WHO, an association between asbestos exposure and pharyngeal, stomach and colorectal cancers was observed (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012), whereas Ngo et al. (2022) reported in a monograph of the European Respiratory Society (ERS) that there was limited evidence of an association of asbestos with nonlaryngeal head and neck and colorectal cancers (Ngo et al., 2022). It was informed in the abovementioned publication that previous studies had also observed an asbestos exposure association with cancer of the oesophagus and prostate, although the strength of the evidence was not evaluated (Ngo et al., 2022).

2.3.2 Benign diseases

Benign diseases caused by asbestos exposure include, in addition to asbestosis, benign pleural diseases including pleural plaques, diffuse pleural fibrosis and pleuritis as well as retroperitoneal fibrosis.

Acute or chronic pleuritis, typically but not always asymptomatic, may be induced by asbestos (Guidotti et al., 2004). Acute pleuritis may induce diffuse pleural fibrosis, which is sometimes accompanied with rounded atelectasis (Lilis et al., 1988; Musk et al., 2020; Tossavainen, 1997). Pleural plaques are usually asymptomatic, whereas diffuse pleural fibrosis can result in restrictive pulmonary function (Kerper et al., 2015; Schwartz et al., 1990; Tossavainen, 1997). The plaques locate in the parietal pleura and they may be calcified (Guidotti et al., 2004).

Plaques can be diagnosed from chest radiograph whereas diagnosis of diffuse pleural fibrosis requires CT imaging (Cha et al., 2016; Suojalehto et al., 2019). Pleural plaques have been the most common abnormality associated with asbestos and even mild asbestos exposure can result in the development of plaques, whereas development of diffuse pleural fibrosis requires moderate exposure (Guidotti et al., 2004; Murray et al., 2016; Suojalehto et al., 2019). Pleural plaques have thus been considered as evidence of asbestos exposure even though they were relatively commonly also seen in elderly Finnish general population (Guidotti et al., 2004; Zitting, 1995). Ehrlich et al. (1992) reported that the presence of pleural abnormalities associated with latency period and was also common at low exposure levels. In 2018, asbestos-related pleural plaques were the most common confirmed occupational disease (257 cases) in Finland (Koskela et al., 2022). Minor amounts, e.g. nine new occupational round atelectasis or visceral pleural fibrosis cases, were confirmed as occupational disease (Koskela et al., 2022).

In retroperitoneal fibrosis, fibrosis is located in the retroperitoneal parts of the body, such as the aorta and urinary tract (Wolff et al., 2015). It is a rare disease (Wolff et al., 2015). Uibu et al. (2004) observed asbestos to be a significant risk factor of retroperitoneal fibrosis in Finland (Uibu et al., 2004). With a history of asbestos exposure, asbestos can be considered as the cause of retroperitoneal fibrosis in patients with asbestos-related parenchymal or pleural disease, or without other asbestos-related disease, also without other risk factors as well (Wolff et al., 2015).

2.4 Asbestosis as an interstitial lung disease

Asbestosis is asbestos-induced pulmonary fibrosis and it is classified as an interstitial lung disease (ILD) (Tossavainen, 1997). ILDs include over 200 diseases, in which asbestosis is categorised into the group of exposure-related ILDs (Wijsenbeek et al., 2022). Other ILD groups include autoimmune-related ILDs, idiopathic ILDs, ILDs with cystic or airspace filling, sarcoidosis and other ILDs (Table 1) (Raghu et al., 2022; Wijsenbeek et al., 2022). The most common fibrotic ILD type is idiopathic pulmonary fibrosis (IPF) (Wijsenbeek et al., 2022). In addition to asbestosis, other exposure-related ILDs include other pneumoconiosis, hypersensitivity pneumonitis, and ILDs induced by medication or radiation (Raghu et al., 2022).

Asbestosis is also classified as pneumoconiosis, which are chronic lung diseases caused by inhalation of dust (Cullinan & Reid, 2013). At present,

asbestosis is the most common form of pneumoconiosis, followed by silicosis (Bennett & Brims, 2020; Cullinan & Reid, 2013). Other forms of pneumoconiosis are siderosis, berylliosis, stannosis, hard metal disease and coal workers' pneumoconiosis, which are more uncommon than asbestosis (Cullinan & Reid, 2013). Although patients with asbestosis comprise a small group among all ILD cases, it is a relevant differential diagnostic dilemma that needs to be taken into account in everyday clinical practice.

Differential diagnostics between IPF and asbestosis as well as assessment of asbestos exposure can be difficult (Suojalehto et al., 2019). Investigations on the association of asbestos with IPF have resulted in discrepant results since in previous studies, asbestos exposure was associated with higher risk of IPF and historic asbestos imports were associated with IPF mortality (Abramson et al., 2020; Barber et al., 2016), whereas in a recent study of Reynolds et al. (2023), no association between asbestos and risk of IPF was observed (Reynolds et al., 2023).

Table 1. Classification of interstitial lung diseases (modified from Raghu et al., 2022 and Wijsenbeek et al., 2022).

ILD classification	Examples
Autoimmune-related ILD	Rheumatoid arthritis and systemic sclerosis-associated ILD, vasculitis-related ILD
Exposure-related ILD	Asbestosis, other pneumoconiosis, hypersensitivity pneumonitis, radiation and medication-related ILD
Idiopathic ILD	Idiopathic pulmonary fibrosis, idiopathic non-specific interstitial pneumonia, unclassifiable ILD
ILDs with cysts or airspace filling	Langerhans cell histiocytosis, lymphangioleiomyomatosis, pulmonary alveolar proteinosis
Sarcoidosis	Sarcoidosis
Other	Eosinophilic pneumonia

ILD = Interstitial lung disease

2.5 Epidemiology of asbestosis

The incidence of asbestosis was at its highest in the 1990s when there were more than 200 new cases per year in Finland (Suojalehto et al., 2019). The incidence of asbestosis cases has decreased in Finland since then (Koskela et al., 2022). Eighteen new asbestosis cases were confirmed as an occupational disease in 2018 when all the patients were over 65 years old (Koskela et al., 2022). In 2014, construction

was the most common industry causing asbestosis, and asbestos-related lung cancer and pleural plaques were accepted as occupational diseases (Koskela et al., 2017). Although the incidence of asbestosis has decreased, there are still prevalent cases which are usually treated and followed up in specialised health care in Finland.

Globally, the incidence of asbestosis has been increasing, with about 9,400 new asbestosis cases in 2017, including about 2,400 cases from the United States, 1,900 cases form China and 1,000 cases from India (Shi et al., 2020). In 2017, the age-standardised incidence of asbestosis was highest in South Africa (0.5 per 100,000), Swaziland (0.44 per 100,000) and the United States (0.43 per 100,000) (Shi et al., 2020; Yang et al., 2020). It was estimated in the Global Burden of Diseases 2017 study that the age-standardised incidence of asbestosis per 100,000 was 0.06 in Finland, 0.05 in Sweden, 0.02 in Denmark, and 0.21 in Norway (Shi et al., 2020).

Asbestos consumption and asbestos exposure were associated with increased mortality from asbestosis (dos Santos Antao et al., 2009; Girardi et al., 2020; Harding et al., 2009). In the Global Burden of Diseases Study 2016, it was estimated that the number of asbestosis deaths has increased since 2006, and that about 3,500 people died of asbestosis and asbestosis caused 61,000 years of life lost globally in 2016. (Naghavi et al., 2017). In Finland, the number of asbestosis deaths has decreased slightly from more than twenty cases to about 15 asbestosis deaths per year during the 2010s (Figure 1) (Statistics Finland, n.d.).

Diandini et al. (2013) reported the average potential years of life lost from asbestosis per decedent, being 13 years, and the age at death from asbestosis 73.4 years in 55 countries globally between 1994 and 2010. The countries included were from all over the world (Europe, North and South America, Asia, Africa, Australia) and also included data from Finland (Diandini et al., 2013). In the United States, the median age at the time of death in patients with asbestosis as underlying cause of death was 79 years and median potential years of life lost per decedent was 8 years between 1999–2010 (Bang et al., 2014).

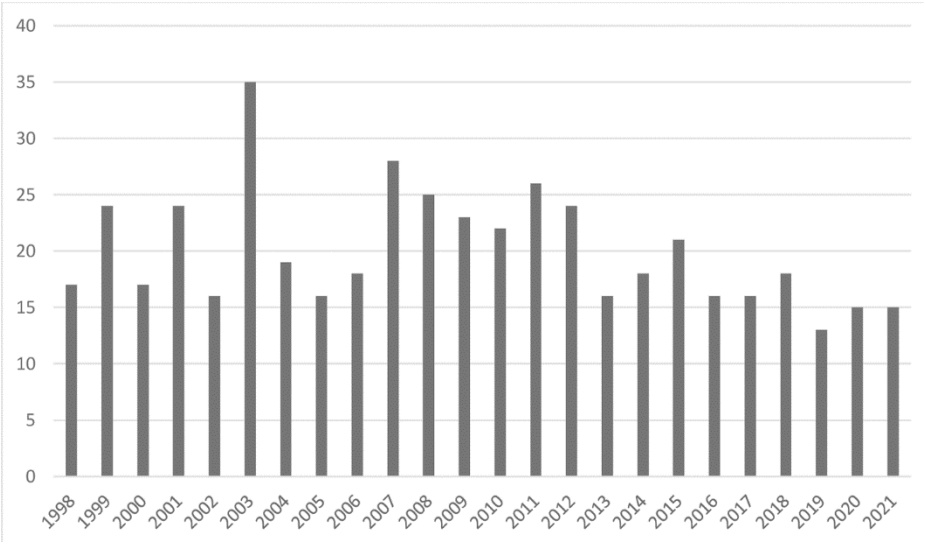

Fig. 1. Number of asbestosis (International Classification of diseases 10th edition code J61) deaths in Finland between 1998–2021 according to the Statistics of Finland (Statistics Finland, n.d.).

2.6 Pathophysiology and pathogenesis of asbestosis

Asbestos fibres enter the lungs with inhaled air. The fibres end up in the bronchioles and alveoli and migrate to the interstitium (Bennett & Brims, 2020; Guidotti et al., 2004). The clearance of asbestos fibres depends on the fibre type so that chrysotile fibres are most effectively eliminated from the lungs compared to amphibole fibres (Albin et al., 1994; Churg & Vedal, 1994). In addition, Lorenzo et al. (1996) reported that asbestosis patients had slower mucociliary clearance compared to asbestos-exposed and non-exposed control subjects (di Lorenzo et al., 1996). Churg et al. (1990) estimated amosite fibres to be more fibrinogenic compared to chrysotile or tremolite fibres (Churg et al., 1990).

The risk of getting asbestosis is associated with cumulative asbestos exposure (Algranti et al., 2001; Ehrlich et al., 1992; Mastrangelo et al., 2009; Paris et al., 2004). In previous studies, the severity of fibrosis correlated with both the asbestos fibre concentration of the lungs and the cumulative exposure history (Churg et al., 1989, 1990; Green et al., 1997; Wagner et al., 1986)

The latency period is typically over 20 years in asbestosis patients (Epler et al., 1982; Guidotti et al., 2004; Yang et al., 2018). The American Thoracic Society (ATS)

estimated that exposure with high intensity but short duration results in shorter latency time, whereas mild intensity but long duration results in longer latency (Guidotti et al., 2004). The risk of developing asbestosis has also been in relation to a longer latency period (Algranti et al., 2001; Barnhart et al., 1990; Epler et al., 1982; Lilis et al., 1986).

Smoking increased the risk of developing asbestosis in asbestos-exposed subjects (Barnhart et al., 1990; Ehrlich et al., 1992; Lilis et al., 1986). The effect of smoking was thought to be probably related to minor fibre clearance (Albin et al., 1994; Churg et al., 1992; Churg & Stevens, 1995).

Inhaled asbestos fibres have been shown to induce an inflammatory response and cause the formation of oxidants (Kamp et al., 1992; Robledo & Mossman, 1999). The fibres also induce the production of cytokines and chemokines in addition to oxidants (Mossman & Churg, 1998). Inflammatory cells accumulate in the airspace and interstitium (Robledo & Mossman, 1999). Macrophages have been shown to associate with disease progression, since these cells are capable of phagocyting fibres and produce oxidants and growth factors (Kamp et al., 1992; Mossman & Churg, 1998; Rom et al., 1987). Epithelial cell injuries are an early process in the pathogenesis of asbestosis (Mossman & Churg, 1998; Robledo & Mossman, 1999). Similarly as in other pulmonary fibroses, increased amounts of various tight and adherens junction proteins and cyclooxygenase-2 (COX-2) were expressed in metaplastic alveolar epithelium in asbestosis (Lappi-Blanco et al., 2006, 2013). Transforming growth factor-beta (TGF-β) and platelet-derived growth factor (PDGF), produced by both macrophages and epithelial cells, induce fibroblast proliferation (Mossman et al., 2011). A marker of collagen synthesis, namely carboxyterminal propeptide of type I procollagen (PICP), was shown to be increased in BAL of patients with asbestosis (Lammi et al., 1999) Elevated plasma adipsin, which is produced by macrophages besides adipose tissue, and serum soluble mesothelin-related protein levels were observed in blood samples of asbestosis patients (Leivo-Korpela et al., 2012; Yu et al., 2015).

2.7 Diagnosis of asbestosis

The Helsinki criteria for the diagnostics of asbestosis were first published in 1997 and updated in 2014 (Tossavainen, 1997; Wolff et al., 2015). The diagnosis of asbestosis requires the fulfilment of the two criteria: evidence of parenchymal pulmonary fibrosis and sufficient exposure to asbestos (Guidotti et al., 2004; Tossavainen, 1997; Wolff et al., 2015). Symptoms, PFT results and latency time are

taken into account in diagnostics (Tossavainen, 1997). The clinical features of asbestosis are nonspecific and exposure history is therefore mandatory for diagnosis (Guidotti et al., 2004; Tossavainen, 1997).

In differential diagnostics, other ILDs have to be taken into account. Sometimes, patients may have combined diseases such as both silicosis and asbestosis (Guidotti et al., 2004). A multidisciplinary evaluation is recommended in uncertain cases (Tossavainen, 1997). Asbestosis is an important differential diagnostic dilemma of IPF with an unidentified cause (Raghu et al., 2022).

2.7.1 Radiology

High-resolution computed tomography (HRCT) imaging is usually used in the evaluation of interstitial lung changes. For diagnostic purposes in pulmonary fibroses, HRCT is superior compared to chest x-ray (Paris et al., 2004; Staples et al., 1989; Terra-Filho et al., 2015). HRCT detects early asbestosis before there are changes in the chest radiograph (Paris et al., 2004; Staples et al., 1989). Subpleural opacities and lines and parenchymal bands are seen in HRCT in the early phases, while honeycombing and intralobular interstitial and interlobular septal thickening are seen in advanced disease (Akira & Morinaga, 2016; Cha et al., 2016). Fibrosis is typically most prominent in the basal areas of the lungs (Craighead et al., 1982; Guidotti et al., 2004). In rare cases, fibrotic changes have been seen in the apical areas of the lungs (Hillerdal, 1990). The Helsinki criteria recommends the use of ICOERD classification for HRCT changes in international research (Suganuma et al., 2009; Wolff et al., 2015). Asbestos diagnosis requires at least sum grade 2 for bilateral irregular opacities in the lower zones or bilateral honeycombing (Suganuma et al., 2009; Wolff et al., 2015).

Novel radiological methods have also been investigated. The utility of ultra-low-dose CT in detecting asbestosis has been studied. One study reported 75% sensitivity and 100% specificity for detecting asbestosis although there were only four asbestosis cases (Schaal et al., 2016). Groot Lipman et al. (2022) presented that artificial intelligence could be a useful aid in the diagnosis of asbestosis in CT, showing that diagnostic accuracy improved when also taking into account DLCO (Groot Lipman et al., 2022).

Pulmonary fibrosis may be seen in chest x-ray, but it is not sensitive or specific enough since normal chest x-ray is not able to exclude the presence of pulmonary fibrosis and on the other hand, there may be overdiagnosis based on chest x-ray (Friedman et al., 1988; Mizell et al., 2009; Paris et al., 2004; Staples et al., 1989;

Terra-Filho et al., 2015). Fibrosis is seen in the chest x-ray as small, irregular opacities focusing in the lower zones (Cha et al., 2016; Zitting et al., 1978). The standardised International Labour Organization (ILO) classification where grade 1/0 is considered as mild asbestosis has been used for research and screening purposes (Guidotti et al., 2004; International Labour Organization, 2011; Tossavainen, 1997).

2.7.2 Exposure assessments

The amount of cumulative asbestos exposure and the duration of the latency period are reviewed when evaluating sufficient exposure to cause asbestosis (Guidotti et al., 2004; Tossavainen, 1997). Cumulative exposure is reported as fibre years, calculated as duration of exposure (years) times fibre counts in a cubic centimetre of breathing air (Tossavainen, 1997; Wolff et al., 2015). Less than ten fibre years is classified as mild, 10–24 fibre years as moderate, and at least 25 fibre years as high-level exposure (Suojalehto et al., 2019).

In international publications, it has been stated that there is no clear limit for when cumulative asbestos exposure is sufficient for asbestosis (Bennett & Brims, 2020). Furthermore, no strict limit for adequate latent period for asbestosis has been defined, although the latent period has usually been long, over 20 years (Epler et al., 1982; Guidotti et al., 2004; Yang et al., 2018). In Finland, asbestosis diagnosis requires at least moderate, generally more than 20 fibre years exposure to asbestos (Suojalehto et al., 2019).

Detailed work history assessment is the primary method for assessing the history of past asbestos exposure (Tossavainen, 1997; Wolff et al., 2015). Patient's entire work history is reviewed and the amount of exposure in different work tasks and duration of exposure are assessed. The amount of cumulative asbestos exposure is calculated based on the evaluation (Suojalehto et al., 2019). If the exposure history information is uncertain, fibres or asbestos body (AB) count in lung tissue or BAL sample may be used in the evaluation. Limit values for high probability of significant asbestos exposure were defined in the Helsinki criteria (Tossavainen, 1997). More than 1 AB/ml in BAL fluid sample has been considered as significant exposure (Karjalainen et al., 1994; Sebastien et al., 1988; Tossavainen, 1997).

ABs are asbestos fibres which are covered by proteins and iron compounds (Craighead et al., 1982). Amphibole asbestos, which was commonly used in Finland, has been estimated to persist in the lungs and to form ABs more easily than chrysotile asbestos (Churg & Wright, 1994; Ministry of Labour, 1989; Roggli

et al., 2010). In previous studies, the number of ABs in BAL has associated with both past asbestos exposure as well as the number of ABs and asbestos fibres in the lung parenchyma (De Vuyst et al., 1988; Karjalainen et al., 1994, 1996; Nuyts et al., 2017; Sebastien et al., 1988; Teschler et al., 1994). Thus, counting BAL ABs is useful when evaluating exposure history. It is, however, noteworthy that the absence of ABs in BAL does not exclude asbestos exposure. (Nuyts et al., 2017; Teschler et al., 1994).

2.7.3 Bronchoalveolar lavage and lung tissue samples

BAL fluid sample may be utilised in the diagnostics of ILDs (Meyer et al., 2012). The BAL fluid sample is taken during bronchoscopy and leucocyte differential count is calculated from the fluid sample. Reference values of BAL cell differential counts based on the international guideline of ATS are as follows: Macrophages ≥ 80–85%, lymphocytes 10–15%, neutrophils ≤ 3%, and eosinophils ≤ 1% (Meyer et al., 2012). Additionally, the number of asbestos bodies may be analysed from BAL if there is known or suspected exposure to asbestos (Tossavainen, 1997).

Lung biopsy samples are not required for asbestosis diagnosis, although in addition to calculating asbestos fibres and bodies, interstitial fibrosis can be detected in histological samples (Guidotti et al., 2004; Roggli et al., 2010; Wolff et al., 2015). A histologic grading scheme for asbestosis was first published in 1982 and updated in 2010 (Craighead et al., 1982; Roggli et al., 2010). The severity of fibrosis is classified from zero to four and the grade is based on mean score of the slides (Roggli et al., 2010). In grade 0, no fibrosis or bronchiolar wall fibrosis exists, while in grades 1–3, fibrosis is detectable in respiratory bronchioles and adjacent alveoli and as the grade increases, fibrosis is seen in more extensive areas. Grade 4 signifies that honeycomb changes are detected (Roggli et al., 2010). The classification has received criticism since it classifies bronchial wall fibrosis to grade 0 (Hammar & Abraham, 2015).

Karjalainen et al. (1996) investigated both BAL and lung tissue samples in 65 Finnish patients, revealing that the concentration of ABs in BAL was in relation to the concentration of ABs in tissue sample. In addition, asbestos fibre count associated with both ABs in tissue sample and BAL. Karjalainen et al. (1996) also studied the association of asbestos fibres and ABs based on the amphibole fibre type. They observed a higher amount of ABs in relation to asbestos fibre count in samples with mainly anthophyllite asbestos compared to similar amounts of asbestos fibres in samples with mainly amosite or crocidolite fibres.

2.8 Clinical features of asbestosis

2.8.1 Symptoms and physical examination

The symptoms of asbestosis are similar to other pulmonary fibrosis since shortness of breath and cough are common (Guenther et al., 2018; Huuskonen, 1978; Walters et al., 2013). Patients with mild asbestosis may also be asymptomatic.

Persistent sputum production was observed in 71% and cough in 79% of the Finnish asbestosis patients, both symptoms being more common in smokers (Huuskonen, 1978). Shortness of breath was very common (89%) associating with lower vital capacity (VC) and forced expiratory volume in one second (FEV1) in spirometry and radiographically more severe asbestosis. Patients estimated that these symptoms had started on average almost four years before the asbestosis diagnosis (Huuskonen, 1978). In the study of Walters et al. (2013), all the 43 patients had symptoms at the time of diagnosis of asbestosis, shortness of breath being the most common symptom (95%) followed by cough (70%).

A typical auscultation finding of pulmonary fibroses is basal fine crackles or crepitation. In previous studies, fine crackles were heard in about 60% of the asbestosis patients (Epler et al., 1978; Huuskonen, 1978). Crackles were early signs of asbestosis and could be heard before changes in chest radiograph (Shirai et al., 1981). Duration of exposure to asbestos was associated with auscultation finding of bilateral basal crackles (Shirai et al., 1981). Furthermore, crepitation was more commonly heard in radiographically more severe asbestosis (Huuskonen, 1978). Crackles associated with lower PFT results, i.e., forced vital capacity (FVC) and DLCO in patients with asbestosis (Epler et al., 1978).

Finger clubbing is seen in some patients, typically in more severe asbestosis (Coutts et al., 1987; Huuskonen, 1978). Finger clubbing is associated with shorter survival, radiographic disease progression and lower DLCO (Coutts et al., 1987). In severe disease hypoxaemia, cyanosis, cor pulmonale and respiratory failure may also occur (Bennett & Brims, 2020). In a Finnish study, asbestosis patients had more often signs of load of the right side of the heart in electrocardiography compared to control cases, although the results were not statistically significant (Kokkola & Huuskonen, 1979).

2.8.2 Pulmonary function tests

A typical finding in spirometry of asbestosis patients is restriction, similarly to other pulmonary fibroses (Algranti et al., 2001; Bégin et al., 1983; Miguel-Reyes et al., 2015; Miller et al., 1996). DLCO examination also reveals decreased values (Alfonso et al., 2005; Bégin et al., 1983; Vierikko et al., 2010; Walters et al., 2013; Yang et al., 2018). DLCO decreases in more early stages of asbestosis, while spirometry values decrease later than DLCO, similarly to other pulmonary fibroses (Miguel-Reyes et al., 2015; Nogueira et al., 2011; Walters et al., 2013; Yang et al., 2018). Previous studies have shown that asbestosis patients had lower FVC, FEV1 and DLCO values compared to asbestos-exposed patients without pulmonary fibrosis (Abejie et al., 2010; Alfonso et al., 2005).

The results of whether asbestos causes obstruction have been contradictory. Yang et al. (2018) observed that longer duration of asbestos exposure associated with lower FEV1/FVC ratio in non-smoking asbestosis patients. Other studies did not find a significant association between asbestos exposure and FEV1/FVC ratio in asbestos-exposed patients (Abejie et al., 2010; Alfonso et al., 2004; Ameille et al., 2010). Wang et al. (2006) reported that smoking was the main cause of obstruction in asbestos-exposed patients while asbestosis associated with restrictive spirometry, that is decreased FVC and elevated FEV1/FVC, when asbestos exposure was in relation to both decreased FVC and DLCO. In the Helsinki criteria 2014 it was reviewed that previous studies have suggested that asbestos-exposed patients may have a component of obstruction, especially small airway obstruction, but it was stated that asbestos does not cause a purely obstructive ventilatory pattern (Wolff et al., 2015).

Yang et al. (2018) observed that among newly diagnosed asbestosis patients, smokers have lower FEV1 and FEV1/FVC compared to non-smokers. Zitting et al. (1978) observed that in mild fibrosis, smokers had decreased FEV1 compared to ex-smokers.

Previous studies have shown an association between decreased PFTs (FVC, FEV1 total lung capacity and DLCO) and more severe radiological changes (Algranti et al., 2001; Lee et al., 2003; Miller et al., 1992, 1996, 2013; Rom, 1992; Schneider et al., 2014; Yang et al., 2018; Zitting et al., 1978). Algranti et al. (2001) observed a decrease in spirometry values, FVC and FEV1 in relation to longer latency period in asbestos-exposed patients. In a previous study, progression of interstitial changes in HRCT associated with decreasing DLCO but not with spirometry value changes in the follow-up (Nogueira et al., 2011). In a Chinese

study, asbestosis patients had decreasing DLCO, FVC and FEV1 in the follow-up, whereas FEV1/FVC was elevated in five- to ten-year follow-up (Wang et al., 2010). DLCO declined most rapidly in asbestos-exposed patients both with and without asbestosis (Wang et al., 2010). A higher cumulative exposure associated, although not significantly, with faster deterioration of DLCO and FVC (Wang et al., 2010).

Schneider et al. (2014) investigated PFTs and maximum cardiopulmonary exercise test in asbestosis patients, revealing that asbestosis associated with lower arterial oxygen pressure at rest and exercise. Furthermore, they found that the severity of asbestosis associated with, for example, lower ventilation volume and oxygen uptake. Lee et al. (2003) observed that lower oxygen saturation during exercise was related to the severity of radiological changes in asbestosis patients, and that weaker DLCO correlated with subjective breathlessness.

2.8.3 Bronchoalveolar lavage

Previous studies investigating BAL cell differential count of asbestosis patients were mostly published in the 1980s and 1990s, and in those studies the number of asbestosis patients was small, on average fewer than 20 patients (Table 2) (al Jarad et al., 1993; Bégin et al., 1986; Bergantini et al., 2021; Callahan et al., 1990; Cantin et al., 1989; Costabel et al., 1987; Garcia et al., 1989; Gellert et al., 1985; Hayes et al., 1988; Kopiński et al., 2006; Lammi et al., 1999; Lenz et al., 1996; Robinson et al., 1987; Rom et al., 1987; Scharfman et al., 1989; Schwartz et al., 1992; Walters et al., 2013; Xaubet et al., 1986). A neutrophilic and eosinophilic cell pattern has typically been observed in BAL of asbestosis patients. However, in most of those studies, the patients' smoking history has not been taken into account (Table 2). In the guideline of ATS, a neutrophilic BAL cell pattern was reported to be typical for asbestosis, similar to IPF (Meyer et al., 2012). Recently, cell differential counts of asbestosis and other ILD patients were reported in which the patients with asbestosis were distinguished from other ILDs with BAL macrophages higher than 74% and eosinophils higher than 0.5% (Bergantini et al., 2021).

Smoking is important to take into consideration when evaluating BAL findings, since healthy smokers have been shown to exhibit higher BAL total cell count, higher macrophage and lower lymphocyte differential counts than non-smokers or ex-smokers (Frye et al., 2020; Heron et al., 2012; Karimi et al., 2012). Similar results have also been found in the previous studies with asbestos-exposed smokers who had higher total cell count and lower lymphocyte differential count than non-

smokers or ex-smokers (Corhay et al., 1990; Cullen & Merrill, 1992; Kokkinis et al., 2011).

Table 2. Studies reporting bronchoalveolar lavage fluid cell differential count in asbestosis patients.

Reference	Number of patients	Neutrophils >3%	Eosinophils >1%
al Jarad et al., 1993[1]	21	x	x
Bégin et al., 1986	19	x	x
Bergantini et al., 2021	41		
Callahan et al., 1990	9	x	x
Cantin et al., 1989	10		x
Costabel et al., 1987	7		
Garcia et al., 1989	12	x	x
Gellert et al., 1985	27	x	x
Hayes et al., 1988	8	x	x
Kopiński et al., 2006	9		
Lammi et al., 1999	5		x
Lenz et al., 1996	6		x
Robinson et al., 1987	10	x	x
Rom et al., 1987	18		
Scharfman et al., 1989	6	x	
Schwartz et al., 1992[2]	25		
Walters et al., 2013	21	x	
Xaubet et al., 1986	27	x	

[1]Mean neutrophils + eosinophils 7%. [2]Absolute number of cell types was reported when higher amounts of macrophages, neutrophils and eosinophils was observed in asbestosis compared to asbestos-exposed subjects.

The association of BAL parameters with lung function tests was studied in patients with heavy asbestos exposure and ILO grade at least 1/0 in chest radiograph, revealing that BAL neutrophils associated with baseline FEV1 and DLCO, but not with annual declines of PFTs in the follow-up (Rom, 1992). In a more recent study, Walters et al. (2013) reported that BAL neutrophils associated with lower baseline DLCO in patients with asbestosis, but they did not observe an association between neutrophils and DLCO decline in the follow-up. Another study reported an association between BAL neutrophils and bilateral crackles in auscultation and decreased partial pressure of oxygen (pO2) in arterial blood in patients with asbestosis (Xaubet et al., 1986).

The number of ABs in BAL fluid has traditionally been utilised in the evaluation of past asbestos exposure. A few previous studies have studied the

association of BAL ABs with the BAL cell profile. Kokkinis et al. (2011) observed that BAL ABs associated with BAL lymphocytosis in asbestos-exposed healthy study subjects while Corhay et al. (1990) noticed that neutrophil differential count was higher in the BAL samples with more than 10 AB/ml compared to those with under 1 AB/ml (Corhay et al., 1990; Kokkinis et al., 2011).

2.8.4 Comorbid diseases

Previous studies published on comorbidities of asbestosis patients have focused on malignant diseases, benign pleural disease, emphysema and neurological signs. Asbestosis patients had increased risk of developing malignant disease, especially lung cancer and mesothelioma (Karjalainen et al., 1999; Oksa et al., 1997; Reid et al., 2005). High risk of developing any cancer, lung cancer or mesothelioma was observed in both middle-aged and elderly asbestosis patients (Oksa et al., 1997).

Lung cancer has been a commonly reported comorbidity of asbestosis patients. In previous studies, standardised incidence ratio also showed increased risk when estimating separately different histological lung cancer subtypes such as adenocarcinoma, squamous cell carcinoma and small cell carcinoma (Karjalainen et al., 1999; Oksa et al., 1997). Both asbestos exposure and asbestosis have been observed to be risk factors for lung cancer (Markowitz et al., 2013; Reid et al., 2005). Patients with asbestosis have been shown to be at high risk of developing lung cancer even when exposure history was taken into account (Hughes & Weill, 1991; Markowitz et al., 2013; Reid et al., 2005). The lung cancer risk of asbestosis patients was also higher compared to patients with benign pleural disease (Karjalainen et al., 1999). Smoking also increased the lung cancer risk in asbestosis patients (Markowitz et al., 2013; Oksa et al., 1997).

Karjalainen et al. (1999) reported increased incidence of laryngeal cancer in addition to any cancer, lung cancer and mesothelioma in patients with asbestosis although a statistically significant increase in incidences of other cancer types was not found (Karjalainen et al., 1999). The lung cancer risk was elevated both at the beginning and at the end of follow-up since notification in the Finnish Registry of Occupational Diseases (Karjalainen et al., 1999). On the other hand, disease progression and severity of asbestosis was associated with increased risk of any cancer and lung cancer in the Finnish studies (Juntunen et al., 1997; Partanen et al., 1995a).

Malignant diseases were abundantly reported in autopsied cases with asbestosis in a Japanese study (Murai & Kitagawa, 2000). Altogether 61% of the

asbestosis cases had cancer, of which the most common types were lung cancer (33%), mesothelioma (14%) and stomach cancer (5.5%). Lymphomas and liver, prostatic, laryngeal, pancreas, rectal and other cancers were also reported (Murai & Kitagawa, 2000). The prevalence of mesothelioma, lung and laryngeal cancers in asbestosis patients was significantly higher compared to cases without asbestosis (Murai & Kitagawa, 2000).

Several Finnish studies investigating serum oncoproteins and cytokines in asbestosis patients were published in the 1990s. Serum tumour necrosis factor alpha (TNF-α) and epidermal growth factor receptor (EGFr) were increased in Finnish asbestosis patients who developed cancer (Partanen et al., 1994, 1995a), while transforming growth factor alpha (TGF-α), mutant p53 protein and the extracellular domain of the erbB-2 receptor did not significantly differ between patients with and without cancer (Hemminki et al., 1996; Partanen et al., 1995b).

In a study from Hong Kong 76% of the patients had some comorbidity at the time of diagnosis of asbestosis, when 16% suffered from malignant disease, mostly lung cancers and mesotheliomas (Chen et al., 2012). Another recent study on British asbestosis patients revealed that 73% had benign pleural disease, 1% had mesothelioma, and 1% had lung cancer at the time of asbestosis diagnosis (Walters et al., 2018).

The prevalence of neurological signs was observed to be high since 21% had peripheral, 14% central and 15% both peripheral and central nervous system disorders (Juntunen et al., 1997). The central nervous system disorders associated with the development of malignant disease (Juntunen et al., 1997). In another Finnish study, no association between nervous system disorders and lung function was found in asbestosis patients (Korhonen et al., 1983).

In a Brazilian study, 81% out of 63 patients with asbestosis had pleural plaques while 44% patients had emphysema in HRCT (Nogueira et al., 2011). PFTs did not significantly differ in subjects with or without pleural plaques or emphysema (Nogueira et al., 2011). Pleural abnormalities were also common in a Chinese study in which 97% of the patients with asbestosis had pleural abnormalities (Yang et al., 2018). In contrast, a Finnish study showed that 57% out of more than a hundred asbestosis patients had pleural thickening and 41% had pleural calcification in chest radiograph at the time of diagnosis of asbestosis, the values being 66% and 59% at the time of re-examination (Zitting et al., 1978). In addition, 14% had emphysema (Zitting et al., 1978). Pleural thickening was associated with lower VC and FEV1 in patients with mild asbestosis whereas pleural calcifications did not associate with PFTs (Zitting et al., 1978).

2.8.5 Prognosis

Asbestosis patients have been shown to have typically mild fibrosis in Finland (Vierikko et al., 2010). On the other hand, asbestosis is a progressive disease and progression is also seen in the decades following the end of the exposure (Cookson et al., 1986; Ehrlich et al., 1992). Disease may also remain stable (Nogueira et al., 2011; Suoranta et al., 1982). Asbestosis is generally thought to be a more slowly progressive disease with better prognosis than IPF, although rapid progression may also be seen occasionally (Cullinan & Reid, 2013; Guidotti et al., 2004). Recently, a definition of progressive pulmonary fibrosis (PPF) in patients with non-IPF ILD was published in which the diagnostic criteria require fulfilment of at least two out of three of the following criteria: worsening of respiratory symptoms and physiological and radiological evidence of disease progression (Raghu et al., 2022). More than 20% of patients with asbestosis have been shown to exhibit a progressive disease (Barnikel et al., 2019).

Asbestosis patients may suffer from AE like patients with other types of pulmonary fibroses (Churg et al., 2011; Yamamoto, 1997). The diagnostic criteria for AE of IPF were published in 2007 and updated in 2016 (Collard et al., 2007, 2016). Salonen et al. (2020b) reported that asbestosis and IPF patients had equally poor survival after hospitalisation due to AE while the survival was shorter compared to other ILD types. Non-IPF ILD patients, including asbestosis patients, had worse survival after AE if they had long-term oxygen therapy before hospitalisation, usual interstitial pneumonia (UIP) pattern in HRCT, or were over 80 years old (Salonen et al., 2020b). Salonen et al. (2020c) studied non-elective hospitalisations of ILD patients, including 22 asbestosis patients, caused by acute respiratory symptoms. They observed that the cause of hospitalisation was associated with prognosis since AE associated with shorter survival than lower respiratory tract infection. On the contrary, hospitalisation due to AE was related to better survival compared to hospitalisation due to cardiovascular or multiple reasons in non-IPF ILD patients (Salonen et al., 2020c).

Previous studies reporting factors associated with survival or disease progression in asbestosis patients have been scarce and published mainly before the year 2000 (Table 3). Cookson et al. (1986) reported that cumulative asbestos exposure was associated with progression of pulmonary fibrosis. In Finnish studies, more severe ILO category at baseline was associated with progression of asbestosis (Oksa et al., 1998; Suoranta et al., 1982). In addition, certain laboratory tests such as higher angiotensin-converting enzyme (ACE), carcinoembryonic antigen (CEA),

complement 3 (C3), erythrocyte sedimentation rate (ESR), fibronectin and immunoglobulin G antinuclear antibody (IgG-ANA) were associated with disease progression, although the authors reported that differences in ACE, ESR and fibronectin values between the patients with and without progression were too small for clinical use (Huuskonen et al., 1984; Järvisalo et al., 1984; Oksa et al., 1998). Suoranta et al. (1982) observed that patients with disease progression were younger and more often smokers while Partanen et al. (1995a) noticed that development of cancer or lung cancer associated with progression of pulmonary fibrosis.

Table 3. Previous studies on factors associated with survival or disease progression of asbestosis.

Reference	Number of study subjects (country)	Factors associated with shorter survival	Factors associated with disease progression
Cookson et al., 1985	354 (Australia)	Baseline ILO category, time since and age at starting the work with asbestos	
Cookson et al., 1986	136 (Australia)		Cumulative exposure
Coutts et al., 1987	167 (Great Britain)	Finger clubbing	Finger clubbing
Huuskonen, 1978	165 (Finland)	Smoking	
Huuskonen et al., 1984	115 (Finland)		C3 and IgG-ANA
Järvisalo et al., 1984	90 (Finland)		CEA
Oksa et al., 1998	85 (Finland)		Baseline ILO category
Partanen et al., 1995a	111 (Finland)		Development of cancer and lung cancer
Suoranta et al., 1982	85 (Finland)		Baseline ILO category

C3 = complement 3, CEA = carcinoembryonic antigen, IgG-ANA = immunoglobulin G antinuclear antibody, ILO = International Labour Organization classification

Little has been known about the factors associated with survival in patients with asbestosis (Guidotti et al., 2004). As far as we are aware, no previous study has reported median survival time in a whole cohort of asbestosis patients. In an Australian study from the 1980s, the severity of radiographic findings in chest x-ray (ILO category), time since starting work with asbestos, and age at starting work with asbestos were associated with all-cause mortality in asbestosis patients (Cookson et al., 1985). The severity of radiographic changes (ILO category) associated with mortality from asbestosis while time since starting the work and age at starting the work associated with mortality from lung cancer. The survival

time since asbestosis compensation claim was longer in lower ILO categories, i.e., 17 years in ILO 1, 12 years in ILO 2, and three years in ILO 3 (Cookson et al., 1985). In a Finnish study, the survival time of non-smokers and ex-smokers was long (23.8 years) while smoking associated with shorter survival (10.6 years) (Huuskonen, 1978) It is worthy of note that the Finnish study also included several patients who were under fifty years old at the time of diagnosis of asbestosis (Huuskonen, 1978). Coutts et al. (1987) reported that finger clubbing was associated with both shorter survival and progression of pulmonary fibrosis.

In an Italian study investigating hospitalisations of asbestosis patients between 2001–2015, 56.8% of the hospitalisations were elective while 42.7% were non-elective (a total of 17,220 hospitalisations) (Ferrante, 2019) In the abovementioned study, the patients stayed on average 8.6 days in hospital and the most common causes for hospitalisation were respiratory disorders (62.8%), and 5.7% of the patients died (Ferrante, 2019). In the study of Salonen et al. (2020c), median time since diagnosis to non-elective hospitalisation due to respiratory reasons was 5.9 years, while survival time after hospitalisation was 1.9 years in non-IPF ILD patients, including asbestosis patients. 45% of the non-elective hospitalisations of asbestosis patients were due to AE, and AE was the most common cause of hospitalisation in non-IPF-ILD patients, followed by lower respiratory tract infection and other ILD-related reasons (Salonen et al., 2020c).

BAL samples are not routinely used for the assessment of prognosis in ILD patients (Meyer et al., 2012). To the best of our knowledge, there are no previous studies of association of BAL cell profile with prognosis in asbestos patients. However, previous studies have investigated BAL cell profile in relation to prognosis in other ILDs, where low lymphocyte, high macrophage, high neutrophil and high eosinophil differential counts have been found to be related to shorter survival (Boomars et al., 1995; Kakugawa et al., 2016; Kinder et al., 2008; Macaluso et al., 2022; Ryu et al., 2007; Thomeer et al., 2004). Salonen et al. (2020a) discovered BAL basophils to associate with both shorter survival time and earlier occurrence of AE in ILD patients, also including asbestosis cases.

The relation of baseline PFTs to survival has been investigated in ILDs but to our knowledge, there are no previous studies in English literature on this topic in asbestosis (Jacob et al., 2017a, 2017b; Kärkkäinen et al., 2019; Nurmi et al., 2017). Risk assessment models such as CPI and GAP, determined on the basis of lung function results, were created for IPF patients to estimate the prognosis (Ley et al., 2012; Wells et al., 2003). CPI and GAP have also been studied in other ILDs (Jacob et al., 2017a, 2017b; Nurmi et al., 2017; Ryerson et al., 2014, 2015). Salonen et al.

(2020c) observed that GAP stage associated with both mortality and risk of AE in an ILD cohort including 22 asbestosis patients. To our knowledge, GAP or CPI has not previously been studied in cohorts with only patients with asbestosis. Table 4 displays the calculation for GAP stage. CPI is calculated with the formula described by Wells et al. (2003): CPI = 91.0 – (0.65 × DLCO percent predicted) – (0.53 × FVC percent predicted) + (0.34 × FEV1 percent predicted).

Table 4. Calculation of GAP points (modified from Ley et al., 2012).

Variable	Classification	Points
Gender	Female	0
	Male	1
Age (years)	At most 60	0
	61 to 65	1
	More than 65	2
Physiology		
FVC percent predicted	More than 75	0
	50 to 75	1
	Less than 50	2
DLCO percent predicted	More than 55	0
	36 to 55	1
	At most 35	2
	Cannot perform	3
GAP		
Stage I		0 to 3
Stage II		4 to 5
Stage III		6 to 8

DLCO = diffusion capacity for carbon monoxide, FVC = forced vital capacity, GAP = gender, age and physiologic variables

2.8.6 Causes of death

Previous studies have observed high overall, all cancer, lung cancer, mesothelioma and respiratory disease mortality in patients with asbestosis (Berry, 1981; Chen et al., 2012; Cookson et al., 1985; Finkelstein et al., 1981; Germani et al., 1999; Huuskonen, 1978; Oksa et al., 1997; Szeszenia-Dąbrowska et al., 2002; Zhong et al., 2008). Chen et al. (2012) also revealed increased mortality from heart diseases and myocardial infarction, although the results were not statistically significant when smoking was taken into account, whereas statistically significantly elevated overall any cancer and lung cancer mortality was observed in both smoking

adjusted and unadjusted analysis. They also observed that duration of asbestos exposure associated with increased overall mortality and several specific mortalities such as asbestosis, any cancer, mesothelioma, lung cancer and pneumonia (Chen et al., 2012). Increased risk of death due to pneumonia was observed in a study on Finnish asbestosis patients (Vehmas et al., 2012). By way of exception, Germani et al. (1999) studied female asbestosis patients and they also found increased mortality for several other malignancies such as ovarian, uterine, colon and sigmoid and peritoneal and retroperitoneal cancer.

Table 5. Previous studies reporting causes of death in patients with asbestosis.

Reference	Number of study subjects (country)	The most common causes of death
Berry, 1981	295 (Great Britain)	Lung cancer (38%)
Chen et al., 2012	86 (Hong Kong)	Asbestosis (24%)
		Mesothelioma (20%)
		Lung cancer (16%)
Cookson et al., 1985	118 (Australia)	Pneumoconiosis (24%)
		Respiratory neoplasm (22%)
		Heart disease (19%)
Finkelstein et al., 1981	61 (Canada)	Non-malignant respiratory disease (36%)
		Lung cancer (15%)
		Mesothelioma (15%)
Harding & Darnton, 2010	477 (Great Britain)	Lung cancer (36%)
		Asbestosis (24%)
		Circulatory system disease (7,5%)
Huuskonen, 1978	62 (Finland)	Asbestosis (42%)
		Lung cancer (32%)
Szeszenia-Dabrowska et al., 2002	276 men, 117 women (Poland)	Circulatory system disease (39% and 39%)[1]
		Malignant neoplasm (33% and 29%)[1]
		Respiratory disease (15% and 17%)[1]

[1]Percentage of men and women

Previous studies have observed that the most common causes of death in asbestosis patients were lung cancer and asbestosis (Table 5) (Berry, 1981; Chen et al., 2012; Cookson et al., 1985; Harding & Darnton, 2010; Huuskonen, 1978). Circulatory system diseases, followed by malignant diseases, were the most common cause of

death in Polish asbestosis patients (Szeszenia-Dąbrowska et al., 2002). Cardiovascular diseases were also relatively common causes of death in asbestosis patients in other studies (Cookson et al., 1985; Harding & Darnton, 2010).

2.9 Treatment

There is currently no curative pharmacological therapy for asbestosis, nor is there any efficient treatment to prevent the development of asbestosis after exposure (Bennett & Brims, 2020; Guidotti et al., 2004). Antifibrotic drugs have been shown to slow down the disease progression in IPF (King et al., 2014; Richeldi et al., 2014). Recent studies, including some subjects with asbestosis, have observed that these drugs may also be effective in other pulmonary fibroses in addition to IPF (Behr et al., 2021; Bennett & Brims, 2020; Flaherty et al., 2019). A recent international guideline gave a conditional recommendation of the use of nintedanib in the treatment of PPF whereas more research of the use of pirfenidone in PPF is needed (Raghu et al., 2022). In February 2022, Kela reimbursement for nintedanib for treatment of PPF in Finland began, enabling the use of nintedanib also with asbestosis cases when the criteria of PPF are met (The Social Insurance Institution of Finland (Kela), n.d.). A recently published study on pirfenidone treatment included 9 patients with asbestosis with progressively decreasing lung function (Miedema et al., 2022). A clinical trial on nintedanib treatment for asbestosis and other pneumoconiosis is registered (*The Nintedanib in Progressive Pneumoconiosis Study (NiPPS): A Collaborative NSW Treatment Trial*, 2019).

Pneumococcal and influenza vaccinations are recommended for asbestosis patients (Wolff et al., 2015). Treatment also includes cessation of smoking and treatment of comorbidities (Bennett & Brims, 2020).

In a randomised controlled trial in 142 ILD patients, including 22 asbestosis patients, exercise training was observed to be effective in improving health-related quality of life and six-minute walk distance (Dowman et al., 2017) The greatest benefit of exercise training was observed in asbestosis patients (Dowman et al., 2017). Ochmann et al. (2012) studied pulmonary rehabilitation in 263 subjects with occupational respiratory disease, including 66 patients with asbestosis. After the rehabilitation period, maximum exercise capacity and muscle strength were improved and anxiety was diminished (Ochmann et al., 2012).

Corticosteroids and antibiotics have been commonly used in the treatment of AE of IPF (Kreuter et al., 2020). Salonen et al. (2020b) reported medications during AE of ILD where corticosteroids and antibiotics were used both for non-IPF ILD,

also including asbestosis, and IPF patients. In addition, antimycotics, antiviral treatment and cyclophosphamide were used in some cases (Salonen et al., 2020b).

Lung transplantation may be considered in some patients. Today, the most common indication for lung transplantation is ILD both in Finland and worldwide (Halme, 2017). In a study from the United States, 29 lung transplantations on patients with asbestosis were conducted between 1991–2018, most of which were unilateral (66%) (Blackley et al., 2020). The asbestosis patients who had undergone lung transplantation were older (62 years) compared to other pneumoconiosis and their mean FVC and FEV1 were about 51%. Survival time after lung transplantation of asbestosis patients was similar to IPF; one-year survival was 82% and three-year survival 65%, with a median survival of 8.2 years (Blackley et al., 2020). In a recent study on lung transplantations of IPF and work-related lung diseases including three asbestosis patients, PFTs or survival after lung transplantation did not significantly differ in IPF and work-related lung disease patients (Ju et al., 2023). In Finland, the ten-year survival rate after lung transplantation with the indication of ILD or other reason is more than 50% (Halme, 2017).

3 Aims of the study

The principal aim of the research was to investigate asbestosis from the perspective of ILDs using similar methods as have been used in other ILDs. Our objective was to reveal clinical features as well as potential prognostic factors in patients with asbestosis.

The more specific aims were:

1. to clarify the BAL cell profile in asbestosis patients taking into account smoking history (I)
2. to study lung function at the time of asbestosis diagnosis (II)
3. to find out the most common comorbid diseases and causes of death including immediate causes of death (III)
4. to study prognosis of asbestosis and potential prognostic factors which have been previously observed to be useful in the evaluation of prognosis of other ILDs, such as BAL cell profile (I), PFTs, risk predicting models (GAP and CPI) (II) and comorbidities (III)

4 Methods

4.1 Study population

The study cohort included patients with asbestosis treated in the Respiratory Medicine Clinic of the Oulu University Hospital. The study population was searched retrospectively from the database of the hospital by utilising the International Classification of Diseases (ICD) 10th edition code J61 for asbestosis. The period from 1996 to 2015 was selected as the time period, since the use of ICD-10 began officially in Finland in the year 1996 (Finnish Institute for Health and Welfare, 2011). The Helsinki criteria have been used in the diagnostics for asbestosis in Finland (Tossavainen, 1997; Wolff et al., 2015). The correctness of asbestosis diagnoses was re-evaluated based on patients' medical records and radiological reports. The exposure history was reported either as fibre years, when the patients were estimated to have at least moderate (10–24 fibre years) asbestos exposure, or as a description of the work history, often combined with a BAL finding, in which case the clinicians had concluded that the exposure was sufficient for the diagnosis of asbestosis. In addition, all the included study subjects were evaluated to have radiologically confirmed pulmonary fibrosis consistent with asbestosis. The patients who did not meet the diagnostic criteria for asbestosis were excluded from the study. In Oulu University Hospital, most patients with suspected ILD are discussed in a multidisciplinary meeting; furthermore, those with probable occupational exposure, such as asbestos exposure, are also discussed in an occupational multidisciplinary meeting. The studies included about 100 patients with asbestosis: 91 patients in study I, 100 patients in study II, and 116 patients in study III. Study I consisted of patients from whom a BAL sample was gathered during bronchoscopy. Study II included patients on whom information was available about the first hospital visit and PFT results were available at the time of asbestosis diagnosis.

4.2 Data collection

Data was gathered from the patients' medical records and death certificates. Electronic medical records have been utilised in Oulu University Hospital for more than 20 years. Data was also collected from card files if the information could not be found from the electronic medical records. The information collected included

dates of birth, initial hospital visit, asbestosis diagnosis, death or latest hospital visit, as well as gender, occupation, smoking status, BAL results, PFTs, comorbid diseases and causes of death. Patients were divided into three smoking groups: current smokers, ex-smokers, and non-smokers. If the smoking history was minor, i.e., three pack-years at most, the patient was classified as a non-smoker. Survival time was the interval from the baseline to death or the latest hospital visit. Baseline date was the date of BAL in study I, the date of spirometry in study II, and the date of diagnosis in study III. Survival data was updated until August 2017 in study I, June 2018 in study II, and January 2022 in study III.

Both patient medical record reports and diagnostic codes were checked, when collecting comorbidities from the hospital medical record system and death certificates. Presence of pleural plaques and emphysema was reviewed from radiological reports. Basal cell carcinomas of the skin were not included when analysing cancers due to their prevalence and relatively good prognosis.

4.3 Bronchoalveolar lavage procedure and data

The BAL procedure has been performed as part of systematic practice for several decades in Oulu University Hospital. In most cases, the BAL sample was collected from the right middle lobe (n = 76) and a total of 200 ml 37°C sterile saline in portions of 20 ml was instilled into the lung segment and aspirated manually. The volume of the recovered sample was on average 123 ml. The BAL samples were prepared in the pathology department and stained with Papanicolaou (PAPA) and May-Grünwald-Giemsa (MGG) stainings. The number of ABs was counted from Berlin blue staining. BAL data was collected from pathologist reports. If a patient had undergone more than one BAL examination, the one closest to the time of asbestosis diagnosis was selected.

BAL results were reported in the whole cohort as well as by smoking status. BAL cell differential count was reported as percentages, since the results are reported as percentages in pathologist reports in the Oulu University Hospital and most of the previous studies have applied percentages as well. In division to groups, we utilised the reference values of BAL cell differential counts as cut-off values: macrophages at least 80%, lymphocytes at most 15%, neutrophils at most 3%, and eosinophils at most 1% (Meyer et al., 2012). We did not analyse survival based on PAPA eosinophils because only two subjects had PAPA eosinophils. 2AB/ml was chosen as cut-off value for BAL ABs to obtain groups of approximately equal size.

4.4 Pulmonary function tests

PFT results were collected closest to the first hospital visit at the time of asbestosis diagnosis. The collected spirometry results included FVC, FEV1 and FEV1/FVC. Both haemoglobin-corrected DLCO and DLCO per unit of lung volume (DLCO/VA) were collected. Finnish reference values from 1982 were used in the evaluation (Viljanen et al., 1982a, 1982b).

4.5 Gender, age and physiologic variables and composite physiologic index

GAP score was calculated according to the Ley et al. (2012) scoring based on gender, age, FVC and DLCO (Table 4). The formula of Wells et al. (2003) for CPI calculation was used: CPI=91.0– (0.65 × DLCO percent predicted) – (0.53 × FVC percent predicted) + (0.34 × FEV1 percent predicted). Cut-off value CPI score 41 was chosen in our analyses based on a previous study in IPF (Mura et al., 2012).

4.6 Ethics

The Regional Ethics Committee of the Northern Ostrobothnia Hospital District approved the study protocol. Statistics Finland gave permission for the use of death certificates. Consent for participation or publication was not collected from the participants because in accordance with Finnish legislation, consent was not required due to the register-based nature of the project.

4.7 Statistics

We performed analyses with IBM SPSS statistics. Results are presented as means, median values or number of patients when appropriate. Chi square tests were used in the comparison of categorical variables. Comparison of means was performed with independent sample t-test or analysis of variance, while comparison of skewed distributions was performed with Mann-Whitney U test or Kruskal-Wallis test. Survival was estimated with Kaplan-Meier survival curves while statistical significance was analysed with log-rank test. Cox regression analysis was used to perform multivariate analyses. A p-value less than 0.05 was interpreted as a statistically significant result.

5 Results

5.1 Patient characteristics (Studies I, II and III)

The study consisted of 91 patients with asbestosis in Study I, 100 patients in Study II, and 116 patients in Study III. Patients were on average 68 years old at the time of asbestosis diagnosis. The diagnoses of asbestosis were set between the years 1981 and 2015, being most common between 1996 and 2010 (n = 79, 68%) (Figure 2). There were only five female patients in the study. Most of the patients had a history of smoking (n = 86, 74%), although many of them (n = 66) had stopped smoking before the asbestosis diagnosis. Construction worker (22%), plumber or pipe fitter (16%), carpenter (7.8%) and car mechanic (6.9%) were the most common occupations. Other common occupations included electrician (5.2%), house painter (5.2%), mechanical engineer or machinist (4.3%), and property manager or caretaker (4.3%).

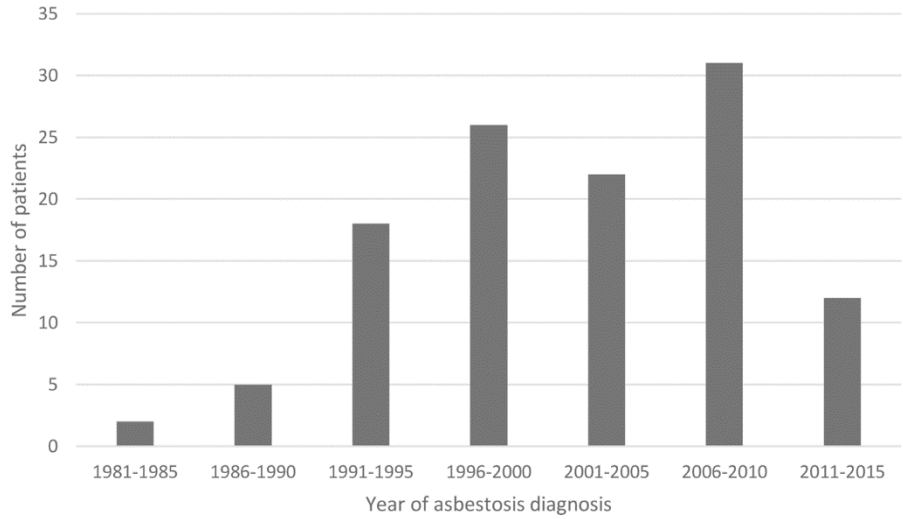

Fig. 2. Year of asbestosis diagnosis

5.2 Bronchoalveolar lavage (Study I)

Detailed information of BAL variables is presented in Table 6. Mean BAL total cell count was 226x10^6/l. Asbestosis patients exhibited a neutrophilic cell pattern in MGG and PAPA staining. Higher total cell count, macrophage differential count and lower lymphocyte differential count was observed in smokers compared to non-smokers and ex-smokers. BAL of non-smoking asbestosis patients showed lymphocytosis.

Table 6. Bronchoalveolar lavage fluid variables in patients with asbestosis. Modified from Paper I.

Variable	All N=91 mean±SD	Non-smokers N=23 mean±SD	Ex-smokers N=55 mean±SD	Smokers N=13 mean±SD	p-value
AB/ml[1]	1.9	1.7	1.4	4.3	NS
Total cell count (x10^6/L)	226±165	180±64	204±153	402±228	0.007
MGG					
Macrophages%	74.3±18.1	67.8±18.7	73.8±18.2	88.0±6.0	<0.001
Lymphocytes%	16.6±15.6	24.8±19.6	15.9±13.7	5.3±2.6	<0.001
Neutrophils%	6.5±11.4	5.3±6.1	7.9±13.9	2.9±2.3	NS
Eosinophils%	2.4±2.8	2.0±2.1	2.3±2.8	3.7±3.9	NS
PAPA					
Macrophages%	72.5±18.0	66.2±17.9	71.3±17.9	88.5±6.0	<0.001
Lymphocytes%	19.1±15.2	27.9±17.8	18.5±13.3	6.0±3.2	<0.001
Neutrophils%	8.4±11.6	5.8±6.4	10.1±14.0	5.5±4.9	NS
Eosinophils%	0.0±0.2	0.0±0.2	0.0±0.3	0.0±0.0	NS

[1]Data is presented as median values. ABs was measured in 89 patients. Means are compared with analysis of variance and ABs with Kruskal Wallis test. AB = asbestos body, MGG = May-Grünwald-Giemsa, NS = non-significant, PAPA = Papanicolaou

The number of ABs varied from 0 to 1,850 AB/ml. The median number of ABs was 1.9/ml. A similar trend as in smoking was seen with ABs in relation to the BAL cell profile, since more than 2AB/ml was related to a higher total cell count (282x10^6/l vs 175x10^6/l; p = 0.002), higher macrophage (MGG 79.1% vs 69.9%; p = 0.016 and PAPA 77.8% vs 67.6%; p = 0.007) and lower lymphocyte (MGG 13.1% vs 19.8%; p = 0.041 and PAPA 14.7% vs 23.1%; p = 0.007) differential counts. There was no significant difference in smoking status between patients with more than 2 AB/ml and at most 2 AB/ml.

5.3 Pulmonary function tests (Study II)

PFT results are presented in Table 7. Mean spirometry values, FVC and FEV1, were near the lower limit of the reference values, i.e., FVC 81% and FEV1 78%. Restrictive spirometry was a common finding. A few patients had obstruction, mostly observed in ever-smokers. Decreased DLCO was observed (mean 65%), while smokers had more decreased DLCO ($p = 0.007$) and DLCO/VA results ($p = 0.043$) (Table 7). FVC, FEV1 or FEV1/FVC did not differ significantly between smoking groups.

Table 7. Pulmonary function results in patients with asbestosis. Modified from Paper II.

Variable	All N=100 N (%) or mean±SD	Non-smokers N=29 N (%) or mean±SD	Ex-smokers N=54 N (%) or mean±SD	Smokers N=17 N (%) or mean±SD
FVC and FEV1/FVC normal[1]	41 (42.3)	11 (40.7)	26 (49.1)	4 (23.5)
Restrictive[1]	35 (36.1)	12 (44.4)	13 (24.5)	10 (58.8)
Obstructive[1]	9 (9.3)	1 (3.7)	7 (13.2)	1 (5.9)
Combined[1]	12 (12.4)	3 (11.1)	7 (13.2)	2 (11.8)
FVC	81.2±16.8	80.4±14.7	84.0±18.1	73.7±13.6
FEV1	77.9±17.0	79.4±16.2	79.2±18.5	71.2±11.5
FEV1/FVC[1]	96.2±11.7	97.8±9.0	94.9±12.8	97.7±11.8
DLCO	65.0±18.9	68.3±17.0	67.2±18.6	52.1±18.5
DLCO/VA[2]	79.4±19.4	84.0±17.0	80.2±19.7	69.4±19.4
CPI	32.2±15.2	30.9±13.4	29.7±15.1	42.3±15.0

Spirometry and diffusion capacity results are reported as percentage of the reference value. [1]Data is missing for two non-smokers and one ex-smoker. [2]Data is missing for one non-smoker. FVC normal = ≥ 80%, FEV1/FVC normal = ≥88%, restrictive = FVC < 80% and FEV1/FVC ≥ 88%, obstructive = FVC ≥ 80% and FEV1/FVC < 88%, combined = FVC < 80% and FEV1/FVC < 88%. CPI = composite physiologic index, DLCO = diffusion capacity for carbon monoxide, DLCO/VA = diffusion capacity for carbon monoxide per unit of volume, FEV1 = forced expiratory volume in one second, FVC = forced vital capacity

5.4 Comorbidities (Study III)

Pleural plaques were observed in nearly every patient (96%). The next most common comorbidities were coronary artery disease (67%) and chronic obstructive pulmonary disease (COPD) (54%). Other cardiovascular diseases were also common, since the prevalence of arteriosclerosis obliterans (ASO), atrial fibrillation, diabetes, heart failure, hypertension and stroke or transient ischemic

attack (TIA) was between 20% to 50%. 23% of the patients had asthma and 8.6% had rheumatoid arthritis. Malignant diseases were common (n = 42, 36%) and of these, lung cancer (n = 18, 16%) and prostate cancer (n = 9, 7.8%) were the most frequent. One patient had mesothelioma and two patients had colorectal cancer. The prevalence of coronary artery disease, any cancer or lung cancer did not differ significantly between non-smokers and ever-smokers.

5.5 Prognostic factors (Studies I, II and III)

5.5.1 Bronchoalveolar lavage (Study I)

Median estimated survival was 132 months in Study I. Several BAL variables were significant prognostic factors since a low percentage of BAL lymphocytes, a high percentage of BAL neutrophils and eosinophils and a high number of BAL ABs associated with shortened survival of the patients. Association of BAL results with survival is presented in more detail in figures 3, 4 and 5. There was no association between BAL macrophages with survival.

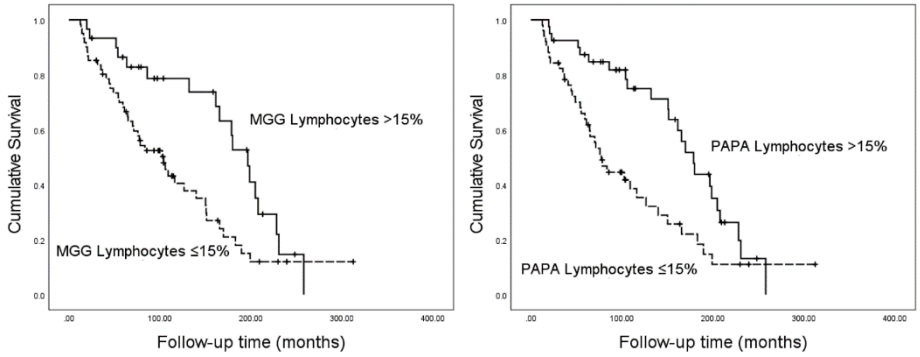

Fig. 3. Bronchoalveolar lavage fluid lymphocytosis associated with longer survival (MGG 196 vs 104 months; p = 0.012 and PAPA 179 vs 77 months; p = 0.005). MGG lymphocytes > 15% n = 30, ≤ 15% n = 61; PAPA lymphocytes > 15% n = 40, ≤ 15% n = 51. Modified from Paper I. MGG = May-Grünwald-Giemsa, PAPA = Papanicolaou

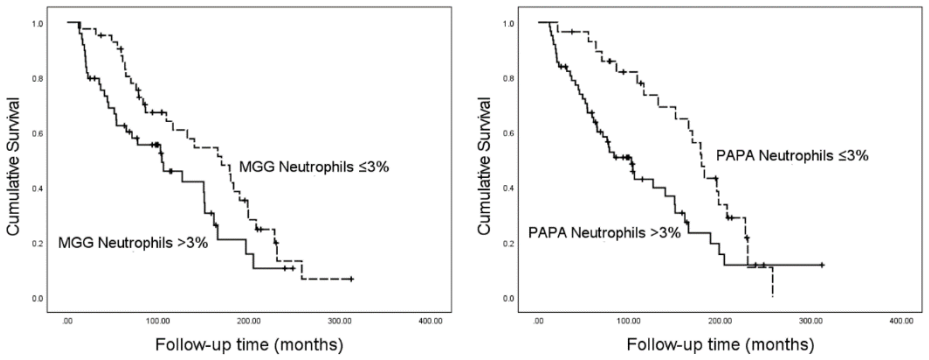

Fig. 4. Increased percentage of bronchoalveolar lavage fluid neutrophils associated with shorter survival (MGG 104 vs 170 months p = 0.038; PAPA 102 vs 180 months, p = 0.016). MGG neutrophils > 3% n = 49, ≤ 3% n = 42; PAPA neutrophils > 3% n = 62, ≤ 3% n = 29. Modified from Paper I. MGG = May-Grünwald-Giemsa, PAPA = Papanicolaou

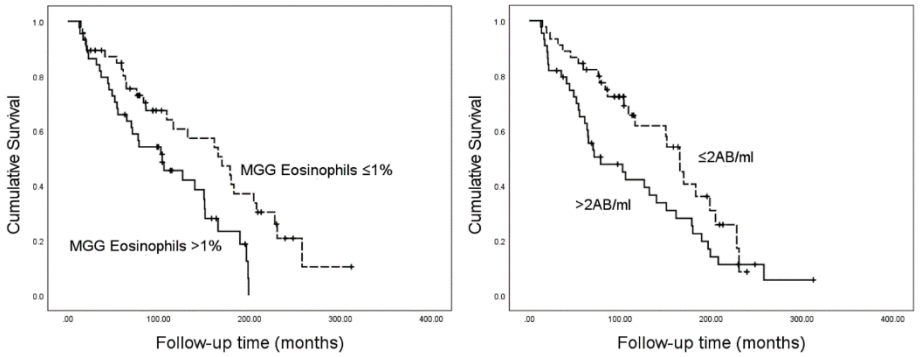

Fig. 5. Increased percentage of bronchoalveolar lavage fluid eosinophils and high number of ABs associated with shorter survival. The median estimated survival in patients with eosinophils > 1% (n = 44) 104 months vs ≤ 1% (n = 47) 170 months, p = 0.007. The median estimated survival in patients with > 2AB/ml (n = 44) 78 months vs ≤ 2AB/ml (n = 45) 165 months, p = 0.042. Modified from Paper I. AB = asbestos body, MGG = May-Grünwald-Giemsa

5.5.2 Pulmonary function tests, gender, age and physiologic variables and composite physiologic index (Study II)

Median survival of Study II subjects was 124 months. Most of the patients belonged to GAP stage I at baseline. No significant difference in smoking status was

observed between the three GAP stages. The observed cumulative mortality in different GAP stages is presented in Table 8. Furthermore, Figure 6 demonstrates survival differences between GAP stages and CPI groups.

Table 8. Observed cumulative mortality in different GAP stages. Modified from Paper II.

Mortality	GAP I (N=71)	GAP II (N=24)	GAP III (N=5)
	N (%)	N (%)	N (%)
1 year	0 (0.0)	1 (4.2)	0 (0.0)
2 years	3 (4.2)	6 (25)	3 (60)
3 years	3 (4.2)	8 (33)	3 (60)
5 years	7 (10)	14 (58)	4 (80)
10 years	23 (39)	18 (86)	5 (100)

Twelve GAP I and three GAP II patients were alive with follow-up time less than ten years, including one GAP I patients with follow-up time less than five years. GAP = gender, age and physiologic variables

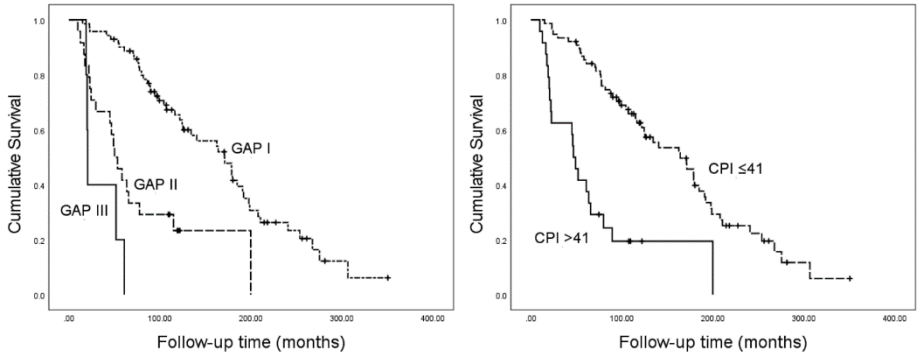

Fig. 6. Both risk predicting models, GAP and CPI, associated with survival in patients with asbestosis (p < 0.001). The median estimated survival of GAP stages I (n = 71), II (n = 24) and III (n = 5) were 171, 50 and 21 months, respectively, and survival of CPI ≤ 41 (n = 76) and > 41 (n = 24) was 164 and 47 months, respectively. Modified from Paper II. CPI = composite physiologic index, GAP = gender, age and physiologic variables

Decreased DLCO and risk-predicting models GAP and CPI were associated with mortality (Table 9). GAP stage II patients had 3.6 times higher and GAP stage III patients had 12.7 times higher mortality risk compared to GAP stage I patients.

Table 9. Univariate analysis of pulmonary function tests and risk predicting models as mortality predictors in asbestosis patients. Modified from Paper II.

Factor	HR (95% CI)	p-value
Age at spirometry	1.08 (1.05–1.12)	<0.001
Smoking		
Non-smoker	Reference group	
Ex-smoker	1.12 (0.65–1.95)	NS
Smoker	1.27 (0.63–2.54)	NS
FVC percent predicted	0.99 (0.97–1.00)	NS
FEV1 percent predicted	0.99 (0.98–1.01)	NS
DLCO percent predicted	0.95 (0.94–0.97)	<0.001
GAP		
Stage I	Reference group	
Stage II	3.58 (2.03–6.34)	<0.001
Stage III	12.69 (4.55–35.43)	<0.001
CPI	1.05 (1.03–1.07)	<0.001

CI = confidence interval, CPI = composite physiologic index, DLCO = diffusion capacity for carbon monoxide, FEV1 = forced expiratory volume in one second, FVC = forced vital capacity, GAP = gender, age and physiologic variables, HR = hazard ratio, NS = non-significant

5.5.3 Comorbidities (Study III)

Univariate analyses did not reveal any significant association between comorbidities and mortality. Instead, in age-adjusted analyses, coronary artery disease was significantly associated with mortality (HR 1.94; 95% CI 1.22 to 3.07; p = 0.005) and hypertension was related to better survival (HR 0.56; 95% CI 0.36 to 0.86; p = 0.008). Lung cancer was related to shorter survival (HR 1.73; 95% CI 1.02 to 2.93; p = 0.042) in multivariate analyses including lung cancer, coronary artery disease, hypertension, age at diagnosis and smoking. Other common comorbidities did not associate with mortality.

5.6 Underlying and immediate causes of death (Study III)

The most common underlying causes of death in patients with asbestosis in order of prevalence were asbestosis or lung fibrosis (36%), coronary artery disease (24%), lung cancer (10%), and other malignant diseases (8%). The most common immediate cause of death was pneumonia (38%) followed by coronary artery disease or myocardial infarction (18%), asbestosis or lung fibrosis (11%), and

malignant diseases (9%), including lung cancer (n = 4). Acute exacerbation of asbestosis was reported as immediate cause of death in two cases.

5.7 Survival after diagnosis of asbestosis (Study III)

The estimated median survival after diagnosis of asbestosis was 125 months. The following results of this study material are previously unpublished. Figure 7 presents the number of deceased patients during the follow-up after diagnosis of asbestosis. Five-year mortality rate was 19%, ten-year morality rate was 48%, while twenty-year mortality rate was 86% in asbestosis patients. Mean age at the time of death was 78.8 years. Patients with survival time less than five years (n = 22, 19%) after diagnosis of asbestosis were on average older (74.0 years vs 66.5 years; $p < 0.001$) and had lower FVC (67.9% vs 83.4%; $p < 0.001$) and DLCO (46.7% vs 68.6%; $p < 0.001$) compared to patients with survival time more than five years. The most common underlying causes of death in patients with survival time less than five years were similar to the whole cohort; that is, asbestosis or lung fibrosis (n = 10) and coronary artery disease (n = 7) were the most frequent underlying causes of death in these patients. In addition, two patients died of lung cancer and stroke and one of mesothelioma.

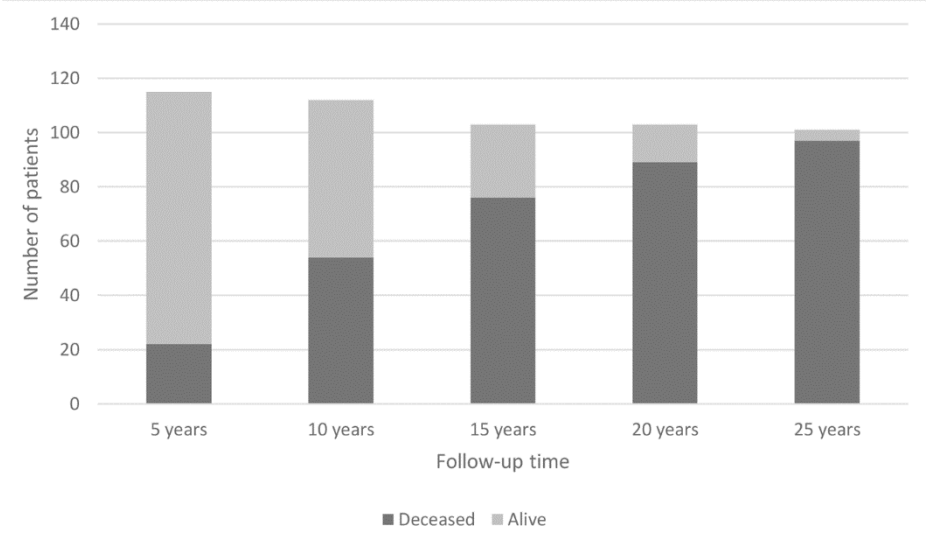

Fig. 7. The number of deceased patients during follow-up after diagnosis of asbestosis.

6 Discussion

Even though the number of new asbestosis cases has been decreasing in Finland (Koskela et al., 2022), the number of asbestosis cases has been increasing globally (Shi et al., 2020; Yang et al., 2020). Furthermore, due to the ongoing use of asbestos in certain countries and the long latency period of more than twenty years, it is not expected that asbestosis will disappear in the near future (Guidotti et al., 2004; Virta, 2006). Asbestosis has been little studied in the 21st century. In recent years, antifibrotic drugs have become available also for asbestosis patients with progressive disease and new drugs for pulmonary fibroses are being studied (*ClinicalTrials.Gov*, n.d.; The Social Insurance Institution of Finland (Kela), n.d.). However, these antifibrotic drugs are expensive and have adverse effects, making it important to identify patients who are likely to benefit from the medication (Flaherty et al., 2019; Miedema et al., 2022). Therefore, studies on factors influencing the prognosis of asbestosis patients are important and currently topical.

6.1 Study design and participants

We applied a retrospective real-life study design and gathered a relatively large number of asbestosis patients who were treated in the Oulu University Hospital between the years 1996 and 2015. We studied extensively the clinical features of asbestosis patients, also taking into consideration smoking history. Furthermore, we investigated factors associated with survival of the patients. Previously, little was known about the factors affecting the prognosis of patients with asbestos-induced pulmonary fibrosis and thus, many of our results are novel. Additionally, none of the previous studies have reported BAL findings in a cohort of asbestosis patients as large as ours and furthermore, none of the previous studies have reported comorbid diseases as comprehensively as we.

In our study, most of the patients were male (96%), as has also been the case in most of the previous studies, which is mostly explained by the fact that exposure to asbestos has been more common in occupations where most of the workers are men (Chen et al., 2012; Huuskonen, 1978; Walters et al., 2018). Instead, in previous Finnish studies with IPF and RA-ILD, there have been more female patients (Table 10). In our study, the patients were on average 68 years at the time of diagnosis of asbestosis, a finding that is similar to recent studies where the patients were 65 years (Yang et al., 2018) and 74 years (Walters et al., 2018). In the Finnish studies from the 1970s and 1990s, the patients were younger, on average 56 years at the

time of investigation (Huuskonen, 1978; Juntunen et al., 1997). Age at the time of diagnosis of pulmonary fibrosis was similar in Finnish studies on IPF and RA-ILD (Table 10). Most of our asbestosis patients had a history of smoking, similarly to many previous studies with patients with asbestosis (Bergantini et al., 2021; Chen et al., 2012; Huuskonen, 1978; Nogueira et al., 2011).

Table 10. Comparison of asbestosis patients to patients with IPF and RA-ILD (Study II, III, Kärkkäinen et al., 2017, 2018, 2019, Nurmi et al., 2016, 2017).

Variable	Asbestosis (n=116)	IPF (n=132)	RA-ILD (n=59)
Gender			
Female (N (%))	5 (4%)	35 (27%)	26 (44%)
Male (N (%))	111 (96%)	97 (73%)	33 (56%)
Age at diagnosis (mean)	68 years	70.5 years	66 years
FVC (mean)	81%	77%	85%
FEV1/FVC (mean)	96%	101%	98%
DLCO (mean)	65%	56%	71%
CPI (mean)	32	40	27
Survival after diagnosis of pulmonary fibrosis (median)	125 months	42 months	107 months
Age at death (mean)	79 years	75 years	75 years
The most common causes of death	Asbestosis (36%)	IPF (68%)	RA-ILD (39%)
	Coronary artery disease (24%)	Coronary artery disease (15%)	Coronary artery disease (21%)
	Lung cancer (10%)	Lung cancer (6%)	RA (15%)

PFTs are reported as percent of predicted value. Information of PFTs and causes of death are missing from a few patients. CPI = composite physiologic index, DLCO = diffusion capacity for carbon monoxide, FEV1 = forced expiratory volume in one second, FVC = forced vital capacity, IPF = idiopathic pulmonary fibrosis, PFTs = pulmonary function tests, RA = rheumatoid arthritis, RA-ILD = rheumatoid arthritis-associated interstitial lung disease

In a recent British study with asbestosis patients diagnosed in a comparable time period (2001 to 2015), the most common workplace or industry was construction (44%), similarly as in a report by the Finnish Institute of Occupational Health from 2014 (Koskela et al., 2017; Walters et al., 2018). The most common occupations in the British study were pipe fitter (13%), carpenter (11%), lagger (10%) and building labourer (6%) (Walters et al., 2018). In a study from Hong Kong with asbestosis patients diagnosed between 1985 to 2008, shipyard (44%), construction site (22%), manufacturing (11%) and mechanical (7%) were the most common occupations

(Chen et al., 2012). We observed that asbestosis patients in the Oulu area had worked in similar types of occupations, such as construction worker, pipe fitter and carpenter, as the asbestosis patients in Britain whereas shipyard work was more common in Hong Kong (Chen et al., 2012; Walters et al., 2018). However, the industry of the regions affects the results. The occupations observed in our study differed from those observed in a study with asbestosis patients diagnosed by the Finnish Institute of Occupational Health, published before the ban on the use of asbestos, where the most common occupations were insulation (41%), asbestos cement product factory (24%), asbestos quarry worker (22%) and asbestos sprayer (6%) (Government Decree on the Prohibition of Manufacture, Import, Trade and Use of Asbestos 3 §; Huuskonen, 1978).

6.2 Bronchoalveolar lavage cell profile

To our knowledge, our study is the largest one reporting BAL cell differential counts in asbestosis patients. Moreover, there have been only a few new publications on this topic during the 2000s (Table 2). Neutrophil differential count was increased in our study, similarly to the previous studies (Table 2). Eosinophil differential count in MGG was also increased, which is in line with the previous studies as well (Table 2). Previous studies reporting a high neutrophil and/or high eosinophil differential count often reported the lymphocyte differential count being under 10% while in almost all other previous studies the lymphocyte differential count was within the reference values (al Jarad et al., 1993; Bégin et al., 1986; Bergantini et al., 2021; Callahan et al., 1990; Cantin et al., 1989; Garcia et al., 1989; Gellert et al., 1985; Hayes et al., 1988; Kopiński et al., 2006; Lammi et al., 1999; Lenz et al., 1996; Robinson et al., 1987; Scharfman et al., 1989; Walters et al., 2013; Xaubet et al., 1986). The lymphocyte differential count was slightly above the reference value in our study when analysing all study subjects without taking into account smoking. Bergantini et al. (2021) reported a combination of macrophages over 74% and eosinophils over 0.5% to be useful in differentiating asbestosis patients from other ILDs; in our study, the MGG differential count for macrophages was 74% and for eosinophils, 2.4%.

To the best of our knowledge, no previous studies have reported BAL cell differential count taking into account the smoking histories of asbestosis patients in the analyses. We observed that smokers had higher total cell count and higher macrophage but lower lymphocyte differential counts. Results with a similar trend have previously been detected in smokers with asbestos exposure history and

without exposure history (Corhay et al., 1990; Cullen & Merrill, 1992; Frye et al., 2020; Heron et al., 2012; Karimi et al., 2012; Kokkinis et al., 2011). Bergantini et al. (2021) reported that in a group with various ILD patients, also including asbestosis patients, smokers exhibited higher macrophage and lower lymphocyte differential counts compared to former smokers and non-smokers. We observed that non-smoking asbestosis patients (n = 23) had a high percentage of lymphocytes (25%) in BAL, which is an interesting result. High percentage of BAL lymphocytes in asbestosis has also been reported in two previous studies (Costabel et al., 1987; Rom et al., 1987). It is notable that there were only seven asbestosis patients in a study of Costabel et al. (1987) with mean lymphocyte differential count 28%. In a study of Rom et al. (1987), there were six non-smokers and twelve patients who had quit smoking at least 5 years ago with mean lymphocyte differential count 21%, which supports the finding of lymphocytosis in non-smoking asbestosis patients observed in our study.

There have been only few previous studies which have reported an association between BAL ABs and cell profile. Interestingly, the number of ABs in BAL fluid associated with a similar type of BAL cell profile as in current smoking in our study. It is worthy of remark that in our study, there was no significant difference in smoking status between the groups based on BAL AB count, and therefore, the association of ABs is not explained by smoking. Kokkinis et al. (2011) reported BAL ABs to have the opposite effect on lymphocytes than in our study since the presence of ABs in BAL associated with increased lymphocytes. Corhay et al. (1990), on the contrary, observed that more than 10 AB/ml associated with increased neutrophil percentage compared to under 1 AB/ml. These previous studies have not, however, studied asbestosis patients, since Kokkinis et al. (2011) studied healthy asbestos-exposed subjects and Corhay et al. (1990) studied asbestos-exposed and possibly exposed patients, some of which suffered from COPD and a few from pleural plaques. Thus, the results of the studies of Kokkinis et al. (2011) and Corhay et al. (1990) are not completely comparable to those of ours.

6.3 Pulmonary function tests

We observed that DLCO (65%) and FVC (81%) were decreased, DLCO more clearly so, at the time of diagnosis. These results were expected based on the knowledge of previous studies showing that usually, DLCO decreased first while spirometry values decreased later as the disease progressed (Nogueira et al., 2011;

Yang et al., 2018). Previous studies reporting PFTs of asbestosis patients at the time of diagnosis have reported more or less coincident values, i.e., mean FVC 77% and DLCO 60% in Chinese asbestosis patients and mean FVC 84.5% and DLCO 52% in British asbestosis patients (Walters et al., 2013; Yang et al., 2018). In the Finnish studies on patients with other ILDs, IPF patients had lower PFTs (mean FVC 77% and DLCO 56%) and RA-ILD patients had higher PFTs (mean FVC 85% and DLCO 71%) at the time of diagnosis of ILD compared to our asbestosis patients (Table 10) (Kärkkäinen et al., 2017; Nurmi et al., 2017).

Restriction has been a typical spirometry finding in ILDs, including asbestosis (Algranti et al., 2001; Bégin et al., 1983; Miguel-Reyes et al., 2015) Many studies have not observed a significant association between asbestos exposure and FEV1/FVC ratio (Abejie et al., 2010; Alfonso et al., 2004; Ameille et al., 2010; Wang et al., 2006) and it was stated in the Helsinki criteria that asbestos does not cause a purely obstructive ventilatory pattern (Wolff et al., 2015). Yang et al. (2018), on the other hand, reported that the duration of asbestos exposure was in relation to FEV1/FVC ratio in asbestosis patients without smoking history. In our study, most of the asbestosis patients had either restrictive or normal spirometry results and nearly all of the few patients with obstructive spirometry had a history of smoking.

6.4 Comorbidities

The patients in our asbestosis cohort suffered from several comorbidities. Similarly, in previous studies with other ILDs, patients had many comorbid diseases (Jovanovic et al., 2022; Kreuter et al., 2016; Mena-Vázquez et al., 2023; Wälscher et al., 2020). Cardiovascular and respiratory comorbidities were common in asbestosis patients, as has also been observed in IPF, chronic hypersensitivity pneumonitis (CHP) and RA-ILD patients (Kärkkäinen et al., 2017; Nurmi et al., 2016; Raghu et al., 2015; Wälscher et al., 2020).

Interestingly, the prevalence of rheumatoid arthritis was as high as 8.6% in our study material, which was much higher than the prevalence of rheumatoid arthritis in general Finnish population (0.8%) (Aho et al., 1998). Furthermore, it is notable that the risk of getting rheumatoid arthritis is higher in females while most of our asbestosis patients (96%) were male (Crowson et al., 2011). On the other hand, smoking increases the risk of rheumatoid arthritis and smoking history was common in our patients (74%) (Padyukov et al., 2004). In addition, asbestos exposure has been shown to be related to a higher risk of rheumatoid arthritis based on the results of a previous Swedish study (Ilar et al., 2019).

The presence of obstructive pulmonary diseases was common in our asbestosis cohort. The prevalence of asthma was 23% (n = 27), which is higher than in general 60- to 69-year-old Finnish male population (6.7%) (Hisinger-Mölkänen et al., 2019). On the other hand, most of the asthma patients in our study had also COPD (n = 18). To our knowledge, there have been no previous studies about the prevalence of asthma in asbestosis patients, although in a Norwegian study, asbestos exposure was associated with higher incidence of asthma symptoms and asthma diagnosis (Eagan et al., 2002). COPD was also common (54%) in asbestosis patients in our study. It is, however, worthy of note that most of the asbestosis patients in our study had a history of smoking (74%). The prevalence of COPD has been variable (6–67%) in patients with IPF according to a previous systematic review (Raghu et al., 2015). In a Finnish study with IPF, the prevalence of COPD was much lower (7.6%) compared to our asbestosis cohort, although almost two-thirds of the patients with IPF had a history of smoking (Kärkkäinen et al., 2017).

Previous studies investigating comorbidities have reported asbestosis patients to be at increased risk of getting cancer, especially lung cancer or mesothelioma (Karjalainen et al., 1999; Oksa et al., 1997; Reid et al., 2005). In line with the previous results, malignant diseases were common in our study on asbestosis patients since 36% of the patients had at least one malignant disease. The results of our study were also in line with those of a previous Finnish study, where 41% of the asbestosis patients had cancer, most commonly lung cancer (Juntunen et al., 1997). The most common malignancies were lung and prostate cancer, while there was only one mesothelioma case in our cohort. Malignant diseases were also frequent in a Japanese study of autopsied cases with asbestosis in which as much as 61% of the asbestosis cases had cancer, the most common types being lung cancer (33%) and mesothelioma (14%) (Murai & Kitagawa, 2000). Compared to the Finnish study of IPF patients, there were higher numbers of lung cancer and other cancers in the asbestosis cohort since the prevalence of lung cancer was 16% in the asbestosis cohort versus 6.8% in the IPF cohort, and for other cancers, 23% vs 12%, respectively (Kärkkäinen et al., 2017).

We observed that 16% of the asbestosis patients suffered from lung cancer. This result was not surprising, since in addition to asbestos exposure, asbestosis has been shown to be an independent risk factor for lung cancer even when exposure history was taken into account (Hughes & Weill, 1991; Markowitz et al., 2013; Reid et al., 2005). Smoking increased the risk of lung cancer also among asbestosis patients (Markowitz et al., 2013; Oksa et al., 1997). Most of our asbestosis patients

had a history of smoking, although there was no significant difference in the prevalence of lung cancer between non-smokers and ever-smokers.

Asbestos is known to be carcinogenic. In addition to lung cancer and mesothelioma, asbestos also causes laryngeal and ovarian cancers (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012; Ngo et al., 2022). However, we observed no laryngeal or ovarian cancers. The absence of ovarian cancers was most likely due to the small number of female patients, since only 5 female patients were included in our study. Previously, an association between asbestos and colorectal cancer was also reported with limited evidence (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012; Kwak et al., 2019; Ngo et al., 2022). In our cohort, two patients had colorectal cancer, which is, on the other hand, the second most common cancer type in Finnish men and women (Pitkäniemi et al., 2022). In addition, asbestos exposure has been related to prostate cancer risk (Dutheil et al., 2020). However, prostate cancer is the most common cancer in Finnish males, the risk being 14.5%, which was probably the reason for the relatively high number of prostate cancers observed in our study (Pitkäniemi et al., 2022).

The most common benign disorder caused by asbestos is pleural plaques, which was also the most prevalent (96%) comorbid disease in our asbestosis patients (Guidotti et al., 2004; Murray et al., 2016). Pleural abnormalities were also very common in the previous studies with asbestosis patients since in a Brazilian study, 81% of the patients, and in a Chinese study, 97% of the patients had benign pleural abnormalities in HRCT (Nogueira et al., 2011; Yang et al., 2018).

6.5 Disease course in asbestosis

To our knowledge, this is the first study reporting median survival time in a whole cohort of asbestosis patients. A few previous studies have reported survival information in variable groups in asbestosis cohorts (Cookson et al., 1985; Coutts et al., 1987; Huuskonen, 1978). In a study by Coutts et al. (1987), more than 60% of patients without finger clubbing were alive while less than 40% of patients with finger clubbing were alive 12 years after diagnosis of asbestosis. However, these patients were younger, about 55 years, compared to our cohort (68 years) at the time of diagnosis (Coutts et al., 1987). We observed similarly long survival, about ten years (125 months), after diagnosis. In addition, the patients with less than five years survival time were older and had worse PFTs; thus it could be deduced that the asbestosis diagnoses were made on average at a more advanced stage of disease.

Cookson et al. (1985) reported median survival time after claiming compensation for asbestosis in different ILO categories where ILO category II patients had nearly similar survival time (12 years). In a previous Finnish study, mean survival after diagnosis was 7.3 years in smokers and more than 14 years in non-smokers and ex-smokers in patients who were at least 50 years old at the time of diagnosis of asbestosis (Huuskonen, 1978).

In the present study, the patients were old, on average 79 years, at the time of death. In the United States, in patients with asbestosis as an underlying cause of death, patients were similarly on average 79 years at the time of death (Bang et al., 2014), while three other previous studies reported average age at death between 73 and 75 years in asbestosis patients (Chen et al., 2012; Diandini et al., 2013; Germani et al., 1999).

Based on the previous studies and our results, asbestosis patients had usually much better prognosis compared to patients with IPF, whose median survival has been shown to be from two to five years (Nathan et al., 2011; Raghu et al., 2011). We observed clearly longer survival in asbestosis than in IPF compared to the previous Finnish study in which IPF-patients survived for 42 months (Kärkkäinen et al., 2019). The median survival time was also estimated to be shorter in RA-ILD patients, i.e., three to seven years (England & Hershberger, 2020). In a previous Finnish study with RA-ILD patients, median survival time (107 months) was shorter than in our asbestosis patients (Nurmi et al., 2016). Moreover, asbestosis patients were older at the time of death compared to IPF and RA-ILD patients (Table 10).

6.6 Prognostic factors

There are relatively few previous studies and no research published in the 21st century reporting factors associated with disease progression or life expectancy in patients with asbestosis (Table 3). Huuskonen (1978) investigated Finnish asbestosis patients more than forty years ago and observed that current smoking associated with shorter survival in patients with asbestosis. In the present study, however, no significant association between smoking and survival was observed. Instead, we observed several other variables to be associated with survival.

6.6.1 Bronchoalveolar lavage

We investigated the association of BAL cell profile and ABs with survival in asbestosis patients. To the best of our knowledge, there have not been any previous studies on this topic in asbestosis patients. We showed that ABs and several cell types in BAL associated with prognosis of survival in asbestosis since high number of ABs, high neutrophil and eosinophil, but low lymphocyte differential count associated with shorter survival. Our results of asbestosis were consistent with previous studies in which association of BAL cell profile with survival was observed in other ILDs, mostly patients with IPF (Boomars et al., 1995; Kakugawa et al., 2016; Kinder et al., 2008; Macaluso et al., 2022; Ryu et al., 2007). Some studies, however, have observed no association or an association of discrepant direction in the percentage of eosinophils with survival (Park et al., 2007; Tabuena et al., 2005; Veeraraghavan et al., 2003). Thomeer et al. (2004) reported that BAL macrophage differential count associated with survival in a cohort with different ILDs. We did not, however, observe an association of macrophages with survival. Two recently published studies, one of which included a few asbestosis patients, reported similarly that high BAL neutrophil but low BAL lymphocyte differential count during AE of ILD related to shorter survival (Kono et al., 2021; Salonen et al., 2020a). Both studies observed that neutrophil percentage was increased during AE compared to stable phase of the disease (Kono et al., 2021; Salonen et al., 2020a).

6.6.2 Pulmonary function tests

It was not previously known whether baseline PFTs are related to prognosis of survival in patients with asbestosis. Baseline DLCO was a significant prognostic factor in our asbestosis cohort; a similar result has also been observed in other ILDs including IPF, RA-ILD and CHP patients (Jacob et al., 2017a; Kärkkäinen et al., 2019; Nurmi et al., 2017). On the other hand, previous studies have observed an association between decreased DLCO and severity of fibrosis based on ILO category in chest x-ray; furthermore, Cookson et al. (1985) reported baseline ILO category to be related to survival in asbestosis patients (Lee et al., 2003; Miller et al., 2013). Previous studies have also reported that spirometry FVC and FEV1 associated with mortality in other ILDs (Jacob et al., 2017a, 2017b; Kärkkäinen et al., 2019; King et al., 2001; Solomon et al., 2016). In our study on asbestosis, however, FVC or FEV1 were not related to survival.

6.6.3 Gender, age and physiologic variables and composite physiologic index

Our study was the first one to investigate the suitability of GAP and CPI in asbestosis. Both GAP model and CPI were associated with survival in our study. Asbestosis patients had, however, a more favourable prognosis than the predicted mortality suggested by GAP stage since three-year mortality was 4% in GAP I, 33% in GAP II, and 60% in GAP III in patients with asbestosis, while predicted mortality was 16%, 42% and 77% in IPF, respectively (Ley et al., 2012). Nurmi et al. (2017) reported one-, two- and three-year mortalities in different GAP stages in Finnish patients with RA-ILD, revealing that RA-ILD patients had worse prognosis in GAP stage I (three-year mortality 18%), but better prognosis in GAP stage II (three-year mortality 27%) compared to our asbestosis patients. None of the RA-ILD patients were in GAP stage III at the time of diagnosis (Nurmi et al., 2017). In our study, GAP stage III was also infrequent at the time of diagnosis of asbestosis since only five patients were in GAP stage III.

CPI has been observed to be a significant prognostic factor in many ILDs including IPF, RA-ILD, CHP and unclassifiable ILD (Jacob et al., 2017a, 2017b; Kärkkäinen et al., 2019; Nurmi et al., 2017). In our study, mean CPI score was 32 at the time of diagnosis of asbestosis, which is higher than in the previous study with RA-ILD patients (27), but lower compared to IPF (40), CHP (48) and unclassifiable ILD (52) (Jacob et al., 2017a, 2017b; Kärkkäinen et al., 2019; Nurmi et al., 2017). Mura et al. (2012) discovered that a CPI limit value more than 41 was significantly associated with increased three-year mortality. A CPI higher than 41 was a significant prognostic factor in our asbestosis cohort as well. Similarly, Ueno et al. (2017) found that preoperative CPI over 41 was also useful in predicting mortality in patients who had undergone lung cancer surgery with all three of the following: lung cancer, pulmonary fibrosis and emphysema (Ueno et al., 2017).

6.6.4 Comorbidities

To the best of our knowledge, the association of comorbidities of asbestosis patients in relation to survival has not been previously studied. We observed that coronary artery disease was both a common comorbidity and cause of death in patients with asbestosis and moreover, associated with shortened survival. Cardiovascular diseases, most importantly coronary artery disease, have associated with shortened survival in patients with IPF (Hyldgaard et al., 2014; Kärkkäinen et al., 2017;

Nathan et al., 2010). Hypertension was related to better survival in our asbestosis cohort whereas hypertension was not associated with prognosis in the previous studies with IPF or RA-ILD patients (Kärkkäinen et al., 2017; Kreuter et al., 2016; Ng et al., 2022).

We noticed that lung cancer was related to shortened survival, similarly as has been observed previously in patients with IPF (Kreuter et al., 2016; Song et al., 2021). To our knowledge, no previous studies have investigated the association of lung cancer with prognosis of survival in asbestosis patients. However, a previous Finnish study observed that development of malignant disease or lung cancer was associated with the progression of fibrosis in chest radiograph in patients with asbestosis (Partanen et al., 1995a).

In addition, previous studies have reported associations of gastroesophageal reflux disease with better survival and of diabetes with worse survival in IPF (Hyldgaard et al., 2014; Kreuter et al., 2016), while COPD has been associated with worse prognosis in RA-ILD (Ng et al., 2022). Nonetheless, we did not observe an association between gastroesophageal reflux disease, diabetes or COPD with the survival of asbestosis patients.

6.7 Causes of death

Previous studies investigating causes of death in patients with asbestosis have discovered asbestosis and lung cancer to be the most common causes of death (Table 5). In addition to these, cardiovascular diseases were also relatively common causes of death in patients with asbestosis (Table 5). Our results are consistent with the previous studies, since the most common underlying causes of death in order of frequency were asbestosis, coronary artery disease, and lung cancer.

Furthermore, previous studies on other ILDs such as IPF, RA-ILD and systemic sclerosis-associated ILD have similarly discovered lung fibrosis to be the most common cause of death (de Oliveira Martins et al., 2022; Kärkkäinen et al., 2018; Marcon et al., 2021; Nurmi et al., 2016). The difference in the number of lung fibrosis deaths was, however, considerably lower in asbestosis than in IPF, since lung fibrosis was the cause of death in about two thirds of the IPF patients and in only one third of the patients with asbestosis, while two thirds of the deaths in asbestosis patients were due to other reasons than lung fibrosis. Furthermore, malignant diseases were more common causes of death in patients with asbestosis compared to the previous studies on other ILDs (de Oliveira Martins et al., 2022; Kärkkäinen et al., 2018; Marcon et al., 2021; Nurmi et al., 2016).

To our knowledge, no previous studies have investigated both underlying and immediate causes of death in asbestosis patients. We revealed that the most commonly recorded immediate cause of death was pneumonia. The high pneumonia mortality was not surprising, since previously, Vehmas et al. (2012) reported increased risk of pneumonia death in asbestosis patients. Pneumonia was also a common immediate cause of death in previous Finnish studies with IPF and RA-ILD patients (Kärkkäinen et al., 2018; Nurmi et al., 2016).

6.8 Strengths and limitations

The retrospective study design caused limitations, including some missing information, since BAL and PFT results were not available in all the patients. Furthermore, we were not able to collect detailed information of exposure history in fibre years because exposure history was reported differently in different patients. However, the retrospective study design enabled us to collect quite a large cohort of asbestosis patients even though the disease is nowadays relatively rare in Finland. The BAL procedure has been performed as part of systematic practice for several decades in Oulu University Hospital and to our knowledge, our study is the largest published study on BAL in patients with asbestosis so far. The retrospective study design enabled a long follow-up time, more than ten years in most of the patients. A long follow-up time is necessary in studies of prognosis of asbestosis patients because the disease is typically slowly progressive.

Another study limitation was that the HRCT images were not re-evaluated by a radiologist for our study. However, the radiological reports were looked over and patients with uncertain diagnoses were excluded. In addition, ILD patients are discussed in multidisciplinary meetings as a routine practice in Oulu University Hospital and are also discussed in occupational multidisciplinary meetings if there is suspicion of occupational exposure such as asbestos. In the multidisciplinary meetings, radiological images are re-evaluated by an experienced thoracic radiologist.

The collection of comorbid diseases turned out to be challenging since the patients had suffered from multiple diseases. Furthermore, not all of the patients' illnesses were mentioned in all follow-up records of various medical specialties. However, we collected information of comorbid diseases by reviewing extensively the medical records of different medical specialties, also using text search as an aid. In addition, information of comorbid diseases was collected from death certificates. By these methods, quite comprehensive data on common comorbid diseases of

asbestosis patients were obtained, which is so far the largest one on comorbidities in patients with asbestosis.

Determination of causes of death always involves a certain amount of uncertainty, which is diminished if an autopsy is performed. Most of the causes of death in our study were determined with medicolegal autopsy, which strengthened the reliability of the data.

6.9 Future perspectives

Most of the previous studies on asbestosis were published before the year 2000, when the diagnosis of pulmonary fibrosis was based on findings in chest radiograph, which has been found to cause both false negative and false positive diagnoses (Paris et al., 2004; Staples et al., 1989; Terra-Filho et al., 2015). There have been rather few recent publications on asbestosis in the era of modern diagnostics. Even though the use of asbestos has been banned in several countries, asbestos is still used in some countries, and the number of asbestosis cases has been increasing globally (Virta, 2006; Yang et al., 2020). Moreover, asbestosis is still a common differential diagnostic dilemma in the diagnosis of other ILDs, especially IPF. Detailed knowledge of clinical features, HRCT and BAL findings in asbestosis are beneficial in the differential diagnostics of ILDs. Thus, it can be estimated that the studies on asbestosis are still useful in many aspects.

Previously, little was known about the factors associated with the prognosis of survival in patients with asbestosis. In present study, we observed several factors to associate with survival. It would be useful to find out whether these prognostic factors could predict who will benefit from antifibrotic treatment, pulmonary rehabilitation or prediction of right time for starting the treatment.

The reference values of Viljanen et al. (1982) for spirometry and diffusion capacity were applied in this study. The updated Finnish reference values for spirometry and diffusion capacity were published in 2015 and 2017 (Kainu et al., 2017, 2016b). The new reference values for spirometry implemented into clinical use between 2015–2017 and the new reference values for diffusion capacity are currently being implemented into clinical use. The old reference values for spirometry from 1982 have been shown to involve overdiagnosis of ventilatory impairment compared to the 2015 reference values (Kainu et al., 2016a). We did not observe any association between spirometry values and prognosis. Instead, DLCO associated with prognosis. It would be interesting to study whether the results would be similar by applying these newer reference values.

Previous studies observed that baseline ILO category and cumulative asbestos exposure associated with radiographic disease progression (Cookson et al., 1986; Oksa et al., 1998; Suoranta et al., 1982). It would be fascinating to investigate whether prognostic factors such as, for example, GAP, CPI or BAL findings, predict radiographic disease progression or phenotype of progressive fibrosis, which is currently an indication for antifibrotic treatment in asbestosis (The Social Insurance Institution of Finland (Kela), n.d.).

Salonen et al. (2020b) observed that AE of asbestosis had a poor prognosis. The prognosis AE of asbestosis was as weak as the prognosis of AE of IPF (Salonen et al., 2020b). High GAP stage and BAL basophils predicted shorter AE-free time in a cohort with different ILD patients (Salonen et al., 2020a, 2020c). It would also be important to investigate factors that predict AE in cohorts with asbestosis patients only and how AE of asbestosis could be prevented. However, these studies are hampered by the difficulty of collecting a sufficiently large number of patients due to the rarity of asbestosis today. Furthermore, it would be useful to investigate the most effective treatments during AE of asbestosis.

The asbestosis patients in our study were mostly men, similarly as in most of the previous studies (Chen et al., 2012; Huuskonen, 1978; Walters et al., 2018). There is a lack of information on the clinical, radiological and BAL features as well as the course of the disease in female patients with asbestosis. Previously, it was observed that female asbestosis patients had increased risk of cancer and non-malignant respiratory disease mortality similarly to male asbestosis patients, and also in one study, the most common causes of death in women and men with asbestosis were similar (Chen et al., 2012; Germani et al., 1999; Szeszenia-Dąbrowska et al., 2002).

7 Conclusions

It was observed that asbestosis patients exhibited both similar and distinct clinical features compared to other ILDs. Asbestosis patients had decreased DLCO and restrictive spirometry, similarly to other ILDs. BAL of asbestosis patients exhibited a neutrophilic cell pattern, similarly as in patients with IPF, for example. Smoking influenced the BAL cell profile. Non-smoking asbestosis patients had lymphocytosis in BAL. High number of BAL ABs associated with a similar kind of BAL cell profile as in smoking.

The most common comorbid diseases of asbestosis patients were cardiovascular and respiratory diseases, similarly to other ILDs. The most common underlying cause of death was lung fibrosis, as has also been the case in other ILDs. Malignant diseases were a more common cause of death in asbestosis patients compared to other ILDs. The most common immediate cause of death in asbestosis patients was pneumonia, which has been a common cause of death in other ILDs as well.

Asbestosis patients lived about ten years after diagnosis of asbestosis and were about 79 years old when they died. Several factors which have previously been observed to be associated with survival in other ILDs were similarly significant prognostic factors in patients with asbestosis. These factors included BAL lymphocyte, neutrophil and eosinophil differential counts, DLCO, GAP, CPI and presence of coronary artery disease and lung cancer, all of which associated with survival. In addition, the number of BAL ABs associated with prognosis. Information of prognostic factors is topical since pharmacological treatment of ILDs is evolving. New drugs have become available and are currently being developed for treatment of different types of ILDs.

References

Abejie, B. A., Wang, X., Kales, S. N., & Christiani, D. C. (2010). Patterns of pulmonary dysfunction in asbestos workers: a cross-sectional study. *Journal of Occupational Medicine and Toxicology*, *5*(1), 12. https://doi.org/10.1186/1745-6673-5-12

Abramson, M. J., Murambadoro, T., Alif, S. M., Benke, G. P., Dharmage, S. C., Glaspole, I., Hopkins, P., Hoy, R. F., Klebe, S., Moodley, Y., Rawson, S., Reynolds, P. N., Wolfe, R., Corte, T. J., & Haydn Walters, E. (2020). Occupational and environmental risk factors for idiopathic pulmonary fibrosis in Australia: case-control study. *Thorax*, *75*(10), 864–869. https://doi.org/10.1136/THORAXJNL-2019-214478

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Aho, K., Kaipiainen-Seppanen, O., Heliovaara, M., & Klaukka, T. (1998). Epidemiology of rheumatoid arthritis in Finland. *Seminars in Arthritis and Rheumatism*, *27*(5), 325–334. https://doi.org/10.1016/S0049-0172(98)80053-X

Akira, M., & Morinaga, K. (2016). The comparison of high-resolution computed tomography findings in asbestosis and idiopathic pulmonary fibrosis. *American Journal of Industrial Medicine*, *59*(4), 301–306. https://doi.org/10.1002/AJIM.22573

al Jarad, N., Gellert, A. R., & Rudd, R. M. (1993). Bronchoalveolar lavage and 99mTc-DTPA clearance as prognostic factors in asbestos workers with and without asbestosis. *Respiratory Medicine*, *87*(5), 365–374. https://doi.org/10.1016/0954-6111(93)90050-A

Albin, M., Pooley, F. D., Stromberg, U., Attewell, R., Mitha, R., Johansson, L., & Welinder, H. (1994). Retention patterns of asbestos fibres in lung tissue among asbestos cement workers. *Occupational and Environmental Medicine*, *51*(3), 205–211. https://doi.org/10.1136/oem.51.3.205

Alfonso, H. S., Fritschi, L., de Klerk, N. H., Olsen, N., Sleith, J., & Musk, A. B. W. (2005). Effects of asbestos and smoking on gas diffusion in people exposed to crocidolite. *The Medical Journal of Australia*, *183*(4), 184–187. https://doi.org/10.5694/J.1326-5377.2005.TB06990.X

Alfonso, H. S., Fritschi, L., de Klerk, N. H., Olsen, N., Sleith, J., & Musk, A. W. (2004). Effects of asbestos and smoking on the levels and rates of change of lung function in a crocidolite exposed cohort in Western Australia. *Thorax*, *59*(12), 1052–1056. https://doi.org/10.1136/THX.2004.022806

Algranti, E., Mendona, E. M. C., Decapitani, E. M., Freitas, J. B. P., Silva, H. C., & Bussacos, M. A. (2001). Non-malignant asbestos-related diseases in Brazilian asbestos-cement workers. *American Journal of Industrial Medicine*, *40*(3), 240–254. https://doi.org/10.1002/AJIM.1095

Ameille, J., Letourneux, M., Paris, C., Brochard, P., Stoufflet, A., Schorle, E., Gislard, A., Laurent, F., Conso, F., & Pairon, J. C. (2010). Does asbestos exposure cause airway obstruction, in the absence of confirmed asbestosis? *American Journal of Respiratory and Critical Care Medicine*, *182*(4), 526–530. https://doi.org/10.1164/RCCM.200812-1815OC

Bang, K. M., Mazurek, J. M., Wood, J. M., & Hendricks, S. A. (2014). Diseases attributable to asbestos exposure: years of potential life lost, United States, 1999-2010. *American Journal of Industrial Medicine*, *57*(1), 38–48. https://doi.org/10.1002/AJIM.22261

Barber, C. M., Wiggans, R. E., Young, C., & Fishwick, D. (2016). UK asbestos imports and mortality due to idiopathic pulmonary fibrosis. *Occupational Medicine*, *66*(2), 106–111. https://doi.org/10.1093/OCCMED/KQV142

Barnhart, S., Thornquist, M., Omenn, G. S., Goodman, G., Feigl, P., & Rosenstock, L. (1990). The degree of roentgenographic parenchymal opacities attributable to smoking among asbestos-exposed subjects. *The American Review of Respiratory Disease*, *141*(5 Pt 1), 1102–1106. https://doi.org/10.1164/AJRCCM/141.5_PT_1.1102

Barnikel, M., Million, P. M., Knoop, H., & Behr, J. (2019). The natural course of lung function decline in asbestos exposed subjects with pleural plaques and asbestosis. *Respiratory Medicine*, *154*, 82–85. https://doi.org/10.1016/J.RMED.2019.06.013

Bégin, R., Cantin, A., Berthiaume, Y., Boileau, R., Péloquin, S., & Massé, S. (1983). Airway function in lifetime-nonsmoking older asbestos workers. *The American Journal of Medicine*, *75*(4), 631–638. https://doi.org/10.1016/0002-9343(83)90449-7

Bégin, R., Drapeau, G., Boileau, R., Vézina, Y., Cantin, A., Desmarais, Y., & Martel, M. (1986). Enzyme activities of lung lavage in asbestosis. *Clinical Biochemistry*, *19*(4), 240–243. https://doi.org/10.1016/S0009-9120(86)80034-0

Behr, J., Prasse, A., Kreuter, M., Johow, J., Rabe, K. F., Bonella, F., Bonnet, R., Grohe, C., Held, M., Wilkens, H., Hammerl, P., Koschel, D., Blaas, S., Wirtz, H., Ficker, J. H., Neumeister, W., Schönfeld, N., Claussen, M., Kneidinger, N., … Froehling, K. P. (2021). Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. *The Lancet Respiratory Medicine*, *9*(5), 476–486. https://doi.org/10.1016/S2213-2600(20)30554-3

Bennett, K., & Brims, F. J. H. (2020). Asbestosis. In J. Feary, H. Suojalehto, & P. Cullinan (Eds.), *Occupational and Environmental Lung Disease* (pp. 125–140). European Respiratory Society. https://doi.org/10.1183/2312508X.10034619

Bergantini, L., d'Alessandro, M., Cameli, P., Perrone, A., Cekorja, B., Boncompagni, B., Mazzei, M. A., Sestini, P., & Bargagli, E. (2021). Integrated approach to bronchoalveolar lavage cytology to distinguish interstitial lung diseases. *European Journal of Internal Medicine*, *89*, 76–80. https://doi.org/10.1016/J.EJIM.2021.04.005

Berry, G. (1981). Mortality of workers certified by pneumoconiosis medical panels as having asbestosis. *British Journal of Industrial Medicine*, *38*(2), 130–137. https://doi.org/10.1136/OEM.38.2.130

Blackley, D. J., Halldin, C. N., Hayanga, J. W. A., & Laney, A. S. (2020). Transplantation for work-related lung disease in the USA. *Occupational and Environmental Medicine*, *77*(11), 790–794. https://doi.org/10.1136/OEMED-2020-106578

Boomars, K. A., Wagenaar, S. S., Mulder, P. F. H., van Velzen-Blad, H., & van den Bosch, J. M. M. (1995). Relationship between cells obtained by bronchoalveolar lavage and survival in idiopathic pulmonary fibrosis. *Thorax*, *50*(10), 1092. https://doi.org/10.1136/THX.50.10.1087

Brims, F. J. H., Kong, K., Harris, E. J. A., Sodhi-Berry, N., Reid, A., Murray, C. P., Franklin, P. J., Musk, A. B., & de Klerk, N. H. (2020). Pleural Plaques and the Risk of Lung Cancer in Asbestos-exposed Subjects. *American Journal of Respiratory and Critical Care Medicine*, *201*(1), 57–62. https://doi.org/10.1164/RCCM.201901-0096OC

Callahan, K. S., Griffith, D. E., & Garcia, J. G. N. (1990). Asbestos exposure results in increased lung procoagulant activity in vivo and in vitro. *Chest*, *98*(1), 112–119. https://doi.org/10.1378/CHEST.98.1.112

Cantin, A., Allard, C., & Begin, R. (1989). Increased alveolar plasminogen activator in early asbestosis. *The American Review of Respiratory Disease*, *139*(3), 604–609. https://doi.org/10.1164/AJRCCM/139.3.604

Cha, Y. K., Kim, J. S., Kim, Y., & Kim, Y. K. (2016). Radiologic diagnosis of asbestosis in Korea. *Korean Journal of Radiology*, *17*(5), 674–683. https://doi.org/10.3348/KJR.2016.17.5.674

Chen, M., Tse, L. A., Au, R. K. F., Yu, I. T. S., Wang, X. rong, Lao, X. qian, & Au, J. S. kei. (2012). Mesothelioma and lung cancer mortality: a historical cohort study among asbestosis workers in Hong Kong. *Lung Cancer*, *76*(2), 165–170. https://doi.org/10.1016/J.LUNGCAN.2011.11.003

Churg, A., & Stevens, B. (1995). Enhanced retention of asbestos fibers in the airways of human smokers. *American Journal of Respiratory and Critical Care Medicine*, *151*(5), 1409–1413. https://doi.org/10.1164/AJRCCM.151.5.7735593

Churg, A., & Vedal, S. (1994). Fiber burden and patterns of asbestos-related disease in workers with heavy mixed amosite and chrysotile exposure. *American Journal of Respiratory and Critical Care Medicine*, *150*(3), 663–669. https://doi.org/10.1164/ajrccm.150.3.8087335

Churg, A., & Wright, J. L. (1994). Persistence of natural mineral fibers in human lungs: an overview. *Environmental Health Perspectives*, *102*(Suppl 5), 229–233. https://doi.org/10.1289/EHP.94102S5229

Churg, A., Wright, J. L., Depaoli, L., & Wiggs, B. (1989). Mineralogic correlates of fibrosis in chrysotile miners and millers. *The American Review of Respiratory Disease*, *139*(4), 891–896. https://doi.org/10.1164/AJRCCM/139.4.891

Churg, A., Wright, J. L., Hobson, J., & Stevens, B. (1992). Effects of cigarette smoke on the clearance of short asbestos fibres from the lung and a comparison with the clearance of long asbestos fibres. *International Journal of Experimental Pathology*, *73*(3), 297.

Churg, A., Wright, J. L., & Tazelaar, H. D. (2011). Acute exacerbations of fibrotic interstitial lung disease. *Histopathology*, *58*(4), 525–530. https://doi.org/10.1111/J.1365-2559.2010.03650.X

Churg, A., Wright, J., Wiggs, B., & Depaoli, L. (1990). Mineralogic parameters related to amosite asbestos-induced fibrosis in humans. *The American Review of Respiratory Disease*, *142*(6 Pt 1), 1331–1336. https://doi.org/10.1164/AJRCCM/142.6_PT_1.1331

ClinicalTrials.gov. (n.d.). U.S. National Library of Medicine. Retrieved March 28, 2023, from https://clinicaltrials.gov/

Collard, H. R., Moore, B. B., Flaherty, K. R., Brown, K. K., Kaner, R. J., King, T. E., Lasky, J. A., Loyd, J. E., Noth, I., Olman, M. A., Raghu, G., Roman, J., Ryu, J. H., Zisman, D. A., Hunninghake, G. W., Colby, T. v., Egan, J. J., Hansell, D. M., Johkoh, T., … Martinez, F. J. (2007). Acute exacerbations of idiopathic pulmonary fibrosis. *American Journal of Respiratory and Critical Care Medicine*, *176*(7), 636–643. https://doi.org/10.1164/RCCM.200703-463PP

Collard, H. R., Ryerson, C. J., Corte, T. J., Jenkins, G., Kondoh, Y., Lederer, D. J., Lee, J. S., Maher, T. M., Wells, A. U., Antoniou, K. M., Behr, J., Brown, K. K., Cottin, V., Flaherty, K. R., Fukuoka, J., Hansell, D. M., Johkoh, T., Kaminski, N., Kim, D. S., … Martinez, F. J. (2016). Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. *American Journal of Respiratory and Critical Care Medicine*, *194*(3), 265–275. https://doi.org/10.1164/RCCM.201604-0801CI

Cooke, W. E. (1924). Fibrosis of the lungs due to the inhalation of asbestos dust. *British Medical Journal*, *2*(3317), 147. https://doi.org/10.1136/BMJ.2.3317.147

Cooke, W. E. (1927). Pulmonary asbestosis. *British Medical Journal*, *2*(3491), 1024–1025. https://doi.org/10.1136/BMJ.2.3491.1024

Cookson, W., de Klerk, N., Musk, A. W., Glancy, J. J., Armstrong, B., & Hobbs, M. (1986). The natural history of asbestosis in former crocidolite workers of Wittenoom Gorge. *The American Review of Respiratory Disease*, *133*(6), 994–998. https://doi.org/10.1164/ARRD.1986.133.6.994

Cookson, W., Musk, A. W., Glancy, J. J., de Klerk, N., Yin, R., Mele, R., Carr, N. G., Armstrong, B., & Hobbs, M. (1985). Compensation, radiographic changes, and survival in applicants for asbestosis compensation. *British Journal of Industrial Medicine*, *42*(7), 461–468. https://doi.org/10.1136/OEM.42.7.461

Corhay, J. L., Delavignette, J. P., Bury, T., Saint-Remy, P., & Radermecker, M. F. (1990). Occult exposure to asbestos in steel workers revealed by bronchoalveolar lavage. *Archives of Environmental Health*, *45*(5), 278–282. https://doi.org/10.1080/00039896.1990.10118746

Costabel, U., Bross, K. J., Huck, E., Guzman, J., & Matthys, H. (1987). Lung and blood lymphocyte subsets in asbestosis and in mixed dust pneumoconiosis. *Chest*, *91*(1), 110–112. https://doi.org/10.1378/CHEST.91.1.110

Coutts, I. I., Gilson, J. C., Kerr, I. H., Parkes, W. R., & Turner-Warwick, M. (1987). Significance of finger clubbing in asbestosis. *Thorax*, *42*(2), 117–119. https://doi.org/10.1136/THX.42.2.117

Craighead, J. E., Abraham, J. L., Churg, A., Green, F. H., Kleinerman, J., Pratt, P. C., Seemayer, T. A., Vallyathan, V., & Weill, H. (1982). The pathology of asbestos-associated diseases of the lungs and pleural cavities: diagnostic criteria and proposed grading schema. Report of the Pneumoconiosis Committee of the College of American Pathologists and the National Institute for Occupational Safety and Health. *Archives of Pathology & Laboratory Medicine*, *106*(11), 596.

Crowson, C. S., Matteson, E. L., Myasoedova, E., Michet, C. J., Ernste, F. C., Warrington, K. J., Davis, J. M., Hunder, G. G., Therneau, T. M., & Gabriel, S. E. (2011). The lifetime risk of adult-onset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. *Arthritis and Rheumatism*, *63*(3), 633–639. https://doi.org/10.1002/ART.30155

Cullen, M. R., & Merrill, W. W. (1992). Association between neutrophil concentration in bronchoalveolar lavage fluid and recent losses in diffusing capacity in men formerly exposed to asbestos. *Chest*, *102*(3), 682–687. https://doi.org/10.1378/CHEST.102.3.682

Cullinan, P., & Reid, P. (2013). Pneumoconiosis. *Primary Care Respiratory Journal*, *22*(2), 252. https://doi.org/10.4104/PCRJ.2013.00055

de Oliveira Martins, L. V., Oliveira, S. M., Silvatti, J., de Amorim, F. G., Agapito Tito, C. v., & Kayser, C. (2022). Mortality in systemic sclerosis-associated interstitial lung disease in Brazil: a real-life, long-term follow-up observational study. *Journal of Clinical Rheumatology*, *28*(2), E532–E538. https://doi.org/10.1097/RHU.0000000000001792

De Vuyst, P., Dumortier, P., Moulin, E., Yourassowsky, N., Roomans, P., De Francquen, P., & Yernault, J. C. (1988). Asbestos bodies in bronchoalveolar lavage reflect lung asbestos body concentration. *The European Respiratory Journal*, *1*(4), 362–367. https://doi.org/10.1183/09031936.93.01040362

di Lorenzo, L., Mele, M., Pegorari, M. M., Fratello, A., Zocchetti, C., & Capozzi, D. (1996). Lung cinescintigraphy in the dynamic assessment of ventilation and mucociliary clearance of asbestos cement workers. *Occupational and Environmental Medicine*, *53*(9), 628–635. https://doi.org/10.1136/oem.53.9.628

Diandini, R., Takahashi, K., Park, E. K., Jiang, Y., Movahed, M., Le, G. V., Lee, L. J. H., Delgermaa, V., & Kim, R. (2013). Potential years of life lost (PYLL) caused by asbestos-related diseases in the world. *American Journal of Industrial Medicine*, *56*(9), 993–1000. https://doi.org/10.1002/AJIM.22206

dos Santos Antao, V. C., Pinheiro, G. A., & Wassell, J. T. (2009). Asbestosis mortality in the USA: facts and predictions. *Occupational and Environmental Medicine*, *66*(5), 335–338. https://doi.org/10.1136/OEM.2008.039172

Dowman, L. M., McDonald, C. F., Hill, C. J., Lee, A. L., Barker, K., Boote, C., Glaspole, I., Goh, N. S. L., Southcott, A. M., Burge, A. T., Gillies, R., Martin, A., & Holland, A. E. (2017). The evidence of benefits of exercise training in interstitial lung disease: a randomised controlled trial. *Thorax*, *72*(7), 610–619. https://doi.org/10.1136/THORAXJNL-2016-208638

Dutheil, F., Zaragoza-Civale, L., Pereira, B., Mermillod, M., Baker, J. S., Schmidt, J., Moustafa, F., & Navel, V. (2020). Prostate cancer and asbestos: a systematic review and meta-analysis. *The Permanente Journal*, *24*, 19.086. https://doi.org/10.7812/TPP/19.086

Eagan, T. M. L., Gulsvik, A., Eide, G. E., & Bakke, P. S. (2002). Occupational airborne exposure and the incidence of respiratory symptoms and asthma. *American Journal of Respiratory and Critical Care Medicine*, *166*(7), 933–938. https://doi.org/10.1164/RCCM.200203-238OC

Ehrlich, R., Lilis, R., Chan, E., Nicholson, W. J., & Selikoff, I. J. (1992). Long term radiological effects of short term exposure to amosite asbestos among factory workers. *British Journal of Industrial Medicine*, *49*(4), 268–275. https://doi.org/10.1136/OEM.49.4.268

Elmes, P. C. (1966). The epidemiology and clinical features of asbestosis and related diseases. *Postgraduate Medical Journal*, *42*(492), 623–635. https://doi.org/10.1136/PGMJ.42.492.623

England, B. R., & Hershberger, D. (2020). Management issues in rheumatoid arthritis-associated interstitial lung disease. *Current Opinion in Rheumatology*, *32*(3), 263. https://doi.org/10.1097/BOR.0000000000000703

Epler, G. R., Carrington, C. B., & Gaensler, E. A. (1978). Crackles (rales) in the interstitial pulmonary diseases. *Chest*, *73*(3), 333–339. https://doi.org/10.1378/CHEST.73.3.333

Epler, G. R., Mcloud, T. C., & Gaensler, E. A. (1982). Prevalence and Incidence of Benign Asbestos Pleural Effusion in a Working Population. *Journal of the American Medical Association*, *247*(5), 617–622. https://doi.org/10.1001/jama.1982.03320300021016

Ferrante, P. (2019). Asbestosis and silicosis hospitalizations in Italy (2001-2015): results from the National Hospital Discharge Registry. *European Journal of Public Health*, *29*(5), 876–882. https://doi.org/10.1093/EURPUB/CKZ003

Finkelstein, M., Kusiak, R., & Suranyi, G. (1981). Mortality among workers receiving compensation for asbestosis in Ontario. *Canadian Medical Association Journal*, *125*(3), 262.

Finnish Cancer Registry. (n.d.). *Cancer statistics*. Retrieved May 6, 2023, from https://cancerregistry.fi/statistics/cancer-statistics/

Finnish Institute for Health and Welfare. (2011). *Third edition of the Finnish version of the International Statistical Classification of Diseases and Related Health Problems*. Finnish Institute for Health and Welfare. https://urn.fi/URN:NBN:fi-fe201205085423

Finnish Institute of Occupational Health. (n.d.). *Asbesti*. Retrieved December 18, 2022, from https://www.ttl.fi/teemat/tyoturvallisuus/altistuminen-tyoympariston-haittatekijoille/kemiallisten-tekijoiden-hallinta-tyopaikalla/kemikaalit-ja-tyo-altistumistietosivusto/asbesti

Flaherty, K. R., Wells, A. U., Cottin, V., Devaraj, A., Walsh, S. L. F., Inoue, Y., Richeldi, L., Kolb, M., Tetzlaff, K., Stowasser, S., Coeck, C., Clerisme-Beaty, E., Rosenstock, B., Quaresma, M., Haeufel, T., Goeldner, R.-G., Schlenker-Herceg, R., & Brown, K. K. (2019). Nintedanib in progressive fibrosing interstitial lung diseases. *The New England Journal of Medicine*, *381*(18), 1718–1727. https://doi.org/10.1056/NEJMOA1908681

Friedman, A. C., Fiel, S. B., Fisher, M. S., Radecki, P. D., Lev-Toaff, A. S., & Caroline, D. F. (1988). Asbestos-related pleural disease and asbestosis: a comparison of CT and chest radiography. *American Journal of Roentgenology*, *150*(2), 269–275. https://doi.org/10.2214/AJR.150.2.269

Frye, B. C., Schupp, J. C., Rothe, M. E., Köhler, T. C., Prasse, A., Zissel, G., Vach, W., & Müller-Quernheim, J. (2020). The value of bronchoalveolar lavage for discrimination between healthy and diseased individuals. *Journal of Internal Medicine*, *287*(1), 54–65. https://doi.org/10.1111/JOIM.12973

Garcia, J. G. N., Griffith, D. E., Cohen, A. B., & Callahan, K. S. (1989). Alveolar macrophages from patients with asbestos exposure release increased levels of leukotriene B4. *The American Review of Respiratory Disease*, *139*(6), 1494–1501. https://doi.org/10.1164/AJRCCM/139.6.1494

Gellert, A. R., Langford, J. A., Winter, R. J. D., Uthayakumar, S., Sinha, G., & Rudd, R. M. (1985). Asbestosis: assessment by bronchoalveolar lavage and measurement of pulmonary epithelial permeability. *Thorax*, *40*(7), 514. https://doi.org/10.1136/THX.40.7.508

Germani, D., Belli, S., Bruno, C., Grignoli, M., Nesti, M., Pirastu, R., & Comba, P. (1999). Cohort mortality study of women compensated for asbestosis in Italy. *American Journal of Industrial Medicine*, *36*, 129–134. https://doi.org/10.1002/(SICI)1097-0274(199907)36:1

Girardi, P., Merler, E., Ferrante, D., Silvestri, S., Chellini, E., Angelini, A., Luberto, F., Fedeli, U., Oddone, E., Vicentini, M., Barone-Adesi, F., Cena, T., Mirabelli, D., Mangone, L., Roncaglia, F., Sala, O., Menegozzo, S., Pirastu, R., Azzolina, D., … Verdi, S. (2020). Factors Affecting Asbestosis Mortality Among Asbestos-Cement Workers in Italy. *Annals of Work Exposures and Health*, *64*(6), 622–635. https://doi.org/10.1093/ANNWEH/WXAA037

Government Decree on the prohibition of manufacture, import, trade and use of asbestos 852/1992

Government Decree on the Safety of Asbestos Work 798/2015

Green, F. H. Y., Harley, R., Vallyathan, V., Althouse, R., Fick, G., Dement, J., Mitha, R., & Pooley, F. (1997). Exposure and mineralogical correlates of pulmonary fibrosis in chrysotile asbestos workers. *Occupational and Environmental Medicine*, *54*(8), 549–559. https://doi.org/10.1136/OEM.54.8.549

Groot Lipman, K. B. W., de Gooijer, C. J., Boellaard, T. N., van der Heijden, F., Beets-Tan, R. G. H., Bodalal, Z., Trebeschi, S., & Burgers, J. A. (2022). Artificial intelligence-based diagnosis of asbestosis: analysis of a database with applicants for asbestosis state aid. *European Radiology*. https://doi.org/10.1007/S00330-022-09304-2/FIGURES/3

Guenther, A., Krauss, E., Tello, S., Wagner, J., Paul, B., Kuhn, S., Maurer, O., Heinemann, S., Costabel, U., Barbero, M. A. N., Müller, V., Bonniaud, P., Vancheri, C., Wells, A., Vasakova, M., Pesci, A., Sofia, M., Klepetko, W., Seeger, W., … Crestani, B. (2018). The European IPF registry (eurIPFreg): baseline characteristics and survival of patients with idiopathic pulmonary fibrosis. *Respiratory Research*, *19*(1), 141. https://doi.org/10.1186/S12931-018-0845-5

Guidotti, T. L., Miller, A., Christiani, D., Wagner, G., Balmes, J., Harber, P., Brodkin, C. A., Rom, W., Hillerdal, G., Harbut, M., & Green, F. H. Y. (2004). Diagnosis and initial management of nonmalignant diseases related to asbestos. *American Journal of Respiratory and Critical Care Medicine*, *170*(6), 691–715. https://doi.org/10.1164/RCCM.200310-1436ST

Halme, M. (2017). Lung transplantation in the treatment of interstitial lung disease. *Finnish Medical Journal*, *72*(38), 2097–2101.

Hammar, S. P., & Abraham, J. L. (2015). Commentary on pathologic diagnosis of asbestosis and critique of the 2010 Asbestosis Committee of the College of American Pathologists (CAP) and Pulmonary Pathology Society's (PPS) update on the diagnostic criteria for pathologic asbestosis. *American Journal of Industrial Medicine*, *58*(10), 1034–1039. https://doi.org/10.1002/AJIM.22512

Harding, A. H., & Darnton, A. J. (2010). Asbestosis and mesothelioma among British asbestos workers (1971-2005). *American Journal of Industrial Medicine*, *53*(11), 1070–1080. https://doi.org/10.1002/AJIM.20844

Harding, A. H., Darnton, A., Wegerdt, J., & McElvenny, D. (2009). Mortality among British asbestos workers undergoing regular medical examinations (1971-2005). *Occupational and Environmental Medicine*, *66*(7), 487–495. https://doi.org/10.1136/OEM.2008.043414

Hayes, A. A., Rose, A. H., Musk, A. W., & Robinson, B. W. S. (1988). Neutrophil chemotactic factor release and neutrophil alveolitis in asbestos-exposed individuals. *Chest*, *94*(3), 521–525. https://doi.org/10.1378/CHEST.94.3.521

Hemminki, K., Partanen, R., Koskinen, H., Smith, S., Carney, W., & Brandt-Rauf, P. (1996). The molecular epidemiology of oncoproteins. Serum p53 protein in patients with asbestosis. *Chest*, *109*(3 Suppl), 46–49. https://doi.org/10.1378/CHEST.109.3_SUPPLEMENT.22S

Heron, M., Grutters, J. C., ten Dam-Molenkamp, K. M., Hijdra, D., van Heugten-Roeling, A., Claessen, A. M. E., Ruven, H. J. T., van den Bosch, J. M. M., & van Velzen-Blad, H. (2012). Bronchoalveolar lavage cell pattern from healthy human lung. *Clinical and Experimental Immunology*, *167*(3), 531. https://doi.org/10.1111/J.1365-2249.2011.04529.X

Hillerdal, G. (1990). Pleural and parenchymal fibrosis mainly affecting the upper lung lobes in persons exposed to asbestos. *Respiratory Medicine*, *84*(2), 129–134. https://doi.org/10.1016/S0954-6111(08)80015-7

Hisinger-Mölkänen, H., Pallasaho, P., Haahtela, T., Lindqvist, A., Sovijärvi, A., & Piirilä, P. (2019). The increase of asthma prevalence has levelled off and symptoms decreased in adults during 20 years from 1996 to 2016 in Helsinki, Finland. *Respiratory Medicine*, *155*, 121–126. https://doi.org/10.1016/J.RMED.2019.07.014

Hughes, J. M., & Weill, H. (1991). Asbestosis as a precursor of asbestos related lung cancer: results of a prospective mortality study. *British Journal of Industrial Medicine*, *48*(4), 229–233. https://doi.org/10.1136/OEM.48.4.229

Huuskonen, M. S. (1978). Clinical features, mortality and survival of patients with asbestosis. *Scandinavian Journal of Work, Environment & Health*, *4*(4), 265–274. https://doi.org/10.5271/SJWEH.2699

Huuskonen, M. S., Koskinen, K., Tossavainen, A., Karjalainen, A., Rinne, J. -P, & Rantanen, J. (1995). Finnish Institute of Occupational Health Asbestos Program 1987-1992. *American Journal of Industrial Medicine*, *28*(1), 123–142. https://doi.org/10.1002/AJIM.4700280111

Huuskonen, M. S., Räsänen, J. A., Juntunen, J., & Partanen, T. (1984). Immunological aspects of asbestosis: patients' neurological signs and asbestosis progression. *American Journal of Industrial Medicine*, *5*(6), 461–469. https://doi.org/10.1002/AJIM.4700050605

Hyldgaard, C., Hilberg, O., & Bendstrup, E. (2014). How does comorbidity influence survival in idiopathic pulmonary fibrosis? *Respiratory Medicine*, *108*(4), 647–653. https://doi.org/10.1016/J.RMED.2014.01.008

IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. (2012). A review of human carcinogens. Arsenic, metals, fibres, and dusts. In *International Agency for Research on Cancer* (Vol. 100C). International Agency for Research on Cancer.

Ilar, A., Klareskog, L., Saevarsdottir, S., Wiebert, P., Askling, J., Gustavsson, P., & Alfredsson, L. (2019). Occupational exposure to asbestos and silica and risk of developing rheumatoid arthritis: findings from a Swedish population-based case-control study. *RMD Open*, *5*(2), e000978. https://doi.org/10.1136/RMDOPEN-2019-000978

International Ban Asbestos Secretariat. (2022, October 28). *Current asbestos bans*. http://www.ibasecretariat.org/alpha_ban_list.php

International Labour Organization. (2011). *Guidelines for the use of the ILO International Classification of Radiographs of Pneumoconioses* (2011th ed.). International Labour Office.

Jacob, J., Bartholmai, B. J., Egashira, R., Brun, A. L., Rajagopalan, S., Karwoski, R., Kokosi, M., Hansell, D. M., & Wells, A. U. (2017a). Chronic hypersensitivity pneumonitis: identification of key prognostic determinants using automated CT analysis. *BMC Pulmonary Medicine*, *17*(1), 81. https://doi.org/10.1186/S12890-017-0418-2

Jacob, J., Bartholmai, B. J., Rajagopalan, S., Egashira, R., Brun, A. L., Kokosi, M., Nair, A., Walsh, S. L. F., Karwoski, R., Nicholson, A. G., Hansell, D. M., & Wells, A. U. (2017b). Unclassifiable-interstitial lung disease: Outcome prediction using CT and functional indices. *Respiratory Medicine*, *130*, 43–51. https://doi.org/10.1016/J.RMED.2017.07.007

Järvisalo, J., Juntunen, J., Huuskonen, M. S., Kivistö, H., & Aitio, A. (1984). Tumor markers and neurological signs in asbestosis patients. *American Journal of Industrial Medicine*, *6*(2), 159–166. https://doi.org/10.1002/AJIM.4700060210

Jovanovic, D. M., Šterclová, M., Mogulkoc, N., Lewandowska, K., Müller, V., Hájková, M., Studnicka, M., Tekavec-Trkanjec, J., Littnerová, S., Vašáková, M., Zembacher, S., Lang, D., Lamprecht, B., Stoeva, N., Mladinov, S., Ilak, D., Vergles, M., Tudoric, N., Vašáková, M., … Jonner, I. (2022). Comorbidity burden and survival in patients with idiopathic pulmonary fibrosis: the EMPIRE registry study. *Respiratory Research*, *23*(1), 135. https://doi.org/10.1186/S12931-022-02033-6

Ju, C., Yang, Y., Lian, Q., Wang, L., Wang, X., Wei, B., Huang, D., Xu, X., & He, J. (2023). Clinical outcomes and survival following lung transplantation for work-related lung disease: a single-center retrospective cohort study. *Journal of Occupational Medicine and Toxicology*, *18*(1), 2. https://doi.org/10.1186/S12995-023-00368-4

Juntunen, J., Oksa, P., Pukkala, E., & Laippala, P. (1997). Neurological signs in relation to cancer in patients with asbestosis. *Occupational and Environmental Medicine*, *54*(10), 746–749. https://doi.org/10.1136/OEM.54.10.746

Kähkönen, H., Lallukka, H., Linnainmaa, M., Aho, P., Mäkelä, E., Junttila, S., Oksa, P., & Nynäs, P. (2019). *Asbestos risk management guidelines for mines*. Finnish Institute of Occupational Health. https://urn.fi/URN:ISBN:978-952-261-624-1

Kainu, A., Lindqvist, A., & Sovijärvi, A. R. A. (2016a). Prevalence of abnormal findings when adopting new national and international Global Lung Function Initiative reference values for spirometry in the Finnish general population. *European Clinical Respiratory Journal*, *3*(1), 30658. https://doi.org/10.3402/ECRJ.V3.30658

Kainu, A., Timonen, K. L., Toikka, J., Qaiser, B., Pitkäniemi, J., Kotaniemi, J. T., Lindqvist, A., Vanninen, E., Länsimies, E., & Sovijärvi, A. R. A. (2016b). Reference values of spirometry for Finnish adults. *Clinical Physiology and Functional Imaging*, *36*(5), 346–358. https://doi.org/10.1111/CPF.12237

Kainu, A., Toikka, J., Vanninen, E., & Timonen, K. L. (2017). Reference values for pulmonary diffusing capacity for adult native Finns. *Scandinavian Journal of Clinical and Laboratory Investigation*, *77*(2), 135–142. https://doi.org/10.1080/00365513.2017.1286519

Kakugawa, T., Sakamoto, N., Sato, S., Yura, H., Harada, T., Nakashima, S., Hara, A., Oda, K., Ishimoto, H., Yatera, K., Ishimatsu, Y., Obase, Y., Kohno, S., & Mukae, H. (2016). Risk factors for an acute exacerbation of idiopathic pulmonary fibrosis. *Respiratory Research*, *17*(1), 79. https://doi.org/10.1186/S12931-016-0400-1

Kamp, D. W., Graceffa, P., Pryor, W. A., & Weitzman, S. A. (1992). The role of free radicals in asbestos-induced diseases. *Free Radical Biology and Medicine*, *12*(4), 293–315. https://doi.org/10.1016/0891-5849(92)90117-Y

Karimi, R., Tornling, G., Grunewald, J., Eklund, A., & Sköld, C. M. (2012). Cell recovery in bronchoalveolar lavage fluid in smokers is dependent on cumulative smoking history. *PloS One*, *7*(3), e34232. https://doi.org/10.1371/JOURNAL.PONE.0034232

Karjalainen, A., Anttila, S., Mäntylä, T., Taskinen, E., Kyyrönen, P., & Tukiainen, P. (1994). Asbestos bodies in bronchoalveolar lavage fluid in relation to occupational history. *American Journal of Industrial Medicine*, *26*(5), 645–654. https://doi.org/10.1002/AJIM.4700260507

Karjalainen, A., Piipari, R., Mäntylä, T., Mönkkönen, M., Nurminen, M., Tukiainen, P., Vanhala, E., & Anttila, S. (1996). Asbestos bodies in bronchoalveolar lavage in relation to asbestos bodies and asbestos fibres in lung parenchyma. *The European Respiratory Journal*, *9*(5), 1000–1005. https://doi.org/10.1183/09031936.96.09051000

Karjalainen, A., Pukkala, E., Kauppinen, T., & Partanen, T. (1999). Incidence of cancer among Finnish patients with asbestos-related pulmonary or pleural fibrosis. *Cancer Causes and Control*, *10*(1), 51–57. https://doi.org/10.1023/A:1008845332422

Kärkkäinen, M., Kettunen, H. P., Nurmi, H., Selander, T., Purokivi, M., & Kaarteenaho, R. (2017). Effect of smoking and comorbidities on survival in idiopathic pulmonary fibrosis. *Respiratory Research*, *18*(1), 160. https://doi.org/10.1186/S12931-017-0642-6

Kärkkäinen, M., Kettunen, H. P., Nurmi, H., Selander, T., Purokivi, M., & Kaarteenaho, R. (2019). Comparison of disease progression subgroups in idiopathic pulmonary fibrosis. *BMC Pulmonary Medicine*, *19*(1), 228. https://doi.org/10.1186/S12890-019-0996-2

Kärkkäinen, M., Nurmi, H., Kettunen, H. P., Selander, T., Purokivi, M., & Kaarteenaho, R. (2018). Underlying and immediate causes of death in patients with idiopathic pulmonary fibrosis. *BMC Pulmonary Medicine*, *18*(1), 69. https://doi.org/10.1186/S12890-018-0642-4

Kerper, L. E., Lynch, H. N., Zu, K., Tao, G., Utell, M. J., & Goodman, J. E. (2015). Systematic review of pleural plaques and lung function. *Inhalation Toxicology*, *27*(1), 15–44. https://doi.org/10.3109/08958378.2014.981349

Kinder, B. W., Brown, K. K., Schwarz, M. I., Ix, J. H., Kervitsky, A., & King, T. E. (2008). Baseline BAL neutrophilia predicts early mortality in idiopathic pulmonary fibrosis. *Chest*, *133*(1), 226–232. https://doi.org/10.1378/CHEST.07-1948

King, T. E., Bradford, W. Z., Castro-Bernardini, S., Fagan, E. A., Glaspole, I., Glassberg, M. K., Gorina, E., Hopkins, P. M., Kardatzke, D., Lancaster, L., Lederer, D. J., Nathan, S. D., Pereira, C. A., Sahn, S. A., Sussman, R., Swigris, J. J., & Noble, P. W. (2014). A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *The New England Journal of Medicine*, *370*(22), 2083–2092. https://doi.org/10.1056/NEJMOA1402582

King, T. E., Tooze, J. A., Schwarz, M. I., Brown, K. R., & Cherniack, R. M. (2001). Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. *American Journal of Respiratory and Critical Care Medicine*, *164*(7), 1171–1181. https://doi.org/10.1164/AJRCCM.164.7.2003140

Kokkinis, F. P., Bouros, D., Hadjistavrou, K., Ulmeanu, R., Serbescu, A., & Alexopoulos, E. C. (2011). Bronchoalveolar lavage fluid cellular profile in workers exposed to chrysotile asbestos. *Toxicology and Industrial Health*, *27*(9), 849–856. https://doi.org/10.1177/0748233711399315

Kokkola, K., & Huuskonen, M. S. (1979). Electrocardiographic signs of cor pulmonale in asbestosis. *International Archives of Occupational and Environmental Health*, *43*(3), 167–175. https://doi.org/10.1007/BF00381188

Kono, M., Miyashita, K., Hirama, R., Oshima, Y., Takeda, K., Mochizuka, Y., Tsutsumi, A., Miwa, H., Miki, Y., Hashimoto, D., Suda, T., & Nakamura, H. (2021). Prognostic significance of bronchoalveolar lavage cellular analysis in patients with acute exacerbation of interstitial lung disease. *Respiratory Medicine*, *186*, 106534. https://doi.org/10.1016/J.RMED.2021.106534

Kopiński, P., Sładek, K., Szczeklik, J., Soja, J., Szlubowski, A., Balicka-Slusarczyk, B., Lackowska, B., Plato, M., & Szpechciński, A. (2006). Expression of insulin-like growth factor-I (IGF-I) in alveolar macrophages and lymphocytes obtained by bronchoalveolar lavage (BAL) in interstitial lung diseases (ILD). Assessment of IGF-I as a potential local mitogen and antiapoptotic cytokine. *Folia Histochemica et Cytobiologica*, *44*(4), 249–258.

Korhonen, O., Juntunen, J., & Huuskonen, M. (1983). Lung function and nervous system involvement in asbestosis. *European Journal of Applied Physiology and Occupational Physiology*, *50*(2), 207–212. https://doi.org/10.1007/BF00422159

Koskela, K., Lehtimäki, J., Aalto-Korte, K., Pesonen, M., Lindström, I., Suojalehto, H., Airaksinen, L., Suuronen, K., & Helaskoski, E. (2022). *Ammattitaudit ja ammattitautiepäilyt 2018 : Työperäisten sairauksien rekisteriin kirjatut uudet tapaukset*. Finnish Institute of Occupational Health.

Koskela, K., Lehtimäki, J., Toivio, P., Aalto-Korte, K., Pesonen, M., Suuronen, K., Lindström, I., Airaksinen, L., Suojalehto, H., & Helaskoski, E. (2017). *Ammattitaudit ja ammattitautiepäilyt 2014 : Työperäisten sairauksien rekisteriin kirjatut uudet tapaukset*. Finnish Institute of Occupational Health. www.ttl.fi

Kreuter, M., Ehlers-Tenenbaum, S., Palmowski, K., Bruhwyler, J., Oltmanns, U., Muley, T., Heussel, C. P., Warth, A., Kolb, M., & Herth, F. J. F. (2016). Impact of Comorbidities on Mortality in Patients with Idiopathic Pulmonary Fibrosis. *PloS One*, *11*(3), e0151425. https://doi.org/10.1371/JOURNAL.PONE.0151425

Kreuter, M., Polke, M., Walsh, S. L. F., Krisam, J., Collard, H. R., Chaudhuri, N., Avdeev, S., Behr, J., Calligaro, G., Corte, T., Flaherty, K., Funke-Chambour, M., Kolb, M., Kondoh, Y., Maher, T. M., Molina, M. M., Morais, A., Moor, C. C., Morisset, J., … Bendstrup, E. (2020). Acute exacerbation of idiopathic pulmonary fibrosis: international survey and call for harmonisation. *The European Respiratory Journal*, *55*(4), 1901760. https://doi.org/10.1183/13993003.01760-2019

Kwak, K., Paek, D., & Zoh, K. E. (2019). Exposure to asbestos and the risk of colorectal cancer mortality: a systematic review and meta-analysis. *Occupational and Environmental Medicine*, *76*(11), 861–871. https://doi.org/10.1136/OEMED-2019-105735

Laaksonen, S., Ilonen, I., Kuosma, E., Sutinen, E., Wolff, H., Vehmas, T., Husgafvel-Pursiainen, K., Salo, J. A., Koli, K., Räsänen, J., & Myllärniemi, M. (2019). Malignant pleural mesothelioma in Finland: regional and gender variation. *Acta Oncologica*, *58*(1), 38–44. https://doi.org/10.1080/0284186X.2018.1532599

Lammi, L., Ryhänen, L., Lakari, E., Risteli, J., Pääkkö, P., Ruotsalainen, E. M., Lähde, S., & Kinnula, V. L. (1999). Carboxyterminal propeptide of type I procollagen in ELF: elevation in asbestosis, but not in pleural plaque disease. *The European Respiratory Journal*, *14*(3), 560–564. https://doi.org/10.1034/J.1399-3003.1999.14C13.X

Lappi-Blanco, E., Kaarteenaho-Wiik, R., Maasilta, P. K., Anttila, S., Pääkkö, P., & Wolff, H. J. (2006). COX-2 is widely expressed in metaplastic epithelium in pulmonary fibrous disorders. *American Journal of Clinical Pathology*, *126*(5), 717–724. https://doi.org/10.1309/PFGX-CLNG-2N17-PJX9

Lappi-Blanco, E., Lehtonen, S. T., Sormunen, R., Merikallio, H. M., Soini, Y., & Kaarteenaho, R. L. (2013). Divergence of tight and adherens junction factors in alveolar epithelium in pulmonary fibrosis. *Human Pathology*, *44*(5), 895–907. https://doi.org/10.1016/J.HUMPATH.2012.08.016

Lee, Y. C. G., Singh, B., Pang, S. C., de Klerk, N. H., Hillman, D. R., & Musk, A. W. (2003). Radiographic (ILO) readings predict arterial oxygen desaturation during exercise in subjects with asbestosis. *Occupational and Environmental Medicine*, *60*(3), 201–206. https://doi.org/10.1136/OEM.60.3.201

Leigh, J., Davidson, P., Hendrie, L., & Berry, D. (2002). Malignant mesothelioma in Australia, 1945-2000. *American Journal of Industrial Medicine*, *41*(3), 188–201. https://doi.org/10.1002/AJIM.10047

Leivo-Korpela, S., Lehtimäki, L., Nieminen, R., Oksa, P., Vierikko, T., Järvenpää, R., Uitti, J., & Moilanen, E. (2012). Adipokine adipsin is associated with the degree of lung fibrosis in asbestos-exposed workers. *Respiratory Medicine*, *106*(10), 1435–1440. https://doi.org/10.1016/J.RMED.2012.07.003

Lenz, A. G., Costabel, U., & Maier, K. L. (1996). Oxidized BAL fluid proteins in patients with interstitial lung diseases. *European Respiratory Journal*, *9*(2), 307–312. https://doi.org/10.1183/09031936.96.09020307

Ley, B., Ryerson, C. J., Vittinghoff, E., Ryu, J. H., Tomassetti, S., Lee, J. S., Poletti, V., Buccioli, M., Elicker, B. M., Jones, K. D., King, T. E., & Collard, H. R. (2012). A multidimensional index and staging system for idiopathic pulmonary fibrosis. *Annals of Internal Medicine*, *156*(10), 684–691.

Liddle, H. v. (1964). Asbestosis; Report of the section on nature and prevalence, Committee on Occupational Diseases of the Chest, American College of Chest Physicians. *Diseases of the Chest*, *45*, 107–111.

Lilis, R., Lerman, Y., & Selikoff, I. J. (1988). Symptomatic benign pleural effusions among asbestos insulation workers: residual radiographic abnormalities. *British Journal of Industrial Medicine*, *45*(7), 443–449. https://doi.org/10.1136/OEM.45.7.443

Lilis, R., Selikoff, I. J., Lerman, Y., Seidman, H., & Gelb, S. K. (1986). Asbestosis: interstitial pulmonary fibrosis and pleural fibrosis in a cohort of asbestos insulation workers: influence of cigarette smoking. *American Journal of Industrial Medicine*, *10*(5–6), 459–470. https://doi.org/10.1002/AJIM.4700100504

Lynch, K. M., & Smith, W. A. (1935). Pulmonary asbestosis III: Carcinoma of lung in asbesto-silicosis. *American Journal of Cancer*, *24*(1), 56–64. https://doi.org/10.1158/ajc.1935.56

Macaluso, C., Boccabella, C., Kokosi, M., Sivarasan, N., Kouranos, V., George, P. M., Margaritopoulos, G., Molyneaux, P. L., Chua, F., Maher, T. M., Jenkins, G. R., Nicholson, A. G., Desai, S. R., Devaraj, A., Wells, A. U., Renzoni, E. A., & Stock, C. J. W. (2022). Short-term lung function changes predict mortality in patients with fibrotic hypersensitivity pneumonitis. *Respirology*, *27*(3), 208. https://doi.org/10.1111/RESP.14204

Marcon, A., Schievano, E., & Fedeli, U. (2021). Mortality associated with idiopathic pulmonary fibrosis in northeastern Italy, 2008-2020: a multiple cause of death analysis. *International Journal of Environmental Research and Public Health*, *18*(14), 7249. https://doi.org/10.3390/IJERPH18147249

Markowitz, S. B., Levin, S. M., Miller, A., & Morabia, A. (2013). Asbestos, asbestosis, smoking, and lung cancer. New findings from the North American insulator cohort. *American Journal of Respiratory and Critical Care Medicine*, *188*(1), 90–96. https://doi.org/10.1164/RCCM.201302-0257OC

Mastrangelo, G., Ballarin, M. N., Bellini, E., Bicciato, F., Zannol, F., Gioffrè, F., Zedde, A., Tessadri, G., Fedeli, U., Valentini, F., Scoizzato, L., Marangi, G., & Lange, J. H. (2009). Asbestos exposure and benign asbestos diseases in 772 formerly exposed workers: dose-response relationships. *American Journal of Industrial Medicine*, *52*(8), 596–602. https://doi.org/10.1002/AJIM.20713

Mcdonald, S. (1927). Histology of pulmonary asbestosis. *British Medical Journal*, *2*(3491), 1025–1026. https://doi.org/10.1136/BMJ.2.3491.1025

Mena-Vázquez, N., Rojas-Gimenez, M., Romero-Barco, C. M., Gandía-Martínez, M., Perez-Gómez, N., Godoy-Navarrete, F. J., Manrique-Arija, S., Garcia-Studer, A., Calvo-Gutiérrez, J., Varela, C. F., Morales-Garrido, P., Pérez, P. C., Mouriño-Rodriguez, C., Añón-Oñate, I., Espildora, F., Aguilar-Hurtado, M. C., Redondo, R., Conde, A. H., de los Ríos, R. A. D., … Fernández-Nebro, A. (2023). Analysis of comorbidity in rheumatoid arthritis-associated interstitial lung disease: a nested case-cohort study. *Biomedicine & Pharmacotherapy*, *157*, 114049. https://doi.org/10.1016/J.BIOPHA.2022.114049

Meyer, K. C., Raghu, G., Baughman, R. P., Brown, K. K., Costabel, U., du Bois, R. M., Drent, M., Haslam, P. L., Kim, D. S., Nagai, S., Rottoli, P., Saltini, C., Selman, M., Strange, C., & Wood, B. (2012). An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. *American Journal of Respiratory and Critical Care Medicine*, *185*(9), 1004–1014. https://doi.org/10.1164/RCCM.201202-0320ST

Miedema, J. R., Moor, C. C., Veltkamp, M., Baart, S., Lie, N. S. L., Grutters, J. C., Wijsenbeek, M. S., & Mostard, R. L. M. (2022). Safety and tolerability of pirfenidone in asbestosis: a prospective multicenter study. *Respiratory Research*, *23*(1), 139. https://doi.org/10.1186/S12931-022-02061-2

Miguel-Reyes, J. L., Gochicoa-Rangel, L., Pérez-Padilla, R., & Torre-Bouscoulet, L. (2015). Functional respiratory assessment in interstitial lung disease. *Revista de Investigacion Clinica*, *67*(1), 5–14.

Miller, A., Lilis, R., Godbold, J., Chan, E., & Selikoff, I. J. (1992). Relationship of pulmonary function to radiographic interstitial fibrosis in 2,611 long-term asbestos insulators. An assessment of the International Labour Office profusion score. *The American Review of Respiratory Disease*, *145*(2 Pt 1), 263–270. https://doi.org/10.1164/AJRCCM/145.2_PT_1.263

Miller, A., Lilis, R., Godbold, J., & Wu, X. (1996). Relation of spirometric function to radiographic interstitial fibrosis in two large workforces exposed to asbestos: an evaluation of the ILO profusion score. *Occupational and Environmental Medicine*, *53*(12), 808–812. https://doi.org/10.1136/OEM.53.12.808

Miller, A., Warshaw, R., & Nezamis, J. (2013). Diffusing capacity and forced vital capacity in 5,003 asbestos-exposed workers: relationships to interstitial fibrosis (ILO profusion score) and pleural thickening. *American Journal of Industrial Medicine*, *56*(12), 1383–1393. https://doi.org/10.1002/AJIM.22239

Ministry of Labour. (1989). Asbestikomitean mietintö (Report of the Asbestos Committee). In *Report series of the Governmental Committees* (Vol. 66).

Mizell, K. N., Morris, C. G., & Carter, J. E. (2009). Antemortem diagnosis of asbestosis by screening chest radiograph correlated with postmortem histologic features of asbestosis: a study of 273 cases. *Journal of Occupational Medicine and Toxicology*, *4*(1), 14. https://doi.org/10.1186/1745-6673-4-14

Mossman, B. T., & Churg, A. (1998). Mechanisms in the pathogenesis of asbestosis and silicosis. *American Journal of Respiratory and Critical Care Medicine*, *157*(5), 1666–1680. https://doi.org/10.1164/ajrccm.157.5.9707141

Mossman, B. T., Lippmann, M., Hesterberg, T. W., Kelsey, K. T., Barchowsky, A., & Bonner, J. C. (2011). Pulmonary Endpoints (Lung Carcinomas and Asbestosis) Following Inhalation Exposure to Asbestos. *Journal of Toxicology and Environmental Health. Part B*, *14*(1–4), 76–121. https://doi.org/10.1080/10937404.2011.556047

Mura, M., Porretta, M. A., Bargagli, E., Sergiacomi, G., Zompatori, M., Sverzellati, N., Taglieri, A., Mezzasalma, F., Rottoli, P., Saltini, C., & Rogliani, P. (2012). Predicting survival in newly diagnosed idiopathic pulmonary fibrosis: a 3-year prospective study. *The European Respiratory Journal*, *40*(1), 101–109. https://doi.org/10.1183/09031936.00106011

Murai, Y., & Kitagawa, M. (2000). Autopsy cases of asbestosis in Japan: a statistical analysis on registered cases. *Archives of Environmental Health*, *55*(6), 447–452. https://doi.org/10.1080/00039890009604044

Murray, C. P., Wong, P. M., Teh, J., de Klerk, N., Rosenow, T., Alfonso, H., Reid, A., Franklin, P., Musk, A. W. B., & Brims, F. J. H. (2016). Ultra low dose CT screen-detected non-malignant incidental findings in the Western Australian Asbestos Review Programme. *Respirology*, *21*(8), 1419–1424. https://doi.org/10.1111/RESP.12826

Murray, R. (1990). Asbestos: a chronology of its origins and health effects. *British Journal of Industrial Medicine*, *47*(6), 361–365. https://doi.org/10.1136/OEM.47.6.361

Musk, A. W., de Klerk, N., Reid, A., Hui, J., Franklin, P., & Brims, F. (2020). Asbestos-related diseases. *The International Journal of Tuberculosis and Lung Disease*, *24*(6), 562–567. https://doi.org/10.5588/IJTLD.19.0645

Naghavi, M., Abajobir, A. A., Abbafati, C., Abbas, K. M., Abd-Allah, F., Abera, S. F., Aboyans, V., Adetokunboh, O., Ärnlöv, J., Afshin, A., Agrawal, A., Kiadaliri, A. A., Ahmadi, A., Ahmed, M. B., Aichour, A. N., Aichour, I., Aichour, M. T. E., Aiyar, S., Al-Eyadhy, A., … Murray, C. J. L. (2017). Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*, *390*(10100), 1151–1210. https://doi.org/10.1016/S0140-6736(17)32152-9

Nathan, S. D., Basavaraj, A., Reichner, C., Shlobin, O. A., Ahmad, S., Kiernan, J., Burton, N., & Barnett, S. D. (2010). Prevalence and impact of coronary artery disease in idiopathic pulmonary fibrosis. *Respiratory Medicine*, *104*(7), 1035–1041. https://doi.org/10.1016/J.RMED.2010.02.008

Nathan, S. D., Shlobin, O. A., Weir, N., Ahmad, S., Kaldjob, J. M., Battle, E., Sheridan, M. J., & Du Bois, R. M. (2011). Long-term course and prognosis of idiopathic pulmonary fibrosis in the new millennium. *Chest*, *140*(1), 221–229. https://doi.org/10.1378/CHEST.10-2572

Ng, K. H., Chen, D. Y., Lin, C. H., Chao, W. C., & Chen, H. H. (2022). Analysis of risk factors of mortality in rheumatoid arthritis patients with interstitial lung disease: a nationwide, population-based cohort study in Taiwan. *RMD Open*, *8*(2), e002343. https://doi.org/10.1136/RMDOPEN-2022-002343

Ngo, P., Sarich, P., Feletto, E., Driscoll, T., Grogan, P., Weber, M., & Canfell, K. (2022). Occupational exposure to respirable carcinogens and the risk of cancer. In M. Á. Martínez-García, M. Gaga, & K. M. Fong (Eds.), *Lung Diseases and Cancer* (Vol. 98, pp. 71–81). European Respiratory Society. https://doi.org/10.1183/2312508X.ERM9822

Nogueira, C. R., Nápolis, L. M., Bagatin, E., Terra-Filho, M., Müller, N. L., Silva, C. I. S., Rodrigues, R. T., Neder, J. A., & Nery, L. E. (2011). Lung diffusing capacity relates better to short-term progression on HRCT abnormalities than spirometry in mild asbestosis. *American Journal of Industrial Medicine*, *54*(3), 185–193. https://doi.org/10.1002/AJIM.20922

Noro, L. (1946). On the histology of asbestosis. *Acta Pathologica et Microbiologica Scandinavica*, *23*(1), 53–59.

Nurmi, H. M., Purokivi, M. K., Kärkkäinen, M. S., Kettunen, H. P., Selander, T. A., & Kaarteenaho, R. L. (2016). Variable course of disease of rheumatoid arthritis-associated usual interstitial pneumonia compared to other subtypes. *BMC Pulmonary Medicine*, *16*(1), 107. https://doi.org/10.1186/S12890-016-0269-2

Nurmi, H. M., Purokivi, M. K., Kärkkäinen, M. S., Kettunen, H. P., Selander, T. A., & Kaarteenaho, R. L. (2017). Are risk predicting models useful for estimating survival of patients with rheumatoid arthritis-associated interstitial lung disease? *BMC Pulmonary Medicine*, *17*(1), 16. https://doi.org/10.1186/S12890-016-0358-2

Nuyts, V., Vanhooren, H., Begyn, S., Nackaerts, K., & Nemery, B. (2017). Asbestos bodies in bronchoalveolar lavage in the 21st century: a time-trend analysis in a clinical population. *Occupational and Environmental Medicine*, *74*(1), 59–65. https://doi.org/10.1136/OEMED-2016-103710

Ochmann, U., Kotschy-Lang, N., Raab, W., Kellberger, J., Nowak, D., & Jrres, R. A. (2012). Long-term efficacy of pulmonary rehabilitation in patients with occupational respiratory diseases. *Respiration*, *84*(5), 396–405. https://doi.org/10.1159/000337271

Oksa, P., Huuskonen, M. S., Järvisalo, J., Klockars, M., Zitting, A., Suoranta, H., Tossavainen, A., Vattulainen, K., & Laippala, P. (1998). Follow-up of asbestosis patients and predictors for radiographic progression. *International Archives of Occupational and Environmental Health*, *71*(7), 465–471. https://doi.org/10.1007/S004200050307

Oksa, P., & Nynäs, P. (2019). Asbesti. In K. Karvala, T. Leino, P. Oksa, T. Santonen, M. Sainio, J. Latvala, & J. Uitti (Eds.), *Altistelähtöinen työterveysseuranta* (1st ed., pp. 2010–2013). Duodecim.

Oksa, P., Pukkala, E., Karjalainen, A., Ojajärvi, A., & Huuskonen, M. S. (1997). Cancer incidence and mortality among Finnish asbestos sprayers and in asbestosis and silicosis patients. *American Journal of Industrial Medicine*, *31*(6), 693–698. https://doi.org/10.1002/(SICI)1097-0274(199706)31:6<693::AID-AJIM4>3.0.CO;2-S

Oliver, T. (1927). Clinical aspects of pulmonary asbestosis. *British Medical Journal*, *2*(3491), 1026–1027. https://doi.org/10.1136/BMJ.2.3491.1026

Padyukov, L., Silva, C., Stolt, P., Alfredsson, L., & Klareskog, L. (2004). A gene-environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis. *Arthritis & Rheumatism*, *50*(10), 3085–3092. https://doi.org/10.1002/art.20553

Paris, C., Benichou, J., Raffaelli, C., Genevois, A., Fournier, L., Menard, G., Broessel, N., Ameille, J., Brochard, P., Gillon, J. C., Gislard, A., & Letourneux, M. (2004). Factors associated with early-stage pulmonary fibrosis as determined by high-resolution computed tomography among persons occupationally exposed to asbestos. *Scandinavian Journal of Work, Environment & Health*, *30*(3), 206–214. https://doi.org/10.5271/SJWEH.781

Park, J. H., Kim, D. S., Park, I. N., Jang, S. J., Kitaichi, M., Nicholson, A. G., & Colby, T. v. (2007). Prognosis of fibrotic interstitial pneumonia: idiopathic versus collagen vascular disease-related subtypes. *American Journal of Respiratory and Critical Care Medicine*, *175*(7), 705–711. https://doi.org/10.1164/RCCM.200607-912OC

Partanen, R., Hemminki, K., Koskinen, H., Luo, J. C., Carney, W. P., & Brandt-Rauf, P. W. (1994). The detection of increased amounts of the extracellular domain of the epidermal growth factor receptor in serum during carcinogenesis in asbestosis patients. *Journal of Occupational Medicine*, *36*(12), 1324–1328. https://doi.org/10.1097/00043764-199412000-00013

Partanen, R., Koskinen, H., & Hemminki, K. (1995a). Tumour necrosis factor-alpha (TNF-alpha) in patients who have asbestosis and develop cancer. *Occupational and Environmental Medicine*, *52*(5), 316–319. https://doi.org/10.1136/OEM.52.5.316

Partanen, R., Koskinen, H., Oksa, P., Hemminki, K., Carney, W., Smith, S., & Brandt-Rauf, P. (1995b). Serum oncoproteins in asbestosis patients. *Clinical Chemistry*, *41*(12), 1844–1847. https://doi.org/10.1093/clinchem/41.12.1844

Pitkäniemi, J., Malila, N., Tanskanen, T., Degerlund, H., Heikkinen, S., & Seppä, K. (2022). Cancer in Finland 2020. In *Cancer Society of Finland*.

Raghu, G., Amatto, V. C., Behr, J., & Stowasser, S. (2015). Comorbidities in idiopathic pulmonary fibrosis patients: a systematic literature review. *The European Respiratory Journal*, *46*(4), 1113–1130. https://doi.org/10.1183/13993003.02316-2014

Raghu, G., Collard, H. R., Egan, J. J., Martinez, F. J., Behr, J., Brown, K. K., Colby, T. V., Cordier, J. F., Flaherty, K. R., Lasky, J. A., Lynch, D. A., Ryu, J. H., Swigris, J. J., Wells, A. U., Ancochea, J., Bouros, D., Carvalho, C., Costabel, U., Ebina, M., … Schünemann, H. J. (2011). An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *American Journal of Respiratory and Critical Care Medicine*, *183*(6), 824. https://doi.org/10.1164/RCCM.2009-040GL

Raghu, G., Remy-Jardin, M., Richeldi, L., Thomson, C. C., Antoniou, K. M., Bissell, B. D., Bouros, D., Buendia-Roldan, I., Caro, F., Crestani, B., Ewing, T., Ghazipura, M., Herman, D. D., Ho, L., Hon, S. M., Hossain, T., Inoue, Y., Johkoh, T., Jones, S., … Wilson, K. C. (2022). Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. *American Journal of Respiratory and Critical Care Medicine*, *205*(9), E18–E47. https://doi.org/10.1164/RCCM.202202-0399ST

Reid, A., de Klerk, N., Ambrosini, G. L., Olsen, N., Pang, S. C., Berry, G., & Musk, A. W. (2005). The effect of asbestosis on lung cancer risk beyond the dose related effect of asbestos alone. *Occupational and Environmental Medicine*, *62*(12), 885–889. https://doi.org/10.1136/OEM.2005.020834

Reynolds, C. J., Sisodia, R., Barber, C., Moffatt, M., Minelli, C., De Matteis, S., Cherrie, J. W., Newman Taylor, A., & Cullinan, P. (2023). What role for asbestos in idiopathic pulmonary fibrosis? Findings from the IPF job exposures case-control study. *Occupational and Environmental Medicine*, *80*(2), 97–103. https://doi.org/10.1136/OEMED-2022-108404

Richeldi, L., du Bois, R. M., Raghu, G., Azuma, A., Brown, K. K., Costabel, U., Cottin, V., Flaherty, K. R., Hansell, D. M., Inoue, Y., Kim, D. S., Kolb, M., Nicholson, A. G., Noble, P. W., Selman, M., Taniguchi, H., Brun, M., le Maulf, F., Girard, M., … Collard, H. R. (2014). Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *The New England Journal of Medicine*, *370*(22), 2071–2082. https://doi.org/10.1056/NEJMOA1402584

Robinson, B. W. S., Rose, A. H., Thompson, P. J., & Hey, A. (1987). Comparison of bronchoalveolar lavage helper/suppressor T-cell ratios in sarcoidosis versus other interstitial lung diseases. *Australian and New Zealand Journal of Medicine*, *17*(1), 9–15. https://doi.org/10.1111/J.1445-5994.1987.TB05041.X

Robledo, R., & Mossman, B. (1999). Cellular and molecular mechanisms of asbestos-induced fibrosis. *Journal of Cellular Physiology*, *180*(2), 158–166. https://doi.org/10.1002/(SICI)1097-4652(199908)180:2<158::AID-JCP3>3.0.CO;2-R

Roggli, V. L., Gibbs, A. R., Attanoos, R., Churg, A., Popper, H., Cagle, P., Corrin, B., Franks, T. J., Galateau-Salle, F., Galvin, J., Hasleton, P. S., Henderson, D. W., & Honma, K. (2010). Pathology of asbestosis- An update of the diagnostic criteria: Report of the asbestosis committee of the college of american pathologists and pulmonary pathology society. *Archives of Pathology & Laboratory Medicine*, *134*(3), 462–480. https://doi.org/10.5858/134.3.462

Rom, W. N. (1992). Accelerated loss of lung function and alveolitis in a longitudinal study of non-smoking individuals with occupational exposure to asbestos. *American Journal of Industrial Medicine*, *21*(6), 835–844. https://doi.org/10.1002/AJIM.4700210606

Rom, W. N., Bitterman, P. B., Rennard, S. I., Cantin, A., & Crystal, R. G. (1987). Characterization of the lower respiratory tract inflammation of nonsmoking individuals with interstitial lung disease associated with chronic inhalation of inorganic dusts. *The American Review of Respiratory Disease*, *136*(6), 1429–1434. https://doi.org/10.1164/AJRCCM/136.6.1429

Ryerson, C. J., O'Connor, D., Dunne, J. v., Schooley, F., Hague, C. J., Murphy, D., Leipsic, J., & Wilcox, P. G. (2015). Predicting mortality in systemic sclerosis-associated interstitial lung disease using risk prediction models derived from idiopathic pulmonary fibrosis. *Chest*, *148*(5), 1268–1275. https://doi.org/10.1378/CHEST.15-0003

Ryerson, C. J., Vittinghoff, E., Ley, B., Lee, J. S., Mooney, J. J., Jones, K. D., Elicker, B. M., Wolters, P. J., Koth, L. L., King, T. E., & Collard, H. R. (2014). Predicting survival across chronic interstitial lung disease: the ILD-GAP model. *Chest*, *145*(4), 723–728. https://doi.org/10.1378/CHEST.13-1474

Ryu, Y. J., Chung, M. P., Han, J., Kim, T. S., Lee, K. S., Chun, E. M., Kyung, S. Y., Jeong, S. H., Colby, T. v., Kim, H., & Kwon, O. J. (2007). Bronchoalveolar lavage in fibrotic idiopathic interstitial pneumonias. *Respiratory Medicine*, *101*(3), 655–660. https://doi.org/10.1016/J.RMED.2006.06.003

Salo, S. A. S., Ilonen, I., Laaksonen, S., Myllärniemi, M., Salo, J. A., & Rantanen, T. (2017). Epidemiology of malignant peritoneal mesothelioma: A population-based study. *Cancer Epidemiology*, *51*, 81–86. https://doi.org/10.1016/J.CANEP.2017.10.008

Salonen, J., Lampela, H., Keskitalo, E., Vähänikkilä, H., Purokivi, M., & Kaarteenaho, R. (2020a). Bronchoalveolar lavage differential cell count on prognostic assessment of patients with stable or acute interstitial lung disease: A retrospective real-life study. *Clinical Immunology*, *220*, 108594. https://doi.org/10.1016/J.CLIM.2020.108594

Salonen, J., Purokivi, M., Bloigu, R., & Kaarteenaho, R. (2020b). Prognosis and causes of death of patients with acute exacerbation of fibrosing interstitial lung diseases. *BMJ Open Respiratory Research*, *7*(1), e000563. https://doi.org/10.1136/BMJRESP-2020-000563

Salonen, J., Vähänikkilä, H., Purokivi, M., & Kaarteenaho, R. (2020c). Causes of acute respiratory hospitalizations predict survival in fibrosing interstitial lung diseases. *PloS One*, *15*(11), e0242860. https://doi.org/10.1371/JOURNAL.PONE.0242860

Sander, O. A. (1955). Silicosis and asbestosis: diagnosis, prevention and treatment. *American Journal of Surgery*, *90*(1), 115–119. https://doi.org/10.1016/0002-9610(55)90665-6

Schaal, M., Severac, F., Labani, A., Jeung, M. Y., Roy, C., & Ohana, M. (2016). Diagnostic performance of ultra-low-dose computed tomography for detecting asbestos-related pleuropulmonary diseases: prospective study in a screening setting. *PloS One*, *11*(12), e0168979. https://doi.org/10.1371/JOURNAL.PONE.0168979

Scharfman, A., Hayem, A., Davril, M., Marko, D., Hannothiaux, M., & Lafitte, J. (1989). Special neutrophil elastase inhibitory activity in BAL fluid from patients with silicosis and asbestosis. *European Respiratory Journal*, *2*(8), 751–757.

Schneider, J., Arhelger, R., & Funk, M. (2014). Spiroergometric parameters at maximal exercise testing assessed functional respiratory impairment in asbestos-induced fibrosis. *The Clinical Respiratory Journal*, *8*(2), 175–184. https://doi.org/10.1111/CRJ.12055

Schwartz, D. A., Fuortes, L. J., Galvin, J. R., Burmeister, L. F., Schmidt, L. E., Leistikow, B. N., Lamarte, F. P., & Merchant, J. A. (1990). Asbestos-induced pleural fibrosis and impaired lung function. *The American Review of Respiratory Disease*, *141*(2), 321–326. https://doi.org/10.1164/AJRCCM/141.2.321

Schwartz, D. A., Galvin, J. R., Merchant, R. K., Dayton, C. S., Burmeister, L. F., Merchant, J. A., & Hunninghake, G. W. (1992). Influence of cigarette smoking on bronchoalveolar lavage cellularity in asbestos-induced lung disease. *The American Review of Respiratory Disease*, *145*(2 Pt 1), 400–405. https://doi.org/10.1164/AJRCCM/145.2_PT_1.400

Sebastien, P., Armstrong, B., Monchaux, G., & Bignon, J. (1988). Asbestos bodies in bronchoalveolar lavage fluid and in lung parenchyma. *The American Review of Respiratory Disease*, *137*(1), 75–78. https://doi.org/10.1164/AJRCCM/137.1.75

Shi, P., Xing, X., Xi, S., Jing, H., Yuan, J., Fu, Z., & Zhao, H. (2020). Trends in global, regional and national incidence of pneumoconiosis caused by different aetiologies: an analysis from the Global Burden of Disease Study 2017. *Occupational and Environmental Medicine*, *77*(6), 407–414. https://doi.org/10.1136/OEMED-2019-106321

Shirai, F., Kudoh, S., Shibuya, A., Sada, K., & Mikami, R. (1981). Crackles in asbestos workers: auscultation and lung sound analysis. *British Journal of Diseases of the Chest*, *75*(4), 386–396. https://doi.org/10.1016/0007-0971(81)90026-7

Solomon, J. J., Chung, J. H., Cosgrove, G. P., Demoruelle, M. K., Fernandez-Perez, E. R., Fischer, A., Frankel, S. K., Hobbs, S. B., Huie, T. J., Ketzer, J., Mannina, A., Olson, A. L., Russell, G., Tsuchiya, Y., Yunt, Z. X., Zelarney, P. T., Brown, K. K., & Swigris, J. J. (2016). Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. *The European Respiratory Journal*, *47*(2), 588–596. https://doi.org/10.1183/13993003.00357-2015

Song, M. J., Kim, S. Y., Park, M. S., Kang, M. J., Lee, S. H., & Park, S. C. (2021). A nationwide population-based study of incidence and mortality of lung cancer in idiopathic pulmonary fibrosis. *Scientific Reports*, *11*(1), 2596. https://doi.org/10.1038/S41598-021-82182-8

Staples, C. A., Gamsu, G., Ray, C. S., & Webb, W. R. (1989). High resolution computed tomography and lung function in asbestos-exposed workers with normal chest radiographs. *The American Review of Respiratory Disease*, *139*(6), 1502–1508. https://doi.org/10.1164/AJRCCM/139.6.1502

Statistics Finland. (n.d.). *Official Statistics of Finland (OSF): Causes of death*. Retrieved April 24, 2023, from https://stat.fi/en/statistics/ksyyt

Stayner, L., Welch, L. S., & Lemen, R. (2013). The worldwide pandemic of asbestos-related diseases. *Annual Review of Public Health*, *34*, 205–216. https://doi.org/10.1146/ANNUREV-PUBLHEALTH-031811-124704

Straif, K., Benbrahim-Tallaa, L., Baan, R., Grosse, Y., Secretan, B., el Ghissassi, F., Bouvard, V., Guha, N., Freeman, C., Galichet, L., & Cogliano, V. (2009). A review of human carcinogens—Part C: metals, arsenic, dusts, and fibres. *The Lancet Oncology*, *10*(5), 453–454. https://doi.org/10.1016/S1470-2045(09)70134-2

Suganuma, N., Kusaka, Y., Hering, K. G., Vehmas, T., Kraus, T., Arakawa, H., Parker, J. E., Kivisaari, L., Letourneux, M., Gevenois, P. A., Tuengerthal, S., Crane, M. D., Shida, H., Akira, M., Henry, D. A., Nakajima, Y., Hiraga, Y., Itoh, H., & Hosoda, Y. (2009). Reliability of the proposed international classification of high-resolution computed tomography for occupational and environmental respiratory diseases. *Journal of Occupational Health*, *51*(3), 210–222. https://doi.org/10.1539/JOH.L8030

Suojalehto, H., Wolff, H., Nynäs, P., Frilander, H., Oksa, P., Lindström, I., & Vehmas, T. (2019). Asbestos-related diseases are still relevant. *Duodecim*, *135*, 933–973.

Suoranta, H., Huuskonen, M. S., Zitting, A., & Juntunen, J. (1982). Radiographic progression of asbestosis. *American Journal of Industrial Medicine*, *3*(1), 67–74. https://doi.org/10.1002/AJIM.4700030109

Szeszenia-Dąbrowska, N., Wilczyńska, U., Szymczak, W., & Strzelecka, A. (2002). Mortality study of workers compensated for asbestosis in Poland, 1970-1997. *International Journal of Occupational Medicine and Environmental Health*, *15*(3), 267–278.

Tabuena, R. P., Nagai, S., Tsutsumi, T., Handa, T., Minoru, T., Mikuniya, T., Shigematsu, M., Hamada, K., Izumi, T., & Mishima, M. (2005). Cell profiles of bronchoalveolar lavage fluid as prognosticators of idiopathic pulmonary fibrosis/usual interstitial pneumonia among Japanese Patients. *Respiration*, *72*(5), 490–498. https://doi.org/10.1159/000087673

Terra-Filho, M., Bagatin, E., Nery, L. E., Nápolis, L. M., Neder, J. A., De Meirelles, G. S. P., Silva, C. I., & Muller, N. L. (2015). Screening of miners and millers at decreasing levels of asbestos exposure: comparison of chest radiography and thin-section computed tomography. *PloS One*, *10*(3), e0118585. https://doi.org/10.1371/JOURNAL.PONE.0118585

Teschler, H., Friedrichs, K. H., Hoheisel, G. B., Wick, G., Soltner, U., Thompson, A. B., Konietzko, N., & Costabel, U. (1994). Asbestos fibers in bronchoalveolar lavage and lung tissue of former asbestos workers. *American Journal of Respiratory and Critical Care Medicine*, *149*(3 Pt 1), 641–645. https://doi.org/10.1164/AJRCCM.149.3.8118631

The nintedanib in progressive pneumoconiosis study (NiPPS): a collaborative NSW treatment trial. (2019, November 13). ClinicalTrials.Gov. https://clinicaltrials.gov/ct2/show/NCT04161014

The Social Insurance Institution of Finland (Kela). (n.d.). *356 Nintedanibi ja pirfenidoni*. Retrieved January 19, 2023, from https://www.kela.fi/laake356

Thomeer, M. J., Vansteenkiste, J., Verbeken, E. K., & Demedts, M. (2004). Interstitial lung diseases: characteristics at diagnosis and mortality risk assessment. *Respiratory Medicine*, *98*(6), 567–573. https://doi.org/10.1016/J.RMED.2003.10.015

Tossavainen, A. (1997). Asbestos, asbestosis, and cancer: the Helsinki criteria for diagnosis and attribution. *Scandinavian Journal of Work, Environment & Health*, *23*(4), 311–316. https://doi.org/10.5271/sjweh.226

Ueno, F., Kitaguchi, Y., Shiina, T., Asaka, S., Miura, K., Yasuo, M., Wada, Y., Yoshizawa, A., & Hanaoka, M. (2017). The preoperative composite physiologic index may predict mortality in lung cancer patients with combined pulmonary fibrosis and emphysema. *Respiration*, *94*(2), 198–206. https://doi.org/10.1159/000477587

Uibu, T., Oksa, P., Auvinen, A., Honkanen, E., Metsärinne, K., Saha, H., Uitti, J., & Roto, P. (2004). Asbestos exposure as a risk factor for retroperitoneal fibrosis. *Lancet*, *363*(9419), 1422–1426. https://doi.org/10.1016/S0140-6736(04)16100-X

United States Geological Survey. (2022). Asbestos. In *Mineral Commodity Summaries*. https://www.usgs.gov/centers/national-minerals-information-center/asbestos-statistics-and-information

Veeraraghavan, S., Latsi, P. I., Wells, A. U., Pantelidis, P., Pantelidis, P., Nicholson, A. G., Colby, T. v., Haslam, P. L., Renzoni, E. A., & du Bois, R. M. (2003). BAL findings in idiopathic nonspecific interstitial pneumonia and usual interstitial pneumonia. *European Respiratory Journal*, *22*(2), 239–244. https://doi.org/10.1183/09031936.03.00105202

Vehmas, T., Pallasaho, P., & Oksa, P. (2012). Lung and pleural fibrosis in asbestos-exposed workers: a risk factor for pneumonia mortality. *Epidemiology and Infection*, *140*(11), 1987–1992. https://doi.org/10.1017/S0950268811002810

Vierikko, T., Järvenpää, R., Toivio, P., Uitti, J., Oksa, P., Lindholm, T., & Vehmas, T. (2010). Clinical and HRCT screening of heavily asbestos-exposed workers. *International Archives of Occupational and Environmental Health*, *83*(1), 47–54. https://doi.org/10.1007/S00420-009-0462-1

Viljanen, A. A., Halttunen, P. K., Kreus, K. E., & Viljanen, B. C. (1982a). Spirometric studies in non-smoking, healthy adults. *Scandinavian Journal of Clinical and Laboratory Investigation. Supplementum*, *159*, 5–20.

Viljanen, A. A., Viljanen, B. C., Halttunen, P. K., & Kreus, K. E. (1982b). Pulmonary diffusing capacity and volumes in healthy adults measured with the single breath technique. *Scandinavian Journal of Clinical and Laboratory Investigation. Supplementum*, *159*, 21–34.

Virta, R. L. (2006). *Worldwide asbestos supply and consumption trends from 1900 through 2003*.

Wagner, J. C., Moncrieff, C. B., Coles, R., Griffiths, D. M., & Munday, D. E. (1986). Correlation between fibre content of the lungs and disease in naval dockyard workers. *British Journal of Industrial Medicine*, *43*(6), 391–395. https://doi.org/10.1136/OEM.43.6.391

Wälscher, J., Gross, B., Morisset, J., Johannson, K. A., Vasakova, M., Bruhwyler, J., & Kreuter, M. (2020). Comorbidities and survival in patients with chronic hypersensitivity pneumonitis. *Respiratory Research*, *21*(1), 12. https://doi.org/10.1186/S12931-020-1283-8

Walters, G., Agarwal, S., Singh, K., Burge, P. S., & McGrath, E. E. (2013). Bronchoalveolar neutrophilia inversely correlates with DLCO at diagnosis in asbestosis but not lung function decline at 1 year. *Journal of Thoracic Disease*, *5*(3), 314–316. https://doi.org/10.3978/J.ISSN.2072-1439.2013.04.18

Walters, G., Robertson, A. S., Bhomra, P. S., & Burge, P. S. (2018). Asbestosis is prevalent in a variety of construction industry trades. *NPJ Primary Care Respiratory Medicine*, *28*(1), 11. https://doi.org/10.1038/S41533-018-0078-6

Wang, X., Wang, M., Qiu, H., Yu, I., & Yano, E. (2010). Longitudinal changes in pulmonary function of asbestos workers. *Journal of Occupational Health*, *52*(5), 272–277. https://doi.org/10.1539/JOH.L10062

Wang, X., Yano, E., Wang, Z., Wang, M., & Christiani, D. C. (2006). Adverse effects of asbestos exposure and smoking on lung function. *American Journal of Industrial Medicine*, *49*(5), 337–342. https://doi.org/10.1002/AJIM.20293

Wegelius, C. (1947). Changes in the lungs in 126 cases of asbestosis observed in Finland. *Acta Radiologica*, *28*(2), 139–152. https://doi.org/10.3109/00016924709135221

Wells, A. U., Desai, S. R., Rubens, M. B., Goh, N. S. L., Cramer, D., Nicholson, A. G., Colby, T. V, du Bois, R. M., & Hansell, D. M. (2003). Idiopathic pulmonary fibrosis: a composite physiologic index derived from disease extent observed by computed tomography. *American Journal of Respiratory and Critical Care Medicine*, *167*(7), 962–969.

Wijsenbeek, M., Suzuki, A., & Maher, T. M. (2022). Interstitial lung diseases. *The Lancet*, *400*(10354), 769–786. https://doi.org/10.1016/S0140-6736(22)01052-2

Wolff, H., Vehmas, T., Oksa, P., Rantanen, J., & Vainio, H. (2015). Asbestos, asbestosis, and cancer, the Helsinki criteria for diagnosis and attribution 2014: recommendations. *Scandinavian Journal of Work, Environment & Health*, *41*(1), 5–15. https://doi.org/10.5271/sjweh.3462

World Health Organization. (2014). *Elimination of asbestos-related diseases*. https://www.who.int/publications/i/item/WHO-FWC-PHE-EPE-14.01

Xaubet, A., Rodriguez-Roisin, R., Bombi, J. A., Marín, A., Roca, J., & Agustí-Vidal, A. (1986). Correlation of bronchoalveolar lavage and clinical and functional findings in asbestosis. *The American Review of Respiratory Disease*, *133*(5), 848–854.

Yamamoto, S. (1997). Histopathological features of pulmonary asbestosis with particular emphasis on the comparison with those of usual interstitial pneumonia. *Osaka City Medical Journal*, *43*(2), 225–242.

Yang, M., Wang, D., Gan, S., Fan, L., Cheng, M., Yu, L., Wang, B., Li, W., Ma, J., Zhou, M., & Chen, W. (2020). Increasing incidence of asbestosis worldwide, 1990-2017: results from the Global Burden of Disease study 2017. *Thorax*, *75*(9), 798–800. https://doi.org/10.1136/THORAXJNL-2020-214822

Yang, X., Yan, Y., Xue, C., Du, X., & Ye, Q. (2018). Association between increased small airway obstruction and asbestos exposure in patients with asbestosis. *The Clinical Respiratory Journal*, *12*(4), 1676–1684.

Ylioinas, P., Kropsu, P., & Oksa, P. (2012). No end in sight for asbestos-related illnesses - the case of an asbestos abatement worker. *Finnish Medical Journal*, *8*, 601–605.

Yu, M., Zhang, Y., Jiang, Z., Chen, J., Liu, L., Lou, J., & Zhang, X. (2015). Mesothelin (MSLN) methylation and soluble mesothelin-related protein levels in a Chinese asbestos-exposed population. *Environmental Health and Preventive Medicine*, *20*(5), 369–378. https://doi.org/10.1007/S12199-015-0477-Z

Zhong, F., Yano, E., Wang, Z. M., Wang, M. Z., & Lan, Y. J. (2008). Cancer mortality and asbestosis among workers in an asbestos plant in Chongqing, China. *Biomedical and Environmental Sciences*, *21*(3), 205–211. https://doi.org/10.1016/S0895-3988(08)60030-6

Zitting, A. (1995). Prevalence of radiographic small lung opacities and pleural abnormalities in a representative adult population sample. *Chest*, *107*(1), 126–131. https://doi.org/10.1378/CHEST.107.1.126

Zitting, A., Huuskonen, M. S., Alanko, K., & Mattsson, T. (1978). Radiographic and physiological findings in patients with asbestosis. *Scandinavian Journal of Work, Environment & Health*, *4*(4), 275–283. https://doi.org/10.5271/SJWEH.2698

Original publications

I Keskitalo, E., Varis, L., Bloigu, R., & Kaarteenaho, R. (2019). Bronchoalveolar cell differential count and the number of asbestos bodies correlate with survival in patients with asbestosis. *Occupational and Environmental Medicine, 76,* 765–771. https://doi.org/10.1136/oemed-2018-105606

II Keskitalo, E., Salonen, J., Vähänikkilä, H., & Kaarteenaho, R. (2021). Survival of patients with asbestosis can be assessed by risk-predicting models. *Occupational and Environmental Medicine, 78,* 516–521. https://doi.org/10.1136/oemed-2020-106819

III Keskitalo, E., Salonen, J., Nurmi, H., Vähänikkilä, H., & Kaarteenaho, R. (2023). Comorbidities and causes of death of patients with asbestosis. This is a non-final version of an article published in final form in *Journal of Occupational and Environmental Medicine, 65,* 349–353. https://doi.org/10.1097/JOM.0000000000002777

Original publications are not included in the electronic version of the dissertation.

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