TOOMAS UIBU

Retroperitoneal Fibrosis

A new asbestos-related disease

ACADEMIC DISSERTATION
To be presented, with the permission of the Faculty of Medicine of the University of Tampere, for public discussion in the Small Auditorium of Building B, Medical School of the University of Tampere, Medisiinarinkatu 3, Tampere, on June 5th, 2009, at 12 o’clock.

UNIVERSITY OF TAMPERE
To my family
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<tr>
<td>AB</td>
<td>asbestos body</td>
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<td>ATS</td>
<td>American Thoracic Society</td>
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<td>BAL</td>
<td>broncho-alveolar lavage</td>
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<td>CI</td>
<td>confidence interval</td>
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<td>CT</td>
<td>computed tomography</td>
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<td>DNA</td>
<td>deoxyribonucleic acid</td>
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<td>DPT</td>
<td>diffuse pleural thickening</td>
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<td>f/g</td>
<td>fibres per gram of dry tissue</td>
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<td>H₂O₂</td>
<td>hydrogen peroxide</td>
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<td>HO⁻</td>
<td>hydroxyl radical</td>
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<td>HRCT</td>
<td>high-resolution computed tomography</td>
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<td>IARC</td>
<td>International Agency for Research on Cancer</td>
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<td>ICD</td>
<td>International Classification of Diseases</td>
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<tr>
<td>IL</td>
<td>interleukin</td>
</tr>
<tr>
<td>ME</td>
<td>mesenteric</td>
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<tr>
<td>NADPH</td>
<td>nicotinamide adenine dehydrogenase</td>
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<tr>
<td>NO</td>
<td>nitric oxide</td>
</tr>
<tr>
<td>O₂⁻</td>
<td>superoxide anion</td>
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<tr>
<td>·ONOO</td>
<td>peroxynitrite</td>
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<tr>
<td>OR</td>
<td>odds ratio</td>
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<tr>
<td>PA</td>
<td>para-aortic</td>
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<td>PAF</td>
<td>population attributable fraction</td>
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<td>PDGF</td>
<td>platelet-derived growth factor</td>
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<td>PET</td>
<td>positron emission tomography</td>
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<tr>
<td>RNS</td>
<td>reactive nitrogen species</td>
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<td>ROC</td>
<td>receiver operating characteristics</td>
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<td>ROS</td>
<td>reactive oxygen species</td>
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<td>RPF</td>
<td>retroperitoneal fibrosis</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>SD</td>
<td>standard deviation</td>
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<td>t</td>
<td>metric ton</td>
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<td>TEM</td>
<td>transmission electron microscopy</td>
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<tr>
<td>TNF-α</td>
<td>tumour necrosis factor α</td>
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<td>TGF-β</td>
<td>transforming growth factor β</td>
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Abstract

**Background:** Retroperitoneal fibrosis (RPF) is an uncommon fibroinflammatory disorder of the retroperitoneal space. The aetiology of RPF is unknown in most cases. Some reports in the literature have suggested an association between RPF and asbestos exposure. However, the data needed to assess the relationship between asbestos exposure and RPF have been missing.

**Aims:** To clarify the possible role of asbestos exposure in the development of RPF and to determine whether patients with RPF have other asbestos-related findings and to assess the presence of asbestos in the para-aortic (PA) and mesenteric (ME) lymph nodes in deceased subjects, who had earlier been exposed to asbestos.

**Methods:** A case-control study of 43 RPF patients treated in three university hospital districts of Finland in 1990–2001 was carried out. For every patient, five population-based matched controls were selected. Of the 215 eligible controls, 179 (83%) participated in the study. Asbestos exposure and medical history were assessed with a postal questionnaire and a personal interview. Chest high resolution-computed tomography (HRCT) was performed on 38 RPF patients and 18 asbestos-exposed controls. In a separate study, PA and ME lymph nodes and lung tissue from 17 persons who underwent medicolegal autopsy for suspicion of asbestos-related disease and from 5 controls were analysed for asbestos fibres using transmission electron microscopy.

**Results:** Asbestos exposure was strongly associated with RPF, with odds ratios of 5.5 (95% CI 1.6-18.7) for <10 fibre-years of exposure and 8.8 (95% CI 2.0-38.5) for ≥10 fibre-years of exposure. Use of ergot derivates, abdominal aortic aneurysm, and smoking for >20 pack-years were the other significant risk factors in the conditional regression analysis. Most of the asbestos-exposed RPF patients and half of the asbestos-exposed controls had bilateral pleural plaques, but only a few had lung fibrosis. RPF without asbestos exposure was not associated with pleural or lung fibrosis. The most distinctive
feature of the asbestos-exposed RPF patients was a thick diffuse pleural thickening (DPT).

High concentrations of amphibole asbestos fibres were detected in several lung tissue samples and in the respective PA and ME lymph nodes among the asbestos-exposed persons. It is evident that even low-level asbestos exposure results in the presence of asbestos fibres in the abdominal lymph nodes.

Conclusions Asbestos fibres, translocated by the lymph flow from the lungs, reach the abdominal and the retroperitoneal space and may induce both peritoneal mesothelioma and RPF. Persons with asbestos-related RPF frequently have asbestos-related pleural fibrosis that suggests a shared aetiology and similar pathogenetic mechanisms. The results show that occupational asbestos exposure seems to be one of the causal agents for RPF. For patients with work-related asbestos exposure, RPF should possibly be considered an occupational disease.
Lyhennelmä

Taustaa: Retroperitoneaalinen fibroosi (RPF) on harvinainen sairaus, jossa vatsakalvon takaiseen tilaan kehittyy tulehdutellinen sidekudosmassa. RPF:n taustalla olevat syyt ovat olleet valtaosassa tapaustilanteen tuntemattomia. Muutamissa tapausselostuksissa on epäilty asbestialtistumisen ja RPF:n yhteyttä, mutta käytettävissä olevat tiedot eivät ole olleet syy-yhteyden osoittamiseen riittäviä.


Erillisessä tutkimuksessa mitattiin keuhkokudoksen ja vatsan alueen imusolmukkeiden asbestikuitupitoisuus 17:ltä henkilöltä, joille asbestisairauden epäilyyn johdosta suoritettiin oikeuslääketieteellinen ruumiinavaus, sekä viideltä verrokkihenkilöltä.


Valtaosalla asbestialtistuneista RPF-potilaista ja puolella asbestialtistuneista verrokeista havaittiin molemminpuolisia keuhkopussin plakkeja, mutta keuhkofibroosia todettiin vain muutamilla. RPF ilman asbestialtistumista ei ollut
yhdeydessä keuhko- tai keuhkopussifibroosiin. Tunnusomainen löyös asbestialtistuneilla RPF-potilailla oli paksu viskeraalipleuran fibroosi.

Monilla asbestialtistuneilla vainajilla todettiin korkeita asbestipitoisuksia sekä retroperitoneaalisissa että mesenteriaalisissa imusolmukkeissa. Tutkimuksen perusteella jo vähäisessäkin asbestialtistumisessa voidaan havaita asbestikuituja myös vatsan alueen imusolmukkeissa.

Introduction

Retroperitoneal fibrosis (RPF), or Ormond’s disease, is a rare condition with fibrosis covering the abdominal aorta and the ureters. The inflammatory reaction may entrap the ureters and cause obstructive nephropathy. The aetiology of RPF is generally unknown, and the syndrome has been called “idiopathic”. It has been classically proposed that approximately one third of RPF cases develop as a secondary condition to aortic aneurysm, abdominal infections, or surgery and as a side effect of several drugs, especially methysergide and other ergot derivates (Graham et al. 1966, Koep and Zuidema 1977, Wagenknecht and Hardy 1978). During recent years, atherosclerotic inflammation and autoimmunity have been proposed as the leading aetiological factors behind “idiopathic” RPF (Vaglio et al. 2006).

Patients with an extensive and fibrotic process of the retroperitoneal space, achieving remission and favourable prognosis in most cases, are memorable for the treating clinicians. Although the disease is rare, over 2400 reports have thus far been published, and multiple conditions have been proposed as being associated with RPF.

Since 1991 there have been some published case reports noting the coexistence of asbestos-related pleural fibrosis and RPF (Maguire et al. 1991, Boulard et al. 1995). The hypothesis leading to the current thesis derived from clinical observations of patients with concomitant asbestos-related pleural and pulmonary fibrosis and RPF in the Finnish Institute of Occupational Health. These observations led to a hypothesis-generating case series of RPF patients (Sauni et al. 1998). The national health system and digitalized databases made it possible a larger epidemiological multicentre population-based study to be conducted, the aim of which was to evaluate the role of asbestos and other clinically suspected risk factors for RPF.

The use of asbestos in Finland peaked in 1970 and declined rapidly after 1975 (State Asbestos Committee 1989), but asbestos-related diseases have a long latency time (30- 40 years). Therefore, the incidence of asbestos-related diseases in Finland
has not yet declined. Although the fibrogenicity and carcinogenicity of asbestos is universally accepted, asbestos production and its use still continues worldwide. Therefore, the asbestos epidemic is not yet over.
1. Asbestos: mineralogy and use

Asbestos (Greek: inextinguishable) is the common name of several naturally occurring, fibrous hydrated silicate minerals. Long and thin asbestos fibres are incombustible and have great tensile strength. Because of these characteristics, asbestos has been a valuable insulation material for the textile and construction industries, as well as for various metal industries. The six major types of asbestos minerals have been divided into the following two groups: serpentine, having a layered silicate structure, and amphibole, having an SiO\textsubscript{4} chain structure. Chrysotile (white asbestos) is the only member of the serpentine group. Chrysotile is a sheet silicate that curls into a thin rolled sheet that forms tiny tubes with an approximate diameter of 20 nm. The sheets are held together by magnesium-silica links that break down in an acid environment. There are five double-chain stick-shaped silicates in the amphibole group: riebeckite asbestos (crocidolite), cummingtonite-grunerite asbestos (amosite), anthophyllite asbestos, tremolite asbestos, and actinolite asbestos (Leake 1978, Leake et al. 1997). Amphiboles do not dissolve as readily in an acid environment and are often considered more bioresistant than chrysotile.

Chrysotile has always been the principal commercially used asbestos in the world, and it is the only currently mined asbestos. Crocidolite and amosite have accounted for most of the remaining asbestos, but the situation has been very different in Finland, where altogether 350 000 metric tons (t) of anthophyllite were mined in 1918-1975 in Paakkila. It has been estimated that 300 000 t of asbestos were been used in Finland in 1905-1988, consisting of 175 000 t of chrysotile, 120 000 t of anthophyllite and, altogether 5000 t of crocidolite and amosite. In Finland, two thirds of asbestos were used in the construction industry. Chrysotile was used in asbestos cement products such as roofing plates and sewage pipes, and anthophyllite
was prominent in various construction products, such as plasters and insulation materials (State Asbestos Committee 1989).

It has been estimated that over 200,000 workers have been exposed to asbestos dust in Finland. The production, marketing, and use of asbestos were banned in 1994, but exposure is still possible during renovation and demolition work (Huuskonen et al. 2006).

2. Exposure rates and translocation

The deposition of airborne particles in the respiratory system is defined as the loss of particles from inhaled air. Most of the inhaled dust is deposited in the upper airways, larynx, and bronchi, and is rapidly cleared by the mucociliary apparatus (Bernstein et al. 2005).

The particles and fibres with aerodynamic diameters of up to 10 µm can pass through the large airways and end up in the lower respiratory tract, the result being long-term particle retention. For example, a 20-µm long fibre with a diameter of 1.7 µm and a density of 2.5 gm/cm³ has an aerodynamic diameter of 5 µm. Under conditions of laminar flow, rod-like fibres that are >5 µm in length align axially with the air stream. The upper level of the fibre diameter that reaches the alveolar region is approximately 3 µm (Morgan 1995). The length of asbestos fibres that reach the lower respiratory tract can be as high as 360 µm (Morgan 1980), but, in general, the proportion of alveolar deposition decreases as the fibre length increases.

Because the alveolar region of the lung is not capable of mucociliary clearance, particles retained in this region are cleared at a much slower rate. Asbestos fibres that reach terminal bronchioles and alveoli are dealt with through several mechanisms, such as dissolution and phagocytosis followed by mucociliary, lymphatic, or vascular translocation to extrapulmonary sites (Oberdorster 2002). Long and thick asbestos fibres have a tendency to be broken down by chemical and physical factors. Shorter fibres with an approximate length of 5 µm can be phagocytized by alveolar macrophages and removed by the ciliated epithelium to the proximal airways (IPCS 1998, Oberdorster 2002). Alveolar macrophages contain lysosomes with acid hydrolases capable of digesting phagocytized particles.
It has been postulated that this acidic dissolution may be more important for the clearance of mineral dust than mucociliary action is (Brain et al. 1994).

In animal studies, chrysotile fibres have not only been found to be taken up by macrophages, but also by type-I epithelial cells and fibroblasts (Brody et al. 1981). Thin asbestos fibres are capable of migrating to the interstitium, where they may be phagocytized by interstitial macrophages or transported through the lymphatics (Oberdorster et al. 1988, Morgan 1995). Morgan and his co-workers (1978) performed repeated broncho-alveolar lavage (BAL) on rats after their exposure to anthophyllite fibres. They found a steady decline in the length of the longest fibres that could be recovered by lavage. This finding suggests that such fibres were being lost preferentially to the interstitium, because long fibres were still present in adjacent lung tissue samples. The authors also concluded that short anthophyllite fibres with an approximate length of 5 µm were effectively cleared via the conducting airways. These findings have been repeated for chrysotile asbestos (Kauffer et al. 1987). The clearance of short fibres is thought to occur via phagocytosis and migration of the alveolar macrophages.

The capability of alveolar macrophages to phagocytize asbestos fibres has been extensively studied in animal models (Oberdorster 2002). According to a popular theory, long fibres are not completely engulfed by macrophages, and “frustrated phagocytosis” results in the chronic release of mediators and failed clearance. The interaction of fibres with pulmonary macrophages results in the generation of oxidants, inflammatory cytokines, and growth factors that play critical roles in fibre-induced disease (Bernstein et al. 2005). Fibres longer than 15-20 µm, which would not be easily engulfed by macrophages, were found to be the most carcinogenic in an animal model (McConnell et al. 1999, Miller et al. 1999).

The reported size of the human alveolar macrophages is between 14 and 21 µm, and the corresponding values for rats are 10.5-13 µm (Oberdorster 2002). Human macrophages are capable of engulfing 20-µm long glass fibres without increased signs of cytotoxicity. In contrast, rat macrophages exhibit both incomplete phagocytosis of long fibres and length-dependent toxicity (Zeidler-Erdely et al. 2006). Nevertheless, even short phagocytized asbestos fibres will elicit an inflammatory response in alveolar macrophages (Oberdorster 2002). The association between fibre-size parameters and the development of lung fibrosis and cancer in humans remains unproven.
Long and relatively thick asbestos fibres retained in human lungs are predisposed to becoming asbestos bodies (ABs) (Morgan et al. 1985). ABs are formed when asbestos fibres are coated by iron-rich ferroproteins, and this reaction is thought to diminish the toxicity of uncoated fibres (Ghio et al. 2004). ABs recovered in BAL and lung tissue are used to assess past asbestos exposure (Consensus report 1997).

Numerous animal studies have been carried out on the clearance of chrysotile and amphibole asbestos from lung tissue. The retention half-time for 20-µm asbestos fibres in rat lung tissue is >100 days for chrysotile and >1000 days for amphibole asbestos. These values can be compared with 6-53 days for biodegradable vitreous fibres (Oberdorster 2002). Amphiboles are often considered more bioresistant than chrysotile, and, therefore, more available for long-term relocation by lymphatic drainage and diffusion (IPCS 1998).

The relocation of asbestos fibres from the lung interstitium, especially to the extrathoracic organs, is far more obscure. It has long been postulated that a systemic dissemination of fibres occurs as macrophages migrate through the pulmonary bloodstream (Holt 1981, Holt 1983) or lymphatics (Lee et al. 1981). Both short- and long-term kinetics have been studied in animal models, but data on humans are limited in this respect. It has been shown that amphibole fibres accumulate subpleurally in alveolar macrophages (Oghiso et al. 1984). Gelzleichter and his co-workers (1999) showed that, when rats and golden hamsters undergo chronic inhalation of kaolin-based refractory ceramic fibres, fibres are present in the pleural space in one week, shorter fibres being more predominant. The fibres induce an influx of inflammatory cells into the pleural space and cause inflammatory changes in pleural mesothelial cells that are more pronounced in the parietal pleura. The intrapleural instillation of asbestos fibres resulted in the presence of asbestos fibres in lung, liver, kidney and brain, as well as in a higher concentration in the thoracic lymph nodes (Bignon et al. 1979).

Animal studies cannot, however, be directly extrapolated to humans. There are several interspecies differences. For example, rats do not form ABs and the maximal respiratory diameter of fibres and the size of alveolar macrophages in rats are clearly lower than in humans.

Knowledge of the routes of the translocation of asbestos fibres in a human body comes mainly from autopsy studies. Taskinen et al. (1973) described a patient with silicosis and macroscopically visible traces of dust in the lymphatic vessels of the
parietal pleura. They proposed that there is a retrograde transport mechanism for the fibres and particles from the mediastinal lymph nodes via the thoracic and intercostal lymphatics to the parietal pleura and the retroperitoneal space. The role of lymphatic translocation is strengthened by the finding that asbestos fibres concentrate in the pulmonary lymph nodes and result in the highest concentrations reported in the human body (Dodson et al. 1990, Tossavainen et al. 1994).

Several researches have found asbestos fibres in the pleural tissue of asbestos-exposed people (Dodson et al. 1990, Kohyama and Suzuki 1991, Gibbs et al. 1991, Suzuki and Yuen 2001). It was noted that the concentrations of asbestos fibres were usually lower in the pleural tissue than in the respective lung parenchymal samples, with a predominance of short chrysotile fibres. Boutin et al. (1996), using thoracoscopic sampling, showed that anthracotic spots located in the lower costal and diaphragmatic areas of the parietal pleura contained high concentrations of amphibole asbestos, whereas the adjacent macroscopically normal pleura did not. The findings were confirmed in a necropsic study of 150 urban dwellers that showed a predominant occurrence of “black spots” in the lower costal and diaphragmatic zones, which corresponded to the anatomic distribution of pleural lacunae but not to the distribution of pleural plaques (Mitchev et al. 2002).

ABs have been found in several extrapulmonary organs of asbestos-exposed workers. Auerbach et al. (1980) found ABs in 30-60% of their studied samples (in kidney, heart, liver, spleen, adrenal glands, and pancreas). Kobayashi et al. (1987) reported that ABs were found preferentially in the oesophagus, pancreas, and spleen, but the study results are somewhat questionable due to the inverse dose-response that was found.

The occurrence of uncoated asbestos fibres has been previously evaluated by several study groups using transmission electron microscopy (TEM). Dodson et al. (2000, 2001) has detected asbestos fibres in the omentum and mesentery of patients with mesothelioma and also in non-occupationally exposed persons. Tossavainen and his co-workers (1994) found a high concentration of asbestos fibres in the kidney tissue of a person with heavy asbestos exposure.

The route of penetration of asbestos fibres to the peritoneal space is still uncertain. It has recently been proposed that it may occur through filtration from blood capillaries or through the lymphatic stomata of the diaphragm (Miserocchi et al. 2008). There is also experimental evidence that small fractions of ingested
asbestos fibres may penetrate through the gastrointestinal tract, but its clinical importance remains unclear (Davis 1989). Extensive studies conducted by United States Department of Health and Human Services in the 1980s on animal feed produced negative results with respect to colorectal or other kinds of cancer in relation to ingested asbestos fibres (HHS 1983a, HHS 1983b, HHS 1985, HHS 1988, HHS 1990).

3. Fibrogenicity and carcinogenicity of asbestos

3.1 Fibre-induced cellular reaction

The alveolar macrophage is a pivotal cell type in asbestos-induced fibrogenesis (Oberdorster 1994). Macrophages phagocytize asbestos fibres, and this action evokes such inflammatory changes as macrophages starting to release reactive oxygen and nitrogen species, various growth factors, and cytokines. In addition, various cell types of the immune system, including neutrophils, T-lymphocytes and mast cells, accumulate in asbestos-exposed lung regions and are implicated in the development of fibrosis (Mossman and Churg 1998).

There is an active ongoing debate about whether the morphology of asbestos fibres affects carcinogenicity and fibrogenicity of the fibres. According to the Stanton hypothesis, long (≥ 8 µm), not easily phagocytable, and thin (≤ 0.25 µm) fibres have a higher toxic and carcinogenic effect than shorter and thicker fibres do (Stanton et al. 1969, Stanton et al. 1981). However, according to these and subsequent animal studies, it cannot be concluded that short asbestos fibres are harmless. In fact, an opposite possibility was recently suggested on the basis of a tissue analysis of mesothelioma patients (Suzuki et al. 2005).

An early event in fibrogenesis is the injury of alveolar type-I epithelial cells, followed by the proliferation of type-II epithelial cells in an attempt to regenerate the alveolar epithelial lining and the activation of fibroblasts (BeruBe et al. 1996). Later, significant increases occur in lung hydroxyproline, an indicator of increased collagen biosynthesis and histopathology confirmative of pulmonary fibrosis.

Fibroblasts are the key cells in fibrogenesis, producing collagen and reticulin and remodelling connective tissue. Fibroblasts also produce cytokines that amplify
fibrogenesis. The proliferation of fibroblasts and an extensive accumulation of connective tissue lead to parenchymal and pleural fibrosis (Robledo and Mossman 1999).

In carcinogenesis, long asbestos fibres have been shown to interfere with mitosis physically. In a study by Jensen et al. (1996), long asbestos fibres phagocytized by epithelial cells became trapped within the intercellular bridge during cell division, and blocked cytokinesis, resulting in binucleated daughter cells and an unequal distribution of chromosomes. Other studies have shown similar chromosomal defects also in the cell lines of human and animal mesothelioma (Kane 1996). Asbestos fibres have also been found to stimulate the proliferation of target cells through several mechanisms, including the activation of growth factor receptors and intracellular pathways and compensatory proliferation in response to cell apoptosis or necrosis (Kane 1996, Bernstein et al. 2005).

### 3.2 Oxidant mechanisms

The most important reactive metabolites in the pathogenesis of asbestos-related diseases are reactive oxygen species (ROS) such as hydrogen peroxide (H$_2$O$_2$), the superoxide anion (O$_2^-$), the hydroxyl radical (HO·), and reactive nitrogen species (Kamp et al. 1992).

Asbestos produces ROS through the use of at least two mechanisms:

1. Asbestos, which always contains iron cations, produces highly reactive HO· in cell-free systems through the Fenton reaction $\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{HO}^- + \text{HO}^·$. Thereafter Fe$^{3+}$ is reduced by superoxide or other biological reducing agents back to Fe$^{2+}$. Ferrous ion can also catalyse the production of free radicals from organic hydroperoxides (ROOH) and the formation of other highly reactive free radicals (Kamp and Weitzman 1999).

2. A second mechanism of free-radical generation occurs via an oxidative burst when fibres are phagocytized by alveolar macrophages, alveolar epithelial cells, and fibroblasts (Churg 1996).

Asbestos fibres may also directly activate ROS-producing enzyme systems such as the nicotinamide adenine dehydrogenase (NADPH) oxidase activation pathway (Kamp and Weitzman 1999).
In addition, nitric oxide (NO) production and the activity of NO-producing inducible NO synthase are found to be increased in asbestos-exposed cells (Thomas et al. 1994, Park and Aust 1998). NO is a free radical and readily reacts with reactive oxygen metabolites, leading to the formation of toxic metabolites, most importantly peroxynitrite (\(\cdot\)ONOO).

ROS and reactive nitrogen species (RNS) have been shown to attack several components of cells like critical macromolecules, such as lipid membranes, deoxyribonucleic acid (DNA), and signal transduction proteins. Asbestos causes iron-catalysed lipid peroxidation, which alters cell membranes and cell function (Kamp et al. 1992). There is also convincing evidence that asbestos causes DNA damage manifesting as altered DNA bases, single-stranded DNA formation, apoptosis, chromosome aberrations, or sister chromatid exchanges (Jaurand 1997). Asbestos mutagenicity is probably due partly to ROS and RNS, which cause multiple genotoxic effects, including single DNA-base substitutions, intra-strand linking, point mutations and large chromosome deletions (Kamp and Weitzman 1999). Oxidants can activate the nuclear transcription factor kappa-B, which is associated with the synthesis of various mediators and pro-oncogenes involved in cell proliferation and apoptosis (Blackwell and Christman 1997, Nymark et al. 2008).

Various antioxidants attenuate asbestos-related toxicity in vitro, and asbestos exposure inducts defensive antioxidant enzymes, but whether the inducibility of antioxidative enzymes protects cells or prevents carcinogenesis is still unclear (Kinnula 1999).

### 3.3 Cytokines

Some growth factors and cytokines have been implicated in clinical studies and in animal models of asbestosis, including interleukin (IL) 1, tumour necrosis factor \(\alpha\) (TNF-\(\alpha\)), transforming growth factor \(\beta\) (TGF-\(\beta\)), platelet-derived growth factor (PDGF) and IL-8. These agents amplify cellular injury and activate fibroblast proliferation and collagen deposition.
IL-1 is an important cytokine in acute and chronic inflammation in a complex network of signalling molecules. Several human and animal studies have revealed the presence of IL-1β in chronic inflamed tissues and in tissues undergoing fibrogenesis, with the accumulation of myofibroblasts and matrix deposition (Pan et al. 1996, Dinarello 1997). The intratracheal installation of IL-1β by adenoviral gene transfer was found to elicit acute alveolar and parenchymal damage with a subsequent induction of TGF-β expression and progressive interstitial fibrogenesis that resembles the histological changes seen in human pulmonary fibrosis (Kolb et al. 2001).

TNF-α is a potent proinflammatory cytokine, found in high concentrations in macrophages from patients with asbestosis (Zhang et al. 1993) and also in macrophages and type-II epithelial cells from patients with idiopathic pulmonary fibrosis (Piguet et al. 1993). Convincing proof of a central role of TNF-α was gained in a study using TNF-α receptor knockout mice, which were found to be protected against the fibrogenic effects of asbestos (Liu et al. 1998). The same strain of mice was found to be resistant also to bleomycin-induced fibrosis (Ortiz et al. 1999). The reconstitution of TGF-β1 expression was sufficient to regenerate fibroproliferative pulmonary disease (Brody et al. 2001).

PDGF is one of the most potent mesenchymal cell (predominantly myofibroblasts in fibrotic lung lesions) mitogens. It stimulates cells to progress from the G1 postmitotic phase to the G1 pre-DNA synthetic phase of the cell cycle. The treatment of fibroblasts with asbestos fibres results in the expression of the PDGF-A chain and its receptor with resultant fibroproliferation (Lasky et al. 1995, Lasky et al. 1998). Defining the role of PDGF in lung fibrogenesis is complicated because PDGF knockout mice are not viable, have a failure in alveogenesis, lack renal glomeruli, and develop bleeds (Lasky and Brody 2000).

Whereas PDGF enhances mesenchymal-cell proliferation, TGF-β1 is a potent inductor of extracellular matrix production and also an inhibitor of matrix degradation (Bienkowski and Gotkin 1995). TGF-β1 inhibits the proliferation of epithelial cells and alterations in its secretion could potentially extend the fibroproliferative phase after lung injury (Khalil et al. 1994).

The treatment of patients with idiopathic pulmonary fibrosis with interferon gamma-1b in three placebo-controlled studies showed a decreased mortality in the
active treatment arm with a hazard ratio of 0.44 (95% CI 0.25-0.69) according to a recent meta-analysis (Bajwa et al. 2005).

In conclusion, results from numerous in vitro studies have proposed a role of multiple molecules in fibrogenesis induced by noxious particles. The role of specific mediators is studied with gene deletion, transduction, and the expression of genes through the use of viral vectors and other novel gene technologies. Detecting the precise mechanisms of fibrogenesis provides us a possibility to affect asbestos-induced fibrosis, which has thus far remained untreatable.

4. Asbestos-related diseases

4.1 History and epidemiological studies

The widespread use of asbestos in the modern world started in the last decade of the 19th century. The first case of asbestosis was recorded by Dr H. Montague Murray at the Charing Cross Hospital in London in 1899. The patient had been the only survivor of 10 men who worked in the carding room of an asbestos factory. The case was presented to a committee for compensation as an industrial disease, but was not published in the mainstream medical literature (Murray 1990). Asbestos use increased enormously in the shipbuilding industry during the First World War, but, understandably, it was not considered to be an imminent danger. Asbestos production in various industries continued to increase with a second rapid rise during World War II, and it peaked in the 1970s (Murray 1990, Virta 2006).

The first case of asbestosis in the medical literature was published by the British pathologist W.E. Cooke (1924). A 33-year-old woman had worked in asbestos factories for 18 years. She was found to have an extensive bilateral lung fibrosis, bilateral pleural thickening, and concomitant tuberculosis. Both tubercle bacilli and asbestos particles were found in a microscopic examination of her the lung tissue.

The first reports of asbestos-related lung cancer were published in 1935 in Great Britain (Gloyne 1935) and the United States (Lynch and Smith 1935). The evidence concerning the carcinogenicity and fibrogenicity of asbestos dust was added piece
by piece from case reports and case series, but it took several decades to gather the epidemiological evidence (Greenberg 1999). In 1950, Sir Richard Doll and Sir Bradford Hill published an epidemiological study showing that tobacco smoke, not polluted air, is the most important risk factor for lung. In 1955, Sir Richard Doll showed a ten fold increase in the risk of lung cancer among asbestos workers of Turner Brothers Asbestos Company in a necropsy-based study (Doll 1955, Greenberg 1999). The first cases of asbestos-related mesothelioma were reported in 1943 in Germany by Wedler, but it took over 20 years before epidemiological proof of the association between mesothelioma and asbestos exposure was published (Wagner et al. 1960). Wagner and his co-workers reported a case series of 30 patients from a crocidolite mining area in South Africa, of whom 8 had asbestosis. They noted all three principal findings in association with this rare malignancy (i.e. a long, 20-40 year latency period, occasional development due to low-level environmental exposure, and a grim prognosis of the disease). The results were strengthened by the work of Selikoff, Churg and Hammond, who found a marked increase in the incidence of mesothelioma among New Jersey shipyard insulators (Selikoff et al. 1964, Selikoff et al. 1965). Using the same cohort, they later reported synergism between smoking and asbestos exposure in the development of lung cancer (Selikoff et al. 1968).

In Finland, the first case of asbestosis was diagnosed in 1938 (Ahlman and Siltanen 1971). The first published reports of asbestosis concerned the employees of the asbestos industry by Noro (1946) and Wegelius (1947). In 1960, Kiviltuo published an extensive radiological investigation on the prevalence of pleural plaques in the vicinity of asbestos mines, and it was followed by a pathoanatomical study by Meurman (1966). These reports established the causal relationship between asbestos exposure and parietal pleural plaques. As of 1967 there were no recorded cases of mesothelioma in a cohort of 1000 asbestos mine employees (Meurman et al. 1974), but four cases had developed by 1991 (Karjalainen et al. 1994a). Due to a relatively small number of exposed persons, the association between anthophyllite exposure and mesothelioma was not evident at first. Asbestos-related diseases have been under intense investigation, and many data have been acquired in the fields of risk assessment and the natural history of asbestos-related diseases. In 1997, the international criteria for the evaluation of asbestos exposure, risk estimation, and diagnosing of asbestos-related diseases were agreed upon Helsinki (Consensus
report 1997). The European Respiratory Society issued the recommendations on the
analysis of mineral fibres in tissue samples (De Vuyst et al. 1998), and the
American Thoracic Society (ATS) has published thorough recommendations on the
diagnosing and management of non-malignant asbestos-related diseases (ATS
2004).

4.2 Evaluation of exposure

In most epidemiological studies, the evaluation of asbestos exposure is based on a
careful personal history, taken by a trained specialist, usually an occupational
hygienist or an occupational physician.

Cumulative asbestos exposure is expressed in fibre-years, similar to the pack-
years used in the assessment of smoking history. A fibre-year is defined as work in a
full shift (40 hours/week) for 1 year at an average dust level of 1 fibre/cm$^3$ of air. At
the current upper limit for asbestos dust of 0.1 fibre/cm$^3$ in workplace air in the
European Union (European Parliament 2003), cumulative exposure for 10 years
without the use of personal protective equipment would be 1 fibre-year.

Asbestos exposure is calculated from data published on dust levels in specific
jobs and tasks. For example, during the dry demolition of sprayed asbestos
insulations, the mean asbestos concentration was 40 fibres/cm$^3$, but demolishing
work could be done with an exposure level of 0.8 fibres/cm$^3$ with the use of
moistening and bagging technique (Riala et al. 1989, HVBG 1996).

For both clinical and medicolegal purposes, a thorough personal history,
supported by the results of structured questionnaires and checklists, is the mainstay
of asbestos exposure evaluations. For scientific purposes or if history data are
unavailable or in other specific situations, past asbestos exposure can be assessed by
counting asbestos bodies (ABs) in BAL fluid or lung tissue, and the measurement of
mineral fibres in lung tissue is carried out with electron microscopy.

For clinical purposes, the following guidelines have been recommended for the
identification of persons with a high probability of occupational asbestos exposure
(Tossavainen 1997):

> 0.1 million amphibole fibres (>5µm)/g dry lung tissue
or > 1 million asbestos fibres (>1µm)/g dry lung tissue
or $>1000$ AB/g dry tissue (=100 AB/g wet tissue)
or $>1$ AB/ml in BAL fluid.

Nevertheless, it should be kept in mind that there is a wide individual difference in the efficiency with which fibres are coated, and this difference influences the number of ABs. Chrysotile induces AB formation clearly less than do amphiboles, and, as chrysotile tends to be cleared from the lungs much faster than the amphiboles are, these limits underestimate the exposure of persons primarily exposed to chrysotile (Tossavainen 1997, Roggli 1997). For amphibole asbestos, a good correlation between BAL ABs, lung tissue ABs, and lung tissue asbestos fibres has been found for Finnish patients (Karjalainen et al. 1996).

### 4.3 Clinical manifestations

#### 4.3.1 Asbestosis

Asbestosis is an interstitial pulmonary fibrosis caused by inhaled asbestos dust. It is clearly a dose-dependent disease. Clinically manifest asbestosis is associated with $>25$ fibre-years of asbestos exposure, which results in an asbestos ($>1$ $\mu$m) content of $>5$ million f/g dry lung tissue (Consensus report 1997). Such high-level exposure is becoming more uncommon, and, in the clinical practice, longer latency periods with less severe disease are more prevalent (ATS 2004). Asbestosis is characterized by slowly progressing interstitial fibrosis that primarily affects the subpleural and lower zones of the lung. The microscopic appearance of well-established asbestosis is similar to that of idiopathic interstitial pulmonary fibrosis, except for the presence of ABs in tissue samples. Asbestosis is usually accompanied by fibrotic changes in the respiratory bronchioles and alveolar ducts (Churg 1989, De Vuyst and Genevois 2002). The College of American Pathologists has developed commonly used histological criteria for asbestosis in clinical practice (Craighead et al. 1982).

The principal symptom of asbestosis is breathlessness. Dry cough, often induced by a deep breath, is frequent in some cases. Inspiratory dry rales are present in most patients with asbestosis, and their absence strongly speaks against asbestosis (Ross
The lung sounds of asbestos-related diseases reflect radiological abnormalities (Piirilä et al. 2000). The characteristic change in pulmonary function observed in asbestosis is restrictive impairment and decreased diffusing capacity.

In chest X-rays, asbestosis is characterized by irregular small opacities that are predominant in the lower lung fields. In the grading of the International Labor Organization, which has been developed for the epidemiological purposes, 1/0 can be considered the level where an early pulmonary fibrosis can be suspected (Consensus report 1997, ATS 2004). HRCT is much more sensitive and specific than chest radiography in the evaluation of diffuse interstitial lung diseases including asbestosis (Padley et al. 1991). Asbestosis is associated with the following typical findings in HRCT: septal lines, intralobular lines, subpleural curvilinear lines, and honeycombing (Akira 2002). However, HRCT findings are not 100% specific to asbestosis, nor are they sensitive, since patients with histopathologically proven asbestosis may have normal HRCT scans (De Vuyst and Genevois 2002).

In Finland, HRCT consensus criteria for a diagnosing of asbestosis have been established (Huuskonen et al. 2001).

It has recently been shown that persons with asbestosis have higher rates of alveolar exhaled NO and high levels of leukotriene B4 and 8-isoprostane in exhaled breath than do healthy controls (Lehtonen et al. 2007). The role of serial NO measurements with respect to persons with asbestosis and other interstitial lung fibrosis needs to be established.

An ongoing debate is in progress about whether asbestosis is independently associated with an increased risk of lung cancer. Although the incidence of lung cancer is strongly increased among asbestosis patients, it seems probable that asbestos fibres per se cause lung cancer, which can develop with or without the presence of asbestosis (Reid et al. 2005).

### 4.3.2 Pleural plaques

Pleural plaques are considered to be an indicator of past asbestos exposure. They are discrete areas on the parietal pleura that consist microscopically of fibro-hyaline connective tissue with very few cells, and they are covered by a single layer of
normal mesothelial cells on the pleural surface. Pleural plaques are frequently bilateral, but not symmetric, and they occur particularly on the posterolateral chest wall and on the dome of the diaphragm (Chapman et al. 2003). The presence of pleural plaques is closely related to earlier exposure to asbestos. It has been estimated that 80-90% of radiologically evident pleural plaques are due to occupational exposure (Hillerdal 1994). Pleural plaques generally appear after 30 years of exposure and tend to progress and calcify from their centres with time. It is evident that, although there is a positive dose-response, pleural plaques can be induced even by short and low-level asbestos exposure (Consensus report 1997).

Pleural plaques seem to be associated with amphibole rather than chrysotile asbestos exposure, anthophyllite probably being the most potent fibre type (Rudd 1996).

The mechanisms behind the development of pleural plaques are still obscure. In 1980, Hillerdal reviewed the existing theories, consisting of mechanical irritation caused by asbestos fibres, bleeding from the visceral pleura, and the like. He proposed that asbestos fibres reach the pleural space along with the lymph, just as the other of inhaled and retained dust does. Short asbestos fibres can penetrate the visceral pleura and follow the normal lymph flow through the lacunae of the parietal pleura, where some of them remain and activate pleural phagocytic cells. This theory is partly supported by the findings of asbestos-containing black spots in the parietal pleura, but, on the other hand, the distribution of black spots differs from the distribution of pleural plaques (Boutin et al. 1996, Mitchev et al. 2002).

Pleural plaques form the commonest asbestos-related disease. In a large population-based study representing the Finnish adult population, the age-adjusted prevalence of bilateral pleural plaques was 7.0% for men and 1.9% for women. There was a clear difference between urban and rural men, 7.7% versus 4.3%, respectively (Zitting 1995). Among Finnish asbestos-exposed industrial workers, the prevalence of bilateral plaques was 17% (Koskinen et al. 1998). However, thoracic X-rays are a relatively insensitive tool, especially in the detection of costal and uncalcified pleural plaques. The prevalence of pleural plaques has been substantially higher in autopsy or computed tomography (CT) studies. Karjalainen et al. (1994b) found that 58% of 300 urban adult males had bilateral pleural plaques, and similar results have been published using CT scanning (Tiitola et al. 2002).

Pleural plaques do not cause pleural adhesions, and they are not associated with clinically significant impairment in lung function unless they are massive (ATS
The presence of bilateral pleural plaques has been interpreted as a marker of an elevated risk of malignancy (Hillerdal 1994, Hillerdal and Henderson 1997), and the follow-up of occupationally exposed groups may be justified (Consensus report 1997). In Finland, bilateral pleural plaques in association with occupational asbestos exposure are classified as an occupational disease, but the radiological follow-up of persons with <10 fibre-years of asbestos exposure is not recommended (Nordman et al. 2007).

4.3.3 Pleural effusion

Pleural effusion is traditionally considered as the earliest indication of asbestos exposure. It can manifest with a <10 years of latency time (Lilis et al. 1988). However, in his studies, Hillerdal (1987) found a mean latency time of 30 years. Benign asbestos-related pleural effusion is strictly a diagnosis of exclusion. The effusion is usually small and may recur. According to current views, diffuse pleural thickening (DPT) is preceded by either silent or symptomatic pleural effusion (Lilis et al. 1988, Chapman et al. 2003).

4.3.4 Diffuse pleural thickening

Diffuse pleural thickening (DPT) is a type of pleural fibrosis that extends continuously over the thoracic cavity. There are adhesions between visceral and parietal pleurae and blunting of the costophrenic angle in most cases. DPT is thought to be a consequence of acute asbestos-related pleurisy (McLoud et al. 1985, Lilis et al. 1988). However, DPT is not specific to asbestos exposure and may also result from other inflammatory conditions, such as infections, trauma, surgery, and drug reactions (e.g., to ergot derivates) (Pfitzenmeyer et al. 1996). DPT is a relatively common finding. In the Mini-Finland population, the prevalence of costophrenic adhesions or other signs of DPT was 14.2 for men and 5.9 for women, DPT being slightly commoner than bilateral pleural plaques (Zitting 1995). The prevalence of DPT (13.5%) and pleural plaques (16.5%) among asbestos-exposed
workers were higher than in the general adult population in the study of McLoud et al. (1985).

Crocidolite-related DPT has been shown to progress in the first 15 years after its diagnosis (de Klerk et al. 1989). DPT, unlike parietal pleural plaques, causes significant restrictive impairment of lung function (Yates et al. 1996, Kee et al. 1996, Piirilä et al. 2008). The restriction is primarily caused by adhesions in the costophrenic sulcus that limit the inspiratory movement of the diaphragm and the rib cage (Singh et al. 1999). The pattern of “entrapped lung” is associated with the relative preservation of diffusion capacity (ATS 2004).

The latency time for DPT is typically >20 years from the beginning of asbestos exposure, although benign asbestos pleurisy can occur earlier (Lilis et al. 1988). This timeframe is somewhat less than for pleural plaques, asbestosis and mesothelioma. DPT can be induced by moderate asbestos exposure, and the amount of exposure required for the development of DPT is probably higher than for parietal pleural plaques (Rudd 1996). In thoracic HRCT, DPT appears as a smooth, uninterrupted density with ill-defined margins that extend across more than one fourth of the pleural surface. Parenchymal bands extending from a pleural thickening to the lung parenchyma, rounded atelectasis, and the involvement of interlobar fissures can be used to differentiate DPT from pleural plaques. These signs are not considered in the diagnosing and grading of asbestososis. Rounded atelectasis, a “Belkovsky’s sign”, often accompanies marked DPT. Radiologically, it is defined as a round or oval mass that abuts the pleural surface and is associated with the curving of pulmonary vessels or bronchi into the edge of the lesion (Akira 2002). In positron emission tomography (PET), DPT has been shown to have a lower glucose avidity than pleural mesothelioma (Benard et al. 1998).

4.3.5 Malignant mesothelioma

Malignant mesothelioma is a rare malignancy closely related to asbestos exposure. Asbestos is thus far the only aetiological factor that has been shown to cause mesothelioma, and therefore the incidence of the disease reflects a past use of asbestos. It is widely accepted that >80% of mesothelioma patients have had some occupational asbestos exposure, and very low asbestos exposure may induce
mesothelioma (Consensus report 1997). Only the minority of mesothelioma patients (approximately 20%) have histological evidence of asbestosis (Roggli 2006). More than 90% of malignant mesotheliomas occur in the pleura, with a right-to-left ratio of about 1.5 to 1 (Henderson 1997). The rest occur in the peritoneum and, occasionally, other sites like the pericardium and tunica vaginalis of the testicles. Malignant mesothelioma has been subdivided into the following three major histological types: epithelial (~60%), biphasic (~30%) and sarcomatoid (~10%). Each type is usually an outcome of past asbestos exposure (Henderson 1997). In an extensive mesothelioma cohort in Germany, only 4.3% of the studied persons had no detectable ABs in their lung samples, and, on the other hand, 84.8% (n=1361) of those studied had more than 22 ABs/cm$^3$ of lung tissue (Neumann et al. 2001).

The highest mortality rates for mesothelioma are found in Australia, the Netherlands, and Great Britain, exceeding 25 deaths per million per year in a male population (Nishikawa et al. 2008). According to current opinion, amphibole asbestos, especially crocidolite and amosite, are the most potent inducers of mesothelioma (BTS 2001, Britton 2002). Nevertheless, chrysotile asbestos also poses some increased risk of mesothelioma in a dose-dependent manner (IPCS 1998). There is no evidence that mesothelioma can be caused by fibreglass or other man-made fibres, smoking, or intrapleural talc (BTS 2001).

Mesothelioma remains a universally fatal disease with a median survival time of 9-12 months. Surgical treatment is rarely an option, either because of the advanced stage of the disease or the high cardiopulmonary performance requirements for the extrapleural pneumectomy (Robinson et al. 2005). In light of recent randomized controlled trials, cisplatin, combined with either pemetrexed or gemcitabine, should be considered the standard of care in chemotherapy for malignant pleural mesothelioma (Vogelzang 2008).

4.3.6 Lung cancer

Since the report of Sir Richard Doll in 1955, several studies have shown an elevated risk of lung cancer in association with asbestos exposure. The International Agency
for Research on Cancer (IARC) classified asbestos as a carcinogen in 1972. Asbestos can cause all types of lung cancer (Churg 1985), and there is no convincing evidence that chrysotile asbestos is less harmful with respect to causing lung cancer than amphiboles are (Berman and Crump 2008). Another disputable issue has been whether the development of asbestosis is needed for an increased risk of lung cancer. Some studies have found an association between asbestos exposure and lung cancer in the absence of asbestosis, and the leading scientific opinion is that asbestos may induce lung cancer without concurrent parenchymal fibrosis (Henderson et al. 2004). The asbestos-related risk of lung cancer is lower than that associated with smoking. The mean relative risk for asbestos exposure in altogether 20 studies was 2.00 (95% CI 1.90-2.11) (Steenland et al. 1996). Unfortunately, many of those exposed to asbestos are current or ex-smokers. Smoking and asbestos were found to act synergistically in the pioneering work of Selikoff and Hammond (1979). They found that occupational exposure to asbestos alone increased lung cancer death rates 5-fold, cigarette smoking alone 11-fold and smoking and asbestos exposure together caused a 53-fold increase. More recent investigations have found the relationship to be intermediate between multiplicative and additive (Liddell 2001, Liddell 2002, Berry and Liddell 2004). The proposed mechanisms behind the synergy are (a) tobacco smoke facilitating fibre penetration into the bronchial wall, (b) carcinogens in cigarette smoke being absorbed onto asbestos fibres, (c) tobacco smoke interfering with the clearance of asbestos from the lungs and, (d) free fatty acids in tobacco translocating iron into cell membranes, and therefore enhancing cell sensitivity to oxidants (Henderson et al. 2004). It has also been shown that quitting smoking will decrease the risk of lung cancer in asbestos-exposed populations, but not to the level of never smokers (Reid et al. 2006).

There is a fairly linear dose-response curve for asbestos exposure and lung cancer, which becomes steeper at the higher levels of exposure. In the Finnish general population, a lung amphibole content of 1.0 to 5.0 million f/g was associated with an increasing lung cancer risk [odds ratio (OR) 1.7] and the OR value for ≥5.0 million f/g was 5.0 (Karjalainen et al. 1994c).

The Helsinki criteria were set for clinical decision making with respect to assessments of whether an individual patient's cancer can be attributed to asbestos exposure with a 50% probability. The line was drawn at 25 fibre-years equalling with 5.0 million amphibole fibres (>1µm)/g dry lung tissue, 5000-15000 ABs/g dry
lung tissue or 5–15 ABs/ml of BAL fluid (Consensus report 1997). These values apply, however, to mixed exposure to amphiboles and chrysotile, but not to pure amphibole or chrysotile exposure (Henderson et al. 2004).

4.3.7 Other malignancies

In addition to the respiratory tract, asbestos has been suspected to cause also cancers in the aerodigestive tract — the pharynx, the larynx, the esophagus, the stomach and the intestine. The Institute of Medicine’s (IOM) Board on Population Health and Public Health Practices in the United States has recently critically evaluated the existing literature in that field. Its appointed committee concluded that there is enough evidence to declare a causal relationship between asbestos and laryngeal cancer, but not enough for other cancers. For stomach and colorectal cancer, epidemiological studies show a slightly increased risk, and no risk increase has been found for oesophageal cancer (Committee on Asbestos 2006).

4.4 Trends in asbestos-related diseases

The worldwide use of asbestos peaked around 1977, when 85 countries were manufacturing asbestos products (Virta 2006). In the European countries and the United States, however, health issues and public opposition led to a rapid decline in asbestos consumption in the late 1970s. The use of chrysotile asbestos still continues however, being 2.1 million metric tons (t) in 2003 that is roughly 40% of the amount consumed in 1980. In 2003, 15 countries still consumed a significant amount of asbestos as follows: China (492 000 t), Russia (429 000 t), India (192 000 t), Kazakhstan (174,000 t), Ukraine (156 000 t), Thailand (133 000 t), Brazil (78 400 t), Iran (75 800 t), Uzbekistan (42 400 t), Vietnam (39 400 t), Indonesia (32 300 t), the Republic of Korea (23 800 t), Kyrgyzstan (23 700 t), Japan (23 400 t), and Mexico (20 100 t) (Virta 2006).

In Finland, the use of asbestos peaked in 1970, being 12 000 t (2.5 kg per person per year), and the consumption quickly dropped after the Paakkila mine was closed in 1975 (State Asbestos Committee 1989). The use of asbestos products was banned
in Finland in 1994, and European Union has not permitted its use since 2005 (Commission of European Communities 1999).

The incidence curves of asbestos-related diseases follow the shape of the consumption curve, with an approximate 30- to 40-year shift. This trend is apparent for mesothelioma in several industrialized countries (Peto et al. 1995, Leigh et al. 2002, Pelucchi et al. 2004). Because of the long latency period, the incidence of asbestos-related diseases will be relatively stable for the next few decades even in the countries that banned asbestos two decades ago (Nishikawa et al. 2008). Currently, about 125 million people in the world are exposed to asbestos at the workplace, and, according to global estimates, at least 90 000 people die each year from asbestos-related lung cancer, mesothelioma, and asbestosis (Driscoll et al. 2005, WHO 2006). In Finland, approximately 50 out of 70 mesotheliomas, 80 asbestos-related lung cancers out of a total of 2250 lung malignancies, and 80 asbestosis are diagnosed as occupational diseases each year (Finnish Register of Occupational Diseases 2009).
5. Retroperitoneal fibrosis

Retroperitoneal fibrosis, also called Ormond’s disease, is an uncommon fibrosing disorder of the retroperitoneal space. It is characterized by a thick fibrotic mass covering the abdominal aorta and other retroperitoneal structures (Figure 1). The fibrotic mass typically extends from the renal arteries to the pelvic region (Lepor and Walsh 1979). Laterally expanding fibrosis may entrap the ureters and cause ureteral obstruction and hydronephrosis.

![Abdominal CT scan](image)

Figure 1. Abdominal CT scan of a former insulator in power plants. There is a thick mass covering the abdominal aorta (white arrows). This follow-up scan was made 15 years after the initial diagnosis of RPF.

5.1 History and epidemiology

The first case reports in the literature were written by Simpson in 1868 and Albarran in 1905. RPF was established as a clinical entity by John K. Ormond, an American urologist. In 1948 Ormond described two cases of bilateral ureteral obstruction caused by retroperitoneal fibrotic plaque. He performed the first liberation procedure of the ureters, combined with omental wrapping to prevent re-stenosis. This procedure remained the treatment of choice for the next five decades. A
comprehensive review of the aetiology, pathogenesis and treatment of RPF by Wagenknecht and Hardy was published in 1978.

After Ormond’s first report, only about 100 cases were described in the next 15 years (Ormond 1965). Koep and Zuidema (1977) reviewed 481 cases from 1948 to 1973. In the 1950s and 1960s an increase in RPF occurred that cannot be explained by better diagnostic methods (Ormond 1965, Hewitt et al. 1969). Currently, 2400 reports of RPF can be found in Medline (www.ncbi.nlm.nih.gov, accessed on 14 March, 2009), most of them presenting case reports or series associated with various medical conditions.

In 1978, Wagenknecht estimated the prevalence of RPF to be 1/200 000 in central Europe. This figure was based on the 430 RPF cases reported in a multicentre survey of 2025 surgeons and radiologists in 70 European clinics (Wagenknecht and Hardy 1978). An incidence of 1/200 000 person-years was reported in the 1990s in the Netherlands (Breems et al. 2000).

In a population-based study conducted in Finland, my colleagues and I found an age-standardized RPF incidence of 0.10/100 000 person-years and a prevalence of 1.38/100 000 inhabitants (Study I). The age-standardized incidence was twice as high for men (0.14) than for women (0.07).

RPF is generally diagnosed between the ages of 40 and 70 years (Wagenknecht and Hardy 1978). The mean age at diagnosis in Study I was 56 years. RPF rarely occurs in children, only 23 cases having been described in the English literature (Miller et al. 2003). One case of foetal RPF has been reported (Duffy 1966).

5.2 Aetiology

Traditionally, RPF has been divided into a secondary form associated with various medical conditions and an idiopathic (primary) form without an obvious causative factor. Knowledge of the conditions related to the development of RPF is based mainly on case reports and series. In comprehensive reviews published in the 1970s, approximately one third of all cases were found to be related to other diseases or processes, and two thirds were considered idiopathic. RPF manifestation has been observed after infections, traumas, haematomas, urinomas, radiation therapy, and retro- or intraperitoneal surgery (Koep and Zuidema 1977, Wagenknecht and Hardy
1978, Lepor and Walsh 1979). All of these factors cause inflammatory tissue reaction that results in fibrogenesis. RPF may also develop in association with malignancy, either due to an invasion of the retroperitoneum by neoplastic cells or to a desmoplastic reaction induced by a tumour. In recent retrospective case series, 11 out of 18 RPF patients had a malignant disease, mainly colorectal cancer treated by surgery and adjuvant radiotherapy (Katz et al. 2002).

Methysergide (Sansert®), an ergot derivative used for migraines and cluster headaches, was found to induce RPF soon after it became more widely used; it caused this side effect in 1% of the patients (Graham et al. 1966). Other ergot drugs, including ergotamine and the Parkinson drug pergolide, have also been found to trigger RPF (Stecker, Jr. et al. 1974, Mondal and Suri 2000). All of these drugs may cause combined pleural, mediastinal, and retroperitoneal fibrosis or solely pleuropulmonary changes, which are partly reversible after the medication is discontinued (Pfitzenmeyer et al. 1996, Bleumink et al. 2002). Although the threshold dose or latency of the fibrosing process is not known, in the described cases, the patients had usually taken ergot drugs daily for several months or years (Graham et al. 1966). The mechanisms causing the fibrogenicity of the ergolines remain unclear. The main theories suggest an excessive serotoninergic activity, vasoconstriction or an autoimmune reaction in which ergot drugs act as a haptene (Stecker et al. 1974).

Other drugs, such as beta-blockers, analgetics in high doses and old antihypertensives, have also been suspected of causing RPF (Buff et al. 1989), but the small number of reports suggests that the use of these drugs is merely coincidental.

Coexistence with abdominal aortic aneurysms was noted during a review of RPF cases (Wagenknecht and Madsen 1970). In 1970, Mitchinson suggested that inflammation in conjunction with idiopathic RPF may be due to a leakage of atherosclerotic material into the adventitia of the abdominal aorta. Mitchinson (1984) and Parums (1990) showed that the histology of periaortic tissue in idiopathic RPF is identical to the changes seen in inflammatory aortic aneurysm. There are similar inflammatory cell infiltrations in aortic adventitia with fibrosis around the atherosclerotic plaques in both diseases. The authors suggested that inflammatory aneurysm, peri-aneurysmal retroperitoneal fibrosis, and idiopathic RPF form a spectrum of the same disease, and they recommended the use of the
unifying term “chronic periaortitis” to mean all three (Mitchinson 1986, Parums 1990).

They also found that all patients with chronic periaortitis had antibodies to oxidized low-density lipoprotein or the aortic insoluble atheroma material ceroid (Parums et al. 1990). The same antibodies were also detected in 50% of elderly healthy controls. The hypothesis of an autoallergic inflammatory trigger was supported by the detection of accumulations of immunoglobulin G in the ceroid mass of patients with chronic periaortitis (Parums et al. 1986). Generally, inflammation plays a major role in the pathogenesis of aortic aneurysm (Alexander 2004), and this role also supports the uniform pathogenesis of inflammatory aneurysm and idiopathic RPF. Current opinion suggests that the inflammatory reaction to advanced atherosclerosis one of the main causes leading to RPF (Jois et al. 2004).

Because RPF is an inflammatory disease by nature, the theory of association with autoimmune disease seems plausible. Coexistence with autoimmune diseases has been noted, but not in most RPF cases (Koep and Zuidema 1977). Nevertheless, recent studies support this relation. Autoimmune diseases were found to be overrepresented in patients with inflammatory aortic aneurysm in a comparison with patients with non-inflammatory aneurysm (Haug et al. 2003). A notable proportion of patients with chronic periaortitis had antinuclear antibodies or small-vessel vasculitis, and some also had antineutrophile cytoplasmic antibodies (Vaglio et al. 2003). Vaglio and his co-workers also found that the frequency of the HLA-DRB1*03 allele was markedly higher in patients with chronic periaortitis than in healthy controls (Martorana et al. 2006). The HLA-DRB1*03 allele is a well known marker of autoimmunity, that is associated with numerous autoimmune diseases, such as diabetes mellitus type 1, systemic lupus erythematosus, autoimmune thyroid disease and myasthenia gravis (Davidson and Diamond 2001, Anaya et al. 2006).

In conclusion, it is evident that there is no specific cause for RPF. “Idiopathic” RPF is probably a disease with multiple aetiologies. Nevertheless, these fibrosing processes of the retroperitoneal space are universally subacute inflammatory reactions that respond to anti-inflammatory treatment.
5.3 Clinical picture

The major initial complaint of almost all RPF patients is poorly localized pain in the abdominal, flank, or back region (Koep and Zuidema 1977). Weight loss, fever, nausea and leg oedema are also sometimes present. The insidious beginning of the disease and its non-specific symptoms and signs may cause a delay in medical attention being sought. Hydronephrosis has developed in most of the cases by the time of diagnosis. Thus laboratory values indicating renal dysfunction are elevated in most patients (Lepor and Walsh 1979). An elevated erythrocyte sedimentation rate, C-reactive protein, and anaemia are frequently seen (Baker et al. 1987). The erythrocyte sedimentation rate also correlates with disease activity.

Historically, intravenous urography has been the most useful examination in the diagnosis of RPF. A typical finding in urography is uni- or bilateral dilatation of the ureter and renal calix and medial deviation of the ureters (Figure 2). Nowadays, abdominal CT and magnetic resonance imaging are routinely used, and they provide excellent information about the extent of fibrosis and also help to differentiate fibrosis from malignant tumours (Dalla-Palma et al. 1981, Brooks et al. 1990, Brooks 1990). Renal sonography is a useful tool in both diagnosis and follow-up (Henry et al. 1978, Erden et al. 1995). Because of the metabolic activity of the inflammatory tissue, PET scanning can be used in the evaluation of disease activity if the CT finding is unclear (Young et al. 2008).
The conditions to be considered in differential RPF diagnosis are lymphomas, sarcomas, and malignancies of the bladder or bowel. Histological confirmation with open or CT-guided biopsy is the rule, but also empirical treatment of the retroperitoneal mass with radiological follow-up is a common strategy (Gilkeson and Allen 1996).

The microscopic appearance of RPF varies from active inflammation with abundant lymphocytes, plasma cells, eosinophils, and macrophages to dense and homogeneous connective tissue containing only occasional fibroblasts and inflammatory cells (Mitchinson 1970, Parums et al. 1991, Wu et al. 2002). Histological diagnosis is usually non-specific inflammation and fibrosis, and the main role of a histological examination is to exclude malignant processes.

5.4 Treatment

Ureterolysis, first performed by J. Ormond in 1946 (Ormond 1948), has remained one of the most effective treatment options. In this procedure, the ureter is dissected from the fibrotic tissue and positioned laterally. The ureter is isolated from fibrotic tissue by omental wrapping or by retroperitoneal fat to prevent re-entrapment.
Laparoscopic ureterolysis can be successfully performed with less postoperative morbidity, although being time-consuming at first (Elashry et al. 1996, Castilho et al. 2000), but with growing experience it is proposed that it will be a primary treatment in the future (Simone et al. 2008). Recently, the first experiences of robot-assisted laparoscopic ureterolysis were reported (Mufarrij et al. 2008, Stifelman et al. 2008).

Ureteric stenting with anti-inflammatory medication has replaced open surgery in some medical centres. The advantages of stenting are the avoidance of surgery and a reduction in hospitalization time, whereas the disadvantages are the smaller mechanical impact and the impossibility to obtain biopsies (Baker 2003).

Corticosteroid therapy is the other mainstay treatment for RPF. The effectiveness of corticosteroids in the reduction of fibrous mass and the alleviation of systemic symptoms has been shown in numerous uncontrolled studies (Wagenknecht and Hardy 1981, van Bommel et al. 1991, Kardar et al. 2002). Corticosteroid therapy can be used alone, but, if ureteric obstruction is presented, it is combined with ureterolysis or ureteric stenting (Baker 2003). Tamoxiphene has been used as an alternative to steroids or as a corticosteroid-sparing agent in some cases (Clark et al. 1991, Frankart et al. 1997). In recent years, several investigators have found mycophenolate mofetil to be useful as a steroid-sparing agent (Scheel et al. 2007, Adler et al. 2008, Swartz et al. 2008). Other immunomodulatory drugs used in steroid-resistant cases are cyclophosphamide and azathioprine (Oosterlinck and Derie 1997). The treatment options depend on the degree of ureteric obstruction and uremia, the existence of co-morbidities, and the operability of the patient. The prognosis is currently favourable for RPF. Recent studies show over 90% remission rates for accurately treated cases (De Luca et al. 1998, Katz et al. 2002).
Aims of the study

- To establish the epidemiological and demographic features of RPF in the Finnish population.

- To assess the significance of risk factors previously suspected to be associated with retroperitoneal fibrosis, including the role of asbestos exposure in a case-control series.

- To determine whether RPF patients have pleural or lung fibrosis and to assess the relations between asbestos exposure and these intra-thoracic fibrotic changes in RPF patients.

- To determine if asbestos fibres reach the retroperitoneal space in humans and, therefore, may induce RPF.
Study design

Study I was a formal case-control study based on cases and randomly assigned, matched controls from the general population. Study II included two different settings: (a) a comparison between exposed cases and unexposed RPF cases for the evaluation of the effect of asbestos exposure in the development of pleural and lung fibrosis and (b) a comparison between asbestos-exposed RPF patients and asbestos-exposed controls in the assessment of the role of RPF in the development of lung and pleural fibrosis. Study III was comprised of persons with suspected occupational asbestos exposure and controls with unlikely exposure. The participants were re-grouped, however, according to the results of mineral fibre analysis of a lung tissue. Study IV was a case report describing asbestos exposure and asbestos contents of the tissue in a patient with RPF.
Subjects and methods

1. Study populations

The data of this study were obtained from two populations. For Studies I and II, all adult patients alive with RPF diagnosed and treated in 12 secondary and tertiary hospitals within three university hospital districts in Finland in 1990-2001 were selected. The catchment area involved 3.62 million inhabitants in 2001. The demographic data were obtained from Statistics Finland.

1.1. Cases

The potential cases were retrieved from the Hospital Discharge Data Register using diagnostic codes 5934A (other ureteric obstruction including idiopathic RPF) in the ninth revision of the International Classification of Diseases (ICD) for 1990-1995 and D20.0 (retroperitoneal benign neoplasm) in the 10th revision of ICD for 1996-2001. Additional cases were searched for in the databases of pathology laboratories. The diagnosis of RPF was confirmed on the basis of the medical records and the histopathological reports. The inclusion criteria consisted of typical clinical features (extensive retroperitoneal fibrous mass) and either histological confirmation or a sufficiently long follow-up time in order to rule out retroperitoneal malignancies. Patients with secondary retroperitoneal fibrosis due to malignancies and radiotherapy were excluded. The proportion of histopathological sampling (42 out of 50) reflected the use of open surgery as a treatment option during previous decades.

We identified 50 living RPF patients and contacted them by telephone or letter. Forty three patients (86%), 29 males and 14 females, were willing to participate in the study (Figure 3). In addition five deceased persons were found who had RPF.
The mean age of the study participants at the time of diagnosis was 56 (range 37-76) years, and the mean year of diagnosis was 1994 (range 1979-2002).

1.2. Controls

For each case, five living controls matched for the exact year of birth, gender, and central hospital district were randomly assigned by the Finnish Population Register Centre. Matching for the central hospital district was used to avoid bias from the different industrial structures in the regions. At the time of enrolment, 1,597,483 people born in 1918-1963 lived in the study area. All of the controls were contacted by a letter, a subsequent reminder, if needed, and a telephone interview. The response proportions of the persons contacted were as follows: 73 (34%) for the first questionnaire, 42 (20%) for the reminder, and 64 (30%) for the telephone interview. The filled-out questionnaires were checked, or structured questionnaires were filled-out during the telephone interview. We were able to collect sufficient data from 179 of the 215 controls (83%) (Figure 3).

**Figure 3.** Flow chart of Studies I and II.
1.3. HRCT study

We asked all of the 43 persons with RPF and the controls with more than 10 fibre-years of asbestos exposure to participate in HRCT study of the lungs. Altogether 38 (88%) of the RPF patients and 18 (86%) of the asbestos-exposed controls were willing to participate (Figure 3).

1.4. Study population for the asbestos fibre analysis

The cases were persons who underwent a medicolegal autopsy because of suspicion of an asbestos-related cause of death (n=17). All of the persons were men, aged 52 to 85 years at the time of death. The controls were selected from men who were referred for medicolegal autopsy for any other reason (n=5). In addition to male sex, the criteria for the controls consisted of age over 55 years, work histories with unlikely occupational exposure to asbestos, and no bilateral parietal pleural plaques detected at autopsy as an indicator of past exposure.

2. Ethical considerations

All of the participants in Study I and Study II gave their informed consent to participate. HRCT was performed on those with RPF and the controls with at least moderate asbestos exposure. The controls with low-level or no exposure were not studied. For Study III, approval was given by the National Authority for Medicolegal Affairs. The Ethics Committee of the Tampere University Hospital approved the study plans.
3. Data collection and evaluation of asbestos exposure

A five-page questionnaire was sent to all of the patients and controls to obtain information on sociodemographic factors, smoking, and medical history (Appendix 1). The questionnaire included 21 questions compiled by the Finnish Institute of Occupational Health for the assessment of asbestos exposure.

The assessment of cumulative asbestos exposure was based on fibre-years as evaluated by an expert according to industrial hygiene knowledge of certain occupations. The following three grades of cumulative exposure were defined before the data collection: 0=no notable asbestos exposure (low-level exposure for <1 week), 1=slight exposure: >1 week of low-level exposure and <10 fibre-years, 2=moderate-to-high exposure: ≥10 fibre-years. All of the participants were interviewed personally with the aid of the returned questionnaires. A senior occupational physician, who was blinded in terms of the case-control status, evaluated the exposure using completed and checked questionnaires.

4. Evaluation of lung and pleural fibrosis

The HRCT was carried out in seven central hospitals. The HRCT scans consisted of 1-mm slices at 20-mm intervals from the first rib to the costophrenic angle in the prone position and with full inspiration. The images were printed at two separate settings appropriate for viewing the lung parenchyma and the mediastinum and the pleura, the windowing depending on the scanner used.

All of the images were reviewed by two experienced thoracic radiologists, who were blinded to all medical information except the participants’ names and identification numbers, which were printed on the films. The images were scored by consensus reading. Lung fibrosis, parietal pleural plaques, and DPT were scored separately. The scoring was modified from earlier classification systems (Oksa et al. 1994, Huuskonen et al. 2001). Model images were not used, and the scoring was carried out in two sessions within 1 week. The maximum DPT thickness was measured subsequently in one session. A definitely abnormal finding that could be related to asbestos exposure was rated class 1 for DPT (unilateral DPT <5 mm) and class 2 for pleural plaques (bilateral plaques on fewer than half of the slices) and
lung fibrosis (at least two abnormal findings on both sides in several slices). The scoring tables are presented in detail in Appendices 2 and 3.

5. Asbestos fibre analysis

Asbestos fibres were analysed from the PA lymph nodes at the level of the renal arteries and from the ME lymph nodes of the small intestine, as well as from lung tissue. The parenchymal samples were taken from the peripheral parts of the lung that did not include the pleura and had no macroscopic evidence of tumour infiltration. For the electron microscopic examination, pooled samples were prepared by cutting 60-200 mg (wet weight) of tissue from 1 to 4 lymph nodes and lung parenchyma. The samples were dried at 80°C overnight and weighed. Low-temperature ashing was used to remove organic tissue. TEM, combined with energy dispersive X-ray analysis, was used to identify and count the asbestos fibres. All of the asbestos fibres longer than 1 µm with an aspect ratio of >3 to 1 were counted at a magnification of 15 000 x. The diameter of such countable fibres was >0.03 µm, and the detection limit ranged from 0.02 to 0.15 million f/g dry tissue. Blank samples and prefiltered solutions were used to exclude any laboratory contamination. This ashing method had earlier been tested and compared to tissue dissolution in a European interlaboratory certification of reference materials for asbestos fibre analysis in lung tissue (Tossavainen et al. 2001).

6. Statistical analysis

The age-standardized incidence was calculated using the European 5-year group standard population (Doll and Cook 1967). The multivariate analysis used in Study I was carried out using conditional logistic regression. The population attributable fraction (PAF) was determined as \( q(\text{OR}-1)/\text{OR} \), where \( \text{OR} \) was the odds ratio and \( q \) was the proportion of cases exposed to the factor (Armitage et al. 2002).
In Study II, the groups were compared using the Kruskal-Wallis and Mann-Whitney tests, as appropriate. An ordinal logistic regression analysis was carried out to assess the risk factors of pleural and parenchymal fibrosis in the asbestos-exposed patients and controls. The analysis was based on proportional odds (i.e., a constant OR value across ordered categories of the response variable: odds of having diagnostic score x or higher relative to having a score below x). The outcome variable was the radiological finding categorized into four classes. The results of the ordinal logistic regression analysis therefore indicated susceptibility to the development of fibrotic changes at the given asbestos exposure. In addition, the susceptibility for asbestos-related pleural fibrosis among the RPF patients was evaluated in a case-case setting (Tager 2000) using logistic regression analysis.

The calculations in Study I were carried out with STATA 7.0, and in Study II STATA 8.0 software (Stata Corporation, College station, TX, USA) was used.

The differences in the asbestos fibre concentrations between the lung tissue, lymph nodes, and exposure groups were analysed with the Mann-Whitney and Wilcoxon signed ranks tests. The Pearson chi-square test was used for the comparison of frequencies. The calculations were made with SPSS 15.0 software (LEAD Technologies Inc., Chicago, Illinois, USA).
Results

1. Incidence and prevalence of retroperitoneal fibrosis

The age-standardized incidence of RPF was 0.10 (95% CI 0.07-0.14) per 100 000 person-years overall, 0.14 (95% CI 0.08-0.21) for men and 0.07 (95% CI 0.04-0.10) for women in 1990-2001. The RPF prevalence was 1.38 per 100 000 inhabitants in the study area, with a catchment population of 3.62 million.

2. Established risk factors for retroperitoneal fibrosis

Asbestos exposure was strongly associated with RPF, with crude OR values ratios 4.2 (95% CI 1.6-11.0) for <10 fibre-years and 4.1 (95% CI 1.4-12.4) for ≥10 fibre-years. After adjustment for the other risk factors, a gradient by level of exposure was found. The adjusted OR was 5.5 for slight asbestos exposure and 8.8 for moderate-to-heavy asbestos exposure (Table 1). Heavy smoking appeared to be an independent risk factor in this model, but there was no statistically significant interaction between smoking and asbestos exposure. Of previously known risk factors, the use of ergotamine derivates and aortic aneurysms were clearly associated with the development of RPF. Atherosclerotic diseases, hypertension, the use of beta-blocking agents, and abdominal surgery did not appear to be a significant risk factors in this analysis, nor did the diagnosis of migraines which was used as a negative control in the modelling (Table 1).
Table 1. Adjusted OR values for potential risk factors for retroperitoneal fibrosis

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asbestos exposure ≥10 fibre-years</td>
<td>8.84 (2.03-38.50)</td>
</tr>
<tr>
<td>Asbestos exposure &lt;10 fibre-years</td>
<td>5.54 (1.64-18.65)</td>
</tr>
<tr>
<td>Use of ergot derivates</td>
<td>9.92 (1.63-60.26)</td>
</tr>
<tr>
<td>Smoking history &gt;20 pack-years</td>
<td>4.73 (1.28-17.41)</td>
</tr>
<tr>
<td>Smoking history ≤20 pack-years</td>
<td>1.47 (0.43-4.96)</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td>6.73 (0.81-56.08)</td>
</tr>
<tr>
<td>Abdominal surgery</td>
<td>2.06 (0.82-5.19)</td>
</tr>
<tr>
<td>Use of beta-blocking agents</td>
<td>2.36 (0.52-10.80)</td>
</tr>
<tr>
<td>Atherosclerotic disease*</td>
<td>1.57 (0.52 – 4.73)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>0.79 (0.20-3.07)</td>
</tr>
<tr>
<td>Migraine</td>
<td>0.78 (0.16-3.72)</td>
</tr>
</tbody>
</table>

* Consists of coronary heart disease, peripheral vascular disease and ischaemic stroke.

3. Characteristics of asbestos exposure

The mean time from the first exposure to the appearance of RPF (the mean latency period) was 30.8 (SD 12.3) years for slight exposure and 33.3 (SD 7.33) years for moderate-to-high exposure. The interval from the beginning of the exposure of the control to the RPF diagnosis of the case was 26.7 (SD 10.6) years for <10 fibre-years of exposure and 33.5 (SD 9.7) years for ≥10 fibre-years of exposure. The asbestos exposures of >10 fibre-years were exclusively occupational. There were two insulators and two construction workers, and one construction cleaner with heavy asbestos exposure among the cases. Most of the exposed controls had worked as construction workers.
4. Attributable fractions for different exposures

The PAF was 25 (95% CI 12-29)% for <10 fibre-years of asbestos exposure and 19 (11-20)% for ≥10 fibre-years, 13 (5-14)% for ergot medication, 10% (0-11) for abdominal aortic aneurysm, and 40 (11-48)% for heavy smoking, when the frequencies among the RPF patients were used. This procedure probably overestimated the PAF in relation to asbestos exposure because men and older age groups with a higher frequency of asbestos exposure were overrepresented. In the entire Finnish population approximately 3% are slightly exposed to asbestos, and 1% are heavily exposed (Huuskonen et al. 1995). These figures would give PAF of 12% and 7%, respectively.

5. Asbestos-related parenchymal and pleural fibrosis and retroperitoneal fibrosis

5.1 Presence of asbestos-related findings

A total of 16 out of 22 (73%) asbestos-exposed RPF patients and 12 out of 18 (67%) exposed controls had asbestos-related pleural pathology in their chest HRCT. The prevalence of pleural plaques, DPT, and lung fibrosis determined for the asbestos-exposed RPF patients was similar to that found for the asbestos-exposed controls, but DPT was clearly more extensive in the asbestos-exposed RPF patients. Only a few RPF patients and controls with >10 fibre-years of asbestos exposure had asbestosis (Figure 4).
Out of studied persons (%)

Figure 4. Percentage of persons with DPT, bilateral parietal pleural plaques, and lung fibrosis among the unexposed patients RPF, the asbestos-exposed patients with RPF, and the asbestos-exposed controls. * Difference between three groups, ** Difference between the unexposed and exposed RPF patients P=0.045.

Most of the asbestos-exposed RPF patients with DPT also had bilateral pleural plaques and vice versa. One person had all three of the distinctive abnormal findings. The most typical findings of the asbestos-exposed controls were bilateral pleural plaques, and one person from the control group had all three notable changes. Twelve (75%) of the unexposed RPF patients, six (27%) of the asbestos-exposed RPF patients, and six (33%) of the asbestos-exposed controls did not have any of these changes.

5.2 Pleural plaques

The unexposed RPF patients had only minor pleural plaques, and the differences between this group and the asbestos-exposed groups were statistically significant (Figure 4). More than 60% of the asbestos-exposed RPF patients and half of the exposed controls had bilateral pleural plaques (Figure 3). There were no differences
between the asbestos-exposed cases and controls with respect to susceptibility to the development of parietal pleural plaques in the ordinal logistic regression analysis. Out of the studied variables, only lung fibrosis was associated with parietal pleural plaques (OR 3.78, 95% CI 1.52-9.43). The grade of pleural plaques was not related to age, smoking history, or DPT grade. In the case-case analysis, the OR value for pleural plaques in relation to asbestos exposure was 12.2 (Table 2).

**Table 2.** Pleural fibrosis consisting of bilateral parietal pleural plaques (PPP) and diffuse pleural thickening (DPT) in the patients with retroperitoneal fibrosis (RPF pts) regarding their asbestos exposure.

<table>
<thead>
<tr>
<th></th>
<th>Unexposed RPF pts</th>
<th>Asbestos-exposed RPF pts</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural fibrosis –</td>
<td>10</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Pleural fibrosis +</td>
<td>6</td>
<td>17</td>
<td>5.7 (1.4 – 23.4)</td>
</tr>
<tr>
<td>PPP +</td>
<td>2</td>
<td>14</td>
<td>12.2 (2.2 – 68.2)</td>
</tr>
<tr>
<td>DPT +</td>
<td>4</td>
<td>12</td>
<td>3.6 (0.9 – 14.7)</td>
</tr>
</tbody>
</table>

5.3 **Diffuse pleural thickening**

DPT was more frequent among the RPF patients with asbestos exposure than among the unexposed patients (P=0.045). There were no differences between the asbestos-exposed RPF patients and controls (P=0.190), and none of the differences between the three groups reached statistical significance (Figure 3). Among the RPF patients, asbestos exposure increased the risk of both DPT and all pleural fibrotic changes (Table 2).

The most distinctive finding for the asbestos-exposed RPF patients was a thick DPT. The mean maximum DPT thickness was 2.8 (SD 1.0) mm for the 4 unexposed RPF patients, 9.8 (SD 5.1) mm for the 12 exposed patients with RPF, and 5.1 (SD 2.7) mm for the 7 exposed controls. The difference between the three groups was significant (P=0.040), and a similar difference was found for contralateral pleural
thickening (P=0.048). The respective values for the contralateral DPT were 2 (SD 0) mm (3 subjects), 6.5 (SD 4.2) mm (10 subjects), and 2.8 (SD 1.0) mm (4 subjects).

In the ordinal logistic regression analysis, the asbestos-exposed RPF patients had a nonsignificantly increased risk for the development of DPT when compared with that of the asbestos-exposed controls (OR 3.06, 95% CI 0.81-11.56). Age at the time of the HRCT, smoking history, pleural plaques, and lung fibrosis grade had no influence on the development of DPT.

5.4 Pleural masses

Exceptionally large pleural masses were observed in three asbestos-exposed patients with RPF (Figure 3). The uniform masses were located anteriorly in the pleural space and continued into the anterior mediastinum. The overall volumes of these masses clearly differed from the plaques and DPT found in the other persons. These unique fibrotic findings were omitted from the DPT thickness assessment, which was measured from the continuous dorsal fibrotic sheet.

![Figure 5](image_url)

**Figure 5.** Pleural masses. A. HRCT scan of the lung of a 55-year-old former pipefitter with RPF. There is a large anterior pleural mass (maximum dimensions of 30 mm x 150 mm) that continues into the mediastinum (arrowheads) and a thinner dorsal diffuse pleural thickening (white arrow) with a rounded atelectasis (black arrow). The patient had undergone left-sided pleural decortication 10 years earlier. B. A 76-year-old female with RPF who had worked as a construction cleaner and had had a high-level asbestos exposure. There is a large plaque-like mass with calcifications and maximum dimensions of 27 mm in thickness and 150 mm in
5.5 Lung fibrosis

There was no notable lung fibrosis in the unexposed RPF patients, but the three groups did not differ statistically in this respect (Figure 4). One asbestos-exposed RPF patient had mild lung fibrosis, and two had moderate fibrotic changes, as did two controls. The exposed RPF patients were not more susceptible to lung fibrosis than the asbestos-exposed controls (OR 1.29, 95% CI 0.25-6.63). Lung fibrosis was associated with the occurrence of pleural plaques (OR 2.73, 95% CI 1.10-6.78). In these series, age, smoking, and DPT did not seem to affect the development of lung fibrosis.

6. Asbestos fibres in abdominal lymph nodes

There were 10 persons with a lung fibre concentration exceeding the 1 million f/g of dry tissue that is widely accepted as the level for a high probability of occupational asbestos exposure (Consensus report 1997). Asbestos fibres were detected in 8 of 10 (80%) of both PA and ME lymph nodes, with a substantially high level in several nodes (Figure 5). All of the 10 exposed men had detectable asbestos fibres either in their PA or ME lymph nodes.

The mean asbestos concentrations were 21.4 million f/g for lung tissue, 0.85 million f/g for the PA nodes and 0.55 million f/g for the ME nodes. The asbestos fibre content was clearly higher in the lung tissue than in the lymph nodes (p=0.005 for both groups), but the differences between the PA and ME nodes were not significant.
Figure 5. Asbestos fibre concentration in the PA and ME lymph nodes of the same persons in relation to the asbestos fibre concentration in their lungs.

The lung asbestos content was less than 1 million f/g for 12 persons, and these results were in line with their work history, which suggested short or low-level exposure. The mean asbestos concentrations for lung tissue, and PA and ME nodes were 0.27, 0.07 and 0.03 million f/g, respectively.

Asbestos fibres were found in 4 of 12 (33%) of the PA lymph nodes and in 3 of 12 (25%) of the ME nodes. Altogether 5 of 12 (42%) men had asbestos fibres either in their PA or ME nodes. In comparison with the group with higher exposure, the differences of the positive result frequencies reached statistical significance for the ME nodes (p=0.035) and for all of the abdominal nodes (p=0.003), but not for the PA nodes (p=0.087).

The pulmonary fibre levels were slightly higher than those determined for the PA (p=0.026) and ME (p=0.003) lymph nodes. As for the first exposure group, no differences were found between the PA and ME nodes (p=0.30).

The concentration of asbestos fibres in the positive samples was 72 (range 0.5-644) times lower in the PA lymph nodes and 60 (range 2-260) times lower in the ME lymph nodes than in the lung tissue. There was a weak linear correlation between the asbestos content of the PA and the ME lymph nodes (correlation coefficient 0.571, p=0.006, Figure 5), but not between the lung tissue and the abdominal nodes.
The analysis for receiver operating characteristics (ROC) showed that the false positive rate for the occurrence of asbestos fibres in either PA or ME lymph nodes reached zero at a lung asbestos level of 0.45 million f/g, with an estimated area of 0.900 for the ROC curve (Figure 6).

![ROC Curve](image)

**Figure 6.** ROC for the presence of asbestos fibres in the PA and ME lymph nodes (LNs) or at least in one location, according to the lung asbestos contents.

7. **Asbestos fibres in a patient with retroperitoneal fibrosis**

Study IV describes a case history and autopsy findings of a patient with asbestos-related diffuse pleural thickening and RPF. The samples of lung parenchymal tissue contained a very high level of amphibole asbestos (59 million f/g). The same types of fibres were also found in samples of the PA lymph nodes and fibrotic retroperitoneal connective tissue. The asbestos concentration of the lymph nodes 0.80 – 1.01 million f/g was 10 times higher than for the RPF tissue (0.09 – 0.14 million f/g).
Discussion

Retroperitoneal fibrosis as an asbestos-related disease: is there enough evidence to declare a causal relationship?

In the case-control study, a strong association was found between past asbestos exposure and RPF. Do these results indicate that asbestos causes RPF? Possibly yes. However, none of the conducted studies justify such a statement on an individual basis. An association found in a case-control study does not necessarily reflect a causal relationship between suspected risk factors and a disease. There may be unknown confounding or other factors that have not been taken into consideration. The coexistence of asbestos-related pleural fibrosis and RPF may merely indicate that RPF is an independent risk factor for a pleural disease. The presence of asbestos fibres in the retroperitoneal lymph nodes does not mean that the same fibres are responsible for the induction of the fibrosing process in the retroperitoneal space.

In 1965, Sir Bradford Hill presented nine aspects that should be considered in the evaluation of causality. Later these nine points became referred as “Bradford Hill’s criteria”. These points were not initially intended to be criteria, but were established so that, in case they were met for a specific factor, there would be greater confidence in the factor being causally related to the disease. However, they were not intended to dismiss a factor as potentially causing the disease and cannot be used as a checklist to establish causation (Kundi 2006). An assessment of these nine points follows that bears in mind the aforementioned considerations.

**Strength** The OR value in the case-control study was 5.54 (95% CI 1.64-18.65) for <10 fibre-years of asbestos exposure and 8.84 (95% CI 2.03-38.50) for ≥10 fibre-years of such exposure. Although the study population was limited in size, it was large enough to show a statistically significant increase in the risk associated
with asbestos exposure. The lower limit of the CI value for the moderate-to-high exposure was above 2, indicating at least a two fold probability of the development of the disease among the exposed persons in a comparison with the unexposed persons.

**Consistency** There are no other epidemiological studies on RPF and asbestos exposure than those done by study group formed by my colleagues and I (Sauni et al. 1998, Study I). It has been difficult to collect persons with such a rare disease. There have been several case reports after our study group’s report was published, and certainly more unpublished cases have occurred. However, there are more than 2400 articles in the literature, and fewer than 10 deal with asbestos exposure. The most likely explanation for the lack of literature is the rarity of the condition, which requires a multicentre approach to its evaluation. The largest series of RPF cases from a single centre comprises only 60 cases. Furthermore, the disease is treated by urologists, but followed up by nephrologists, and it is difficult to suspect an occupational aetiology even for traditional work-related diseases if they are not specifically kept in mind.

There were two key factors that made study group’s research possible. The first was formed by the comprehensive statutory national health care system, and computerized hospital databases have been available in Finland since 1990, the combination of which enabled a population-based ascertainment of RPF patients. The second was the widespread asbestos exposure during 1960-1980, which resulted in disease manifestation after 30 years. It is possible that the past use of anthophyllite and other amphibole types of asbestos contributed to some of the country-specific differences, just as it did for pleural plaques and mesothelioma.

**Specificity** The assumption of specificity has been under heavy criticism. It is obvious that one exposure can cause multiple diseases, and RPF may have many aetiologies. Asbestos exposure is certainly not the only factor leading to the fibrotic process—known and suspected risk factors by are, for example, traumas, ergot drugs, advanced atherosclerosis, and autoimmune diseases.

**Temporality** RPF has a latency time of 30 years, which is typical for asbestos-related diseases. It is very rare in children and young adults. In the current study, pleural changes preceded RPF in most of the cases.

**Biological gradient** The adjusted OR values in the case-control study increased with increasing exposure, but the crude OR values did not. Study III showed that the
presence of asbestos fibres in the abdominal lymph nodes is related to the asbestos content of the lung tissue, an established marker of asbestos exposure. The level of 0.45 million f/g in the lungs refers to low-level exposure that is in line with the results of the case-control study, which showed an increased risk in association with <10 fibre-years of asbestos exposure.

**Plausibility** It is known that asbestos induces a fibrotic reaction in lung tissue, and intraperitoneal injections have been used to induce fibrosis in test animals. Study III showed that asbestos reaches retroperitoneal lymph nodes. The asbestos fibres in the retroperitoneal lymph nodes were the same type of amphiboles that were found in patients lung samples; chrysotile was found only in some samples. Asbestos fibres have been not only found in lymph nodes, but also in ME tissue of asbestos-exposed patients with mesothelioma (Dodson et al. 2000). Asbestos fibres were detected both in lymph nodes and in retroperitoneal fibrotic tissue in one RPF patient included in the current study.

**Coherence** The subjects of Study II were a representative sample of the participants of Study I, which was a population-based case-control study. The results of Study II, especially in respect to the prevalence of pleural plaques, confirm that the evaluation of asbestos exposure in Study I was a success. Therefore, it strengthens the validity of the risk estimations.

**Experiment** If the hypothesis of our study group is correct, the incidence of RPF should decrease in the next 20 years as a reflection of decreasing asbestos exposure in the Finnish population and the female-to-male ratio will increase from that of 1 to 2. The trends would be very difficult to follow because of the multiple aetiology and the rareness of the condition.

**Analogy** Study II showed that asbestos-exposed RPF patients have thick pleural fibrous tissue that resembles retroperitoneal masses and that does not occur among unexposed patients. The coexistence of large masses in the pleural and retroperitoneal space suggests a common aetiology.

All of Bradford Hill’s criteria except the consistency favour our study group’s hypothesis. It is a matter of a lack of knowledge rather than being due to existing evidence against the theory. There are a few counter-arguments, however. Probably the most problematic issue in Study I was heavy smoking, which acted as a risk factor in the conditional regression analysis. The influence of chance has been
excluded with the statistical analysis. It would be difficult to understand why RPF is such a rare disease while over 20% of the adult population in Finland are still current smokers. RPF has been traditionally suspected to be induced by atherosclerotic inflammation of the abdominal aorta (Parums 1990). In the modelling in Study I, atherosclerosis, defined as a patient-reported disease, had an OR value of 1.6 but it did not reach statistical significance. Therefore, we suggest that heavy smoking acted as a confounding factor for atherosclerotic diseases. It is possible that asbestos exposure should have been evaluated with the use of exact fibre-years. A more robust division of three categories of exposure had been planned, however, since the evaluation of past asbestos exposure is always an approximation. The reliable calculation of the exact number of fibre-years is probably possible only in very specific situations, such as for workers in asbestos plants where dust concentrations and complete employment durations have been recorded systematically.

Retroperitoneal, pleural and lung fibrosis

From a radiological aspect, the most distinctive feature of the asbestos-exposed RPF patients was a thick DPT, frequently associated with round atelectasis. This qualitative impression was also supported by the statistics. DPT was the most frequent among the asbestos-exposed RPF patients, and it was thicker than in the asbestos-exposed controls or in the unexposed RPF patients. DPT is thought to be a consequence of acute asbestos-related pleurisy (McLoud et al. 1985). However, DPT, resulting from traumas and various infectious and inflammatory conditions, is a common finding in the Finnish adult population (Zitting et al. 1996). Crocidolite-related DPT has been shown to progress in the first 15 years after its diagnosis, and this progression concurs with clinical experience with the past use of amphibole asbestos in Finland. It is proposed that the thinner DPT seen in unexposed RPF patients may be the result of short-lasting injury, such as surgery or infection, and the thicker DPT found in asbestos-exposed persons is probably related to continuous
insult from bioresistant amphibole fibres. Although ergotamine induces both pleural and retroperitoneal fibrosis, no signs of DPT were found in five persons with ergotamine-related RPF in the present data.

Pleural plaques were frequent in both asbestos-exposed groups, as could be expected. The prevalence of bilateral plaques was comparable with the results of other asbestos-exposed cohorts studied with HRCT or during autopsy (Karjalainen et al. 1994b, Tiitola et al. 2002). There were also two unexposed persons with some bilateral pleural plaques. A high prevalence of bilateral pleural plaques was found in the autopsy study of 300 urban Finnish men, in which 40% of the unexposed persons had moderate or widespread pleural plaques (Karjalainen et al. 1994b). These figures reflect the high potency of amphibole asbestos in the induction of pleural plaques during a person’s lifetime.

Only a few RPF patients and controls with ≥10 fibre-years of asbestos exposure had clinical asbestosis. It seems that the exposure level associated with the development of RPF is comparable with that associated with the development of pleural fibrosis rather than with the high level of exposure that induces asbestosis.

What is the probable link between DPT and RPF? On the basis of the results presented in this thesis, it can be argued that RPF is an independent risk factor for pleural fibrosis. The results of the case-control setting indicate that RPF patients were more prone towards the development of severe DPT than the exposed controls. However, DPT is far commoner than RPF, and it is evident that asbestos exposure occurs mainly via the respiratory system. Therefore asbestos-exposed persons with pleural fibrosis evidently develop concomitant RPF because of their higher individual susceptibility for such a biological reaction.

**Retroperitoneal fibrosis as an occupational disease**

Based on the studies covered by this thesis, the following criteria are proposed for RPF as an occupational disease: (i) occupational asbestos exposure of ≥10 fibre-years or (ii) occupational asbestos exposure of <10 fibre-years combined with bilateral pleural plaques or DPT or both pleural plaques and DPT. The presence of asbestosis (parenchymal fibrosis) should not to be required for the diagnosis of
asbestos-related RPF. Asbestos-related RPF, like asbestos-related pleurisy, should be a diagnosis of exclusion. Nevertheless, asbestos-related pleural findings should be taken into account also in the presence of other risk factors, such as ergotamine medication or abdominal aortic aneurysm.

Translocation of asbestos fibres in the human body

During the last 50 years, several theories have been proposed for the translocation of asbestos from the lungs to pleurae and extrapulmonary sites, including macrophage migration, retrograde lymph flow, and blood embolization. The latest review proposes a sophisticated scheme based on variable pressure and flow gradients in the lungs (Miserocchi et al. 2008). The authors suggest that fibre translocation to the pleural space may partly occur via direct translocation of the fibres from the lung to the pleura, but that the extrapulmonary translocation takes place solely through blood circulation.

It has been known for more than a decade that asbestos fibres and other inorganic dust concentrates in the pulmonary lymph nodes (Dodson et al. 1990, Tossavainen et al. 1994), obviously transported there by lymph flow. The lymph from the peripheral bronchial tree first flows towards the visceral pleura and subsequently drains into the hilar lymph nodes and parietal pleura. Short asbestos fibres may reach the pleural space by penetrating the pulmonary parenchyma and the visceral pleura and then follow the normal lymphatic flow through the parietal pleura, where some of them remain (Hillerdal 1980). Asbestos fibres penetrating the visceral pleura have been visualized by electron microscopy (Müller 2002).

The lymph vessels have been found to descend to the PA lymph nodes from the posterior part of the diaphragm (Souilamas et al. 2001). In some cases, the lymph vessels were also connected directly to the thoracic duct. The posterior part of the diaphragm is the lowest part of the pleural space in both the upright and the supine position, and, for this reason, it accounts for a considerable amount of pleural fluid turnover. Proteins, particles, and cells are removed through the stomas of the parietal pleura of the same area (Miserocchi 1997, Zocchi 2002).
The results presented in this thesis support the concept of the lymph circulation playing an important role in asbestos translocation. The mean content of asbestos fibres in the abdominal lymph nodes was 0.43 million f/g for the PA lymph nodes and 0.27 for the ME (i.e., 60-70 times lower than in the lungs). Nevertheless, these values are 1000 times higher than previously reported asbestos concentrations in the omentum and mesentery of patients with mesothelioma (range 0.0002-0.0066 million f/g fibres >1µm in length) (Dodson et al. 2000, Dodson et al. 2001). The lung asbestos concentrations in these patients were similar to those found in Study III. These figures indicate that asbestos fibres concentrate in the lymph nodes of the abdominal cavity in the same way as in the thoracic cavity.

On the basis of the results presented in this thesis, the following mechanism for the translocation of asbestos fibres to the extrapulmonary organs can be suggested: asbestos fibres reach the parietal pleura through the normal pleural fluid flow, they are absorbed from the pleural space through the lacunae and are translocated by the lymph flow into the subdiaphragmatic region. Depending on anatomic variations, some fibres accumulate in the PA and other subdiaphragmatic lymph nodes, and some are drained into the thoracic duct and venous systemic circulation.

**Asbestos fibres in the abdominal tissues**

Study III showed that the retroperitoneal lymph nodes of asbestos-exposed persons contain substantial numbers of asbestos fibres. However, this finding does not necessarily mean that the fibres trapped in the lymph nodes trigger a fibrotic reaction. Study IV showed, for the first time in the literature, that asbestos fibres can be found in the fibrotic tissue of asbestos-exposed RPF patients. The asbestos concentrations were higher in the PA lymph nodes and, therefore, indicated that fibres are translocated by lymph flow. Although RPF typically develops from the level of the renal arteries, with abundant lymph nodes, the other asbestos-related fibrotic processes develop in the periphery of the lungs and pleural space. Therefore it seems more likely that fibrosis is induced by asbestos fibres that penetrate the lymph ducts or blood capillaries to the retroperitoneal connective tissue.
Conclusions

The studies covered by this thesis established the prevalence and incidence rates for retroperitoneal fibrosis in the Finnish population. Retroperitoneal fibrosis was strongly associated with asbestos exposure in the case-control study. There was a positive biological gradient for asbestos exposure. The role of abdominal aortic aneurysm and ergotamine medication was confirmed as a risk factor for retroperitoneal fibrosis. The presence of atherosclerotic diseases did not appear as a risk factor in the statistic modelling. And RPF is evidently a disease with multiple aetiologies.

An asbestos-related pleural finding was common for the asbestos-exposed RPF patients, but only a few of these patients had parenchymal lung fibrosis. RPF without asbestos exposure was not associated with pleural or lung fibrosis. The most distinctive feature of the asbestos-exposed RPF patients was a thick DPT, combined with exceptionally large pleural masses located anteriorly in the pleural space in three RPF patients.

Asbestos exposure was associated with DPT in comparisons between RPF patients and controls (case-control analysis), as well as among RPF patients (case-case analysis). The findings suggest a shared aetiology for RPF and pleural fibrosis and, furthermore, possibly similar pathogenetic mechanisms.

A high concentration of asbestos fibres was observed in the retroperitoneal and ME lymph nodes of asbestos-exposed persons. Even low-level occupational exposure resulted in the presence of both amphibole and chrysotile asbestos in these abdominal lymph nodes. The results support the hypothesis of lymph drainage as an important translocation mechanism for asbestos in the human body.
In conclusion, the results show that occupational asbestos exposure seems to be one of the causal agents for RPF. All RPF patients should be evaluated for asbestos exposure, and lung HRCT should be carried out if appropriate. For patients with work-related asbestos exposure, RPF should be possibly considered an occupational disease.
Acknowledgements

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and

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Padley SP, Hansell DM, Flower CD and Jennings P (1991): Comparative accuracy of high resolution computed tomography and chest radiography in the


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Appendices

Appendix 1 – Questionnaire in Study I.

Henkilötiedot

Sukupuoli

- mies
- nainen

Ikä (vuotta)

Ammatti (nykyinen tai viimeinen)

Eläkkeelle siirtymisvuosi (eläkelääsi) -

Pitkäaikaissairaudet: (esim. verenpainetauti, sepelvaltimotauti, valtimokovettumatauti, aivoverenkiertohäiriöt, munuaissairaus, astma, krooninen keuhkoputken tulehdus, keuhkohtaumatauti, keuhkofibroosi, reuma, migreeni, pahanlaatuiset kasvaimet)

Leikkaukset, erityisesti vatsan alueeseen kohdistuvat (esim. umpisuolileikkaus, tyräleikkaus, keisarinleikkaus, sappileikkaus, leikkaus suolitukoksen vuoksi, munuaiseen ja virtsateihin kohdistuvat leikkaukset, kohdunpoisto, kasvainten vuoksi tehdyt leikkaukset jne)

Onko Teillä todettu rinta - tai vatsa-aorton pullistuma?

- ei
- kyllä (ympäröikää) rinta-aorton / vatsa-aorton

seurataan vuodesta ......................

leikattu vuonna ......................
Migreenilääkitys
Oletteko käyttäneet seuraavia ergotamiinia sisältäviä migreenilääkkeitä:
Metysergidi\textsuperscript{®}, Methergin\textsuperscript{®}, Myomergin\textsuperscript{®}, Cafegrot\textsuperscript{®}, Anervan\textsuperscript{®}, Cafegrot comp\textsuperscript{®}, Hemicranin\textsuperscript{®}, Migri\textsuperscript{®}, Trimigrin\textsuperscript{®}, Orstanorm\textsuperscript{®}, Vasogin\textsuperscript{®}, Artergin\textsuperscript{®}, Senart\textsuperscript{®}, Hydergin\textsuperscript{®}

<table>
<thead>
<tr>
<th>vuodesta</th>
<th>vuoteen</th>
<th>Käytän edelleen</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>(x)</td>
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</tbody>
</table>

Muu lääkitys
Tähän pyydämmme merkitsemään myös Teidän aikaisemmat lääkkeet

<table>
<thead>
<tr>
<th>vuodesta</th>
<th>vuoteen</th>
<th>käytän edelleen</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(x)</td>
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</tbody>
</table>

Onko Teille tehty kasvainautien vuoksi leikkausia, annettu sädehoitoa tai sytostaattihoidoja?
Sairaus | annetut hoidot | sairaala ja ajankohta

TYÖTERVEYSLAITOS
ASBESTIALTISTUMISLOMAKE
TYÖALATIEDOT

Merkitkää työskentelyaika (vuodesta vuoteen) niiden työalojen ja työtehtävien kohdalle, joilla olette työskennellyt pääasiassa (esim. vuosina 45-46, 63-68, 75).

<table>
<thead>
<tr>
<th>Talonrakennusala</th>
<th>Vuosina</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Uusien putkien asennus</td>
<td></td>
</tr>
<tr>
<td>2 Vanhojen putkistojen purku</td>
<td></td>
</tr>
<tr>
<td>3 Putkieristystyöt</td>
<td></td>
</tr>
<tr>
<td>4 Muut eristystyöt</td>
<td></td>
</tr>
<tr>
<td>5 Sähköasennustyöt</td>
<td></td>
</tr>
<tr>
<td>6 Muut rakennustyöt</td>
<td></td>
</tr>
<tr>
<td>uuidisrakennuksilla</td>
<td></td>
</tr>
<tr>
<td>7 Muut rakennustyöt</td>
<td></td>
</tr>
<tr>
<td>korjausrakentamisessa</td>
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</table>

<table>
<thead>
<tr>
<th>Telakkateollisuus</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>8 Varustelytöt (vesillelaskun jälkeen)</td>
<td></td>
</tr>
<tr>
<td>9 Työt korjauslaivoilla</td>
<td></td>
</tr>
<tr>
<td>10 Asbestiruiskutus ja -eristystyöt</td>
<td></td>
</tr>
<tr>
<td>11 Muut työt telakkateollisuudessa</td>
<td></td>
</tr>
</tbody>
</table>

91
<table>
<thead>
<tr>
<th>Työaluineen</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Asbestituoteteollisuus ja -kaivos</td>
<td></td>
</tr>
<tr>
<td>12 Työt asbestituotteiden valmistuksessa</td>
<td></td>
</tr>
<tr>
<td>13 Työt asbestikaivoksilla</td>
<td></td>
</tr>
<tr>
<td>14 Muut työt asbestituoteteollisuudessa</td>
<td></td>
</tr>
<tr>
<td>Autokorjaamot</td>
<td></td>
</tr>
<tr>
<td>15 Jarru- ja kytkintyöt</td>
<td></td>
</tr>
<tr>
<td>16 Muut työt autokorjaamossa</td>
<td></td>
</tr>
<tr>
<td>17 Muut työalat</td>
<td></td>
</tr>
</tbody>
</table>

Luetelkaa muut työalat kuin edellä mainitut, joilla olette pääasiallisesti toiminut. Mainitkaa ammattinne näiltä työaloilta.

<table>
<thead>
<tr>
<th>Ammatti (esim. maanviljelijä)</th>
<th>Vuosina</th>
</tr>
</thead>
</table>

Oletteko altistunut asbestille rakentaessanne tai korjatessanne omia rakennuksianne? Vuosina
Oletteko tehnyt seuraavia työtehtäviä, joissa oli mahdollisuus joutua tekemisiin asbestia sisältävien tuotteiden kanssa? Vastatkaa merkitsemällä rasti (X) ruutuun oikean vaihtoehdon kohdalle.

Jos vastaatte kyllä, niin merkitkää ne vuodet, jolloin teitte tällaisia töitä (esim. vuosina 56-66, 68-82).

<table>
<thead>
<tr>
<th></th>
<th>Ei</th>
<th>En</th>
<th>Kyllä</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>osaa</td>
<td>sanoa</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Purkanut asbestipitoisia materiaaleja</td>
<td>□ □ □</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Tehnyt asbestiruiskutustöitä (palonsuojaus, lämpö- ja akustiikka eristys)</td>
<td>□ □ □</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Tehnyt putkieristystöitä käyttäen eristysmassaa</td>
<td>□ □ □</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Asentanut pannujen, uunien, lämminvesikattiloiden, koneiden ja sähköläitteiden lämpö ja paloeristeitä</td>
<td>□ □ □</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Asentanut ulkokatuo asbestisementti levyjä, kattohuopaa</td>
<td>□ □ □</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Asentanut seinälevyjä, sisäkatollevyjä, sisäverhouslevyjä, akustiikkalevyjä ja palonsuojalevyjä (esim. Minerit, Lujalevy, Tuulensuojat-Luja</td>
<td>□ □ □</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Purkanut vinyylimattoja tai massalattioita</td>
<td>□ □ □</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Siivonut tiloja, joissa on käytetty asbestia tai asbestipitoisia tuotteita</td>
<td>□ □ □</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Käyttänyt asbestia sisältäviä maaleja (esim. Kenitex), kittejä, lattiatasojiteita tai kiinnityslaasteja (Vetonit, Pukkila)</td>
<td>□ □ □</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Onko läheisyydessänne (samoissa työtiloissa) tehty yllä mainittuja töitä?</td>
<td>□ □ □</td>
<td></td>
</tr>
</tbody>
</table>
11. Toiminut asbestituotetehtaaassa tai asbestilouhoksella varsinaisessa tuotannossa, varastossa tai kuljetuksessa

12. Toiminut telakoilla asbestiruiskutuksessa, samoissa tiloissa myöhemmin työskentelemässä tai asbestipitoisten levyjen työstössä, siivouksessa tai vanhojen laivojen korjaustöissä

13. Teollisuuden huoltotöissä, jossa altistunut asbestille

14. Oletteko jossain muussa työtehtävissä käsitellyt asbestia sisältäviä materiaaleja? Missä työtehtävässä?

15. Ovatko lähiomaisen teokyseen ammatissa, jossa olisivat runsaasti altistuneet asbestille?

TUPAKOITTEKO?

En ole koskaan tupakoinut säännöllisesti

En tupakoi nykyään, mutta olen aikaisemmin tupakoinut säännöllisesti

vuodesta _______________ Alkaen
vuoteen _______________
yhteensä _______________ Vuotta

Olen tupakoinut säännöllisesti

vuodesta _______________ Alkaen
yhteensä _______________ Vuotta

Mikä on tai oli tavanomainen tupakan kulutuksen päivässä? (koskee myös lopettaneita)

savuketta _______________
pipiullista

TARKASTAKAA VIELÄ, ETTÄ VASTASITTE JOKAISEEN KYSYMÝKSEEN. KIITOS!
Appendix 2 – Classification of the pleural findings.

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parietal pleural plaques</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Normal finding</td>
</tr>
<tr>
<td>1</td>
<td>Subnormal finding, plaques suspected or unilateral plaques</td>
</tr>
<tr>
<td>2</td>
<td>Bilateral plaques on less than half of the slices</td>
</tr>
<tr>
<td>3</td>
<td>Bilateral plaques on at least half of the slices</td>
</tr>
<tr>
<td>4</td>
<td>Bilateral plaques on at least two-thirds of the slices</td>
</tr>
<tr>
<td>5</td>
<td>Bilateral plaques exceeding 50% of the total pleural area</td>
</tr>
<tr>
<td><strong>Diffuse pleural thickening</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Normal finding</td>
</tr>
<tr>
<td>1</td>
<td>Unilateral pleural thickening of &lt;5 mm</td>
</tr>
<tr>
<td>2</td>
<td>Bilateral pleural thickening of &lt;5 mm</td>
</tr>
<tr>
<td>3</td>
<td>Uni- or bilateral pleural thickening of ≥5 mm</td>
</tr>
</tbody>
</table>
Appendix 3 – Classification of lung fibrosis.

<table>
<thead>
<tr>
<th>Assessed abnormalities*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subpleural nodules/ irregular opacities</td>
</tr>
<tr>
<td>Septal lines (5 per lung on a slice on at least 2 slices)</td>
</tr>
<tr>
<td>Curvilinear opacities at least on 1 slice</td>
</tr>
<tr>
<td>Intralobular fibrosis at least on 2 slices</td>
</tr>
<tr>
<td>Parenchymal bands at least on 2 slices</td>
</tr>
<tr>
<td>Honeycombing</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fibrosis Classes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Normal</td>
<td>Normal finding by all criteria</td>
</tr>
<tr>
<td>1 Subnormal</td>
<td>1-2 criteria, no honeycombing</td>
</tr>
<tr>
<td>2 Mild fibrosis</td>
<td>At least 2 criteria on both sides in several slices, no honeycombing</td>
</tr>
<tr>
<td>3 Moderate fibrosis</td>
<td>Several criteria on at least 5 slices or extending deep into the lung; no honeycombing</td>
</tr>
<tr>
<td>4 Severe fibrosis</td>
<td>Several criteria as in class 3 and honeycombing; lung architectural change</td>
</tr>
<tr>
<td>5 Extreme fibrosis</td>
<td>Extremely severe and various fibrotic changes, little normally aerated lung left</td>
</tr>
</tbody>
</table>

* Abnormalities clearly associated with processes unrelated to asbestos-related diseases (eg, focal scarring and fibrosis related to centrilobular emphysema) were not included in the fibrosis scale.
Original publications
Asbestos exposure as a risk factor for retroperitoneal fibrosis

Toomas Uibu, Panu Oksa, Anssi Auvinen, Eero Honkanen, Kaj Metsärinne, Heikki Saha, Jukka Uitti, Pekka Roto

Summary

Background Retroperitoneal fibrosis (RPF) is an uncommon disease with unknown causation in most cases. The pathognomonic finding is a fibrous mass covering the abdominal aorta and the ureters. Our aim was to clarify the possible role of asbestos exposure in the development of RPF. The hypothesis was based on the ability of asbestos to cause fibrosis in pulmonary and pleural tissue.

Methods We undertook a case-control study of 43 patients with the disease (86% of eligible cases) treated in three university hospital districts of Finland in 1990–2001. For every patient, five population-based controls were selected, matched by age, sex, and central hospital district. We assessed asbestos exposure and medical history using a postal questionnaire and a personal interview. Of the 215 eligible controls, 179 (83%) participated in the study.

Findings The age-standardised incidence of RPF was 0.10 (95% CI 0.07–0.14) per 100 000 person-years. The disease was strongly associated with asbestos exposure. The odds ratio (OR) was 5.54 (1.64–18.65) for less than 10 fibre-years of asbestos exposure and 8.84 (2.03–38.50) for 10 or more fibre-years, the attributable fraction being 82% and 89%, respectively. Other risk factors were previous use of ergot derivates (OR 9.92 [1.63–59.36]), abdominal aortic aneurysm (OR 6.73 [0.81–56.08]), and smoking for more than 20 pack-years (OR 4.73 [1.28–17.41]).

Interpretation Our results show that occupational asbestos exposure is an important causal factor for RPF. For patients with work-related asbestos exposure, RPF should be considered an occupational disease.

Lancet 2004; 363: 1422–26

Introduction

Idiopathic retroperitoneal fibrosis, Ormond’s disease, is a rare condition that was first described by Albarran in 1905, with comprehensive characterisation by Ormond in 1948. The pathognomonic feature of retroperitoneal fibrosis (RPF) is a thick retroperitoneal fibrotic mass covering the abdominal aorta and compressing the ureters (figure). The process of fibrosis can result in obstruction of the ureters and renal failure. The main treatment options include surgical liberation of the ureters and systemic administration of corticosteroids. Investigators have reported remission rates exceeding 90%.

Previous work on the cause of this disease have been mainly case reports and series, which indicate that RPF can be induced by different factors. About a third of cases develop as a result of malignant disease, radiation therapy, abdominal surgery, pancreatitis, haematomas, and infections. RPF has also been associated with the use of several drugs, especially methysergide and other ergotamine derivates. Little is known about the role of occupational factors such as asbestos exposure in RPF. Asbestos fibres cause interstitial lung fibrosis (asbestosis), pleural fibrosis, pleural plaques, lung cancer, and pleural and peritoneal mesothelioma. Asbestos exposure has been proposed as a causal factor for pleural and retroperitoneal fibrosis in three previous case reports. RPF has been suggested as the most severe form of chronic periaortitis, caused by the autoimmune response to the components of atherosclerotic plaques. The histological appearances of RPF and atherosclerotic chronic periaortitis are often identical.

An association between abdominal aortic aneurysms and RPF has also been shown. The inflammatory nature of idiopathic RPF is supported by an elevated erythrocyte sedimentation rate at presentation and positive antinuclear antibodies, good response to anti-inflammatory drugs, and an occasional association with different autoimmune diseases. However, in most cases, the causative factors remain elusive. Our aim was to assess the aetiological significance of occupational asbestos exposure in the development of RPF in a case-control study.

Methods

Patients

We selected all adult patients alive with RPF diagnosed and treated in 12 secondary and tertiary hospitals within three university hospital districts in Finland in 1990–2001. The population of the catchment area was 3.62 million in 2001. Demographic data were obtained from Statistics Finland. The ethics committee of Tampere University Hospital approved the study plan.

Potential cases were retrieved from the hospital discharge data register. Case identification was based on diagnostic codes 5934A (other ureteric obstruction including idiopathic RPF) in ICD 9 (International
We also recorded five deceased individuals with RPF. Two male patients refused to participate, one female patient did not attend the study despite her initial consent, three women had neurocognitive disease that affected the interview and one woman could not be contacted. Mean age at diagnosis was 56 years, and the ratio of men to women was 2:1 (table 1).

**Controls**

For every case, five living controls matched for year of birth, sex, and central hospital district were randomly assigned from the Finnish population register centre. Matching for central hospital district was used to avoid bias from different industrial structures in the regions. At the time of enrolment, 1,597,483 people born in 1918–63 lived in the study area.

**Data collection**

A five-page questionnaire was sent to all patients and controls to obtain information about sociodemographic factors, smoking, and medical history (including chronic diseases, abdominal surgery, aortic aneurysm, migraine and migraine medication used, and other permanent medication and malignant diseases). A structured questionnaire with 21 questions compiled and validated by the Finnish Institute of Occupational Health was used for assessment of asbestos exposure.

Postal questionnaires are prone to misclassification, especially with respect to occupational exposure. To avoid this problem, all individuals were interviewed personally after they had returned the completed questionnaires. All participants were interviewed by the same physician (TU). The interviews were done mainly by telephone. If a participant could not recall whether they had had medical conditions or medication that would affect the outcome of the study, their medical records were reviewed with their consent.

One reminder was sent to the controls who did not respond to the first request. The remaining non-responding controls were contacted directly by telephone and asked the same questions as in the questionnaire.

We obtained sufficient data from 179 (83%) of the 215 controls. Eight refused to participate, and three were not willing to answer all of the questions. One person died after enrolment. We were unable to contact 24 persons. The response proportions of the participants were as follows: 73 (34%) for the first questionnaire, 42 (20%) for the reminder, and 64 (30%) for the telephone interview.

**Evaluation of asbestos exposure**

Assessment of cumulative asbestos exposure was based on fibre-years as determined by an expert according to industrial hygiene knowledge of certain occupations. A fibre-year was defined as working in a full shift (40 hours per week) for 1 year at an average dust level of 1 fibre/mL of air. The cumulative dose of 10 fibre-years has been
estimated to cause a 1% risk of developing clinically
recognisable asbestosis.1 We defined three grades of
cumulative exposure before obtaining data: 0=no notable
asbestos exposure (low-level-exposure less than 1 week); 1=slight exposure, more than 1 week of low-level
exposure and less than 10 fibre-years; and 2=moderate to
high exposure, 10 fibre-years or more. A senior
occupational physician (PO) who was masked to case-
control status assessed asbestos exposure.

Analysis
We calculated age-standardised incidence using the
European 5-year group standard population.17
Multivariate analysis was done with conditional logistic regression in STATA (version 7.0). The attributable
fraction (proportion of cases caused by exposure) was calculated with the formula (OR-1)/OR and the
population attributable fraction (PAF) was determined as
\( q \frac{\text{OR}-1}{\text{OR}} \), in which OR was the odds ratio and q was
the proportion of cases exposed to the factor.19 In
calculation of the CIs, q was assumed to be constant.

Role of the funding source
The funding sources of the study had no role in the study
design, data collection, data analysis, data interpretation,
or writing of the report.

Results
The age-standardised incidence of RPF was 0-10 (95% CI
0-07–0-14) per 100 000 person-years overall, 0-14
(0-08–0-21) for men and 0-07 (0-04–0-10) for women, in

The prevalence of the disease was 1·38 per 100 000
inhabitants in the study area. 22 (51%) cases and 48
(27%) controls had a positive asbestos exposure history (table 2). Exposures exceeding 10 fibre-years were
exclusively occupational (table 3). Asbestos exposure was
strongly associated with RPF, with crude OR 4·2 (95% CI
1-6–11-0) for less than 10 fibre-years and 4·1 (1-4–12-4)
for 10 or more fibre-years. After adjustment for the other
risk factors, we noted a gradient by level of exposure.

Compared with controls, individuals exposed to asbestos
for less than 10 fibre-years were over five times more likely
to develop RPF and those exposed for 10 fibre-years or
more were nearly nine times more likely to develop the
disease (table 4). There was no significant interaction
between smoking and asbestos exposure.

Mean time from the first exposure to the appearance of
RPF (the mean latency period) was 30-0 (SD 12-3) years
for slight exposure and 33·3 (7-3) years for moderate to
high exposure. The shorter mean latency period of the
group with less than 10 fibre-years exposure was a result
of two outlier cases having probable asbestos exposure
during repair work in their residences. Omission of these
cases lengthened the mean latency period to 34·6 (range
23–46) years. The interval from the beginning of the
exposure of the control to the RPF diagnosis of the case
was 26·7 (SD 10·6) years for less than 10 fibre-years of

<table>
<thead>
<tr>
<th>Occupation</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases (n=9)</td>
<td></td>
</tr>
<tr>
<td>Construction worker</td>
<td>2</td>
</tr>
<tr>
<td>Insulator</td>
<td>2</td>
</tr>
<tr>
<td>Construction cleaner</td>
<td>1</td>
</tr>
<tr>
<td>Asbestos plant technical assistant</td>
<td>1</td>
</tr>
<tr>
<td>Electrician</td>
<td>1</td>
</tr>
<tr>
<td>Shipyard worker and insulator</td>
<td>1</td>
</tr>
<tr>
<td>Ship technology engineer</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Controls (n=21)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Construction worker</td>
<td>12</td>
</tr>
<tr>
<td>Demolisher of furnaces</td>
<td>2</td>
</tr>
<tr>
<td>Car mechanic</td>
<td>2</td>
</tr>
<tr>
<td>Air conditioning mechanic</td>
<td>1</td>
</tr>
<tr>
<td>Welder</td>
<td>1</td>
</tr>
<tr>
<td>Furnace worker</td>
<td>1</td>
</tr>
<tr>
<td>Shipyard worker</td>
<td>1</td>
</tr>
<tr>
<td>Sailor (worked in engine room demolition)</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 3: Occupations associated with >=10 fibre-years of
asbestos exposure among the RPF cases and the controls

<table>
<thead>
<tr>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asbestos exposure &gt;=10 fibre-years</td>
</tr>
<tr>
<td>Asbestos exposure &lt;10 fibre-years</td>
</tr>
<tr>
<td>Use of ergot derivatives before index time*</td>
</tr>
<tr>
<td>Smoking history &gt;20 pack-years</td>
</tr>
<tr>
<td>Smoking history &lt;=20 pack-years</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
</tr>
<tr>
<td>Abdominal surgery before index time</td>
</tr>
<tr>
<td>Use of ß blocking agents before index time</td>
</tr>
<tr>
<td>Atherosclerotic disease†</td>
</tr>
<tr>
<td>Arterial hypertension before index time</td>
</tr>
<tr>
<td>Migraine</td>
</tr>
</tbody>
</table>

*Index time for cases was the time of RPF diagnosis and for controls the time of
diagnosis of the corresponding case. †Coronary heart disease, peripheral
vascular disease and ischaemic stroke.

Table 4: Adjusted odds ratios for potential risk factors for
retroperitoneal fibrosis

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Asbestos fibres have been found in the mesenteric and omental tissue of patients with mesothelioma and in those exposed to asbestos through sources other than their occupation. Intrapertitoneal asbestos fibre injections have been used to study asbestos-induced fibrosis and its carcinogenicity in animal models. That asbestos fibres can induce fibrosis in the peritoneal space is therefore well-documented.52

In RPF, fibrotic tissue around the abdominal aorta typically begins at the level of the renal arteries. In the same area, the efferent lymph vessels from the posterior part of the diaphragm drain into the para-aortic lymph nodes at the origin of the thoracic duct.53 Asbestos fibres can relocate from lung tissue to extrapulmonary sites via the lymphatic system.54 The highest concentrations of asbestos fibres in human tissue have been found in hilar lymph nodes.55 We propose that asbestos fibres penetrating through the parietal diaphragmatic pleura are drained into para-aortic lymph vessels and nodes, where they might trigger an inflammatory process.

We used prevalence sampling (ie, both cases and controls had to be alive at the time of the study). With this approach, we could not distinguish between factors associated with the risk of disease and those related to favourable outcomes. However, RPF seemed to have a good prognosis, and overall, only five patients were excluded because of death. Hence, any distortion of aetiological effects was likely to be small.

In order to keep information bias to a minimum, we used masked exposure grading. It was not feasible, however, to interview masked participants because the disease status would be revealed during the interview. Since no non-occupational aetiology of the disease had been identified, the history of asbestos exposure has not been investigated at the time of diagnosis or treatment. The study hypothesis was not described to the participants. Therefore, recall of exposure was probably not affected by the case-control status.

The prevalence of RPF in our study was 1·38 per 100 000 inhabitants, which is twice as high as the previous estimate of 1 per 200 000.56 Because of the rarity of the disease, there have been no other population-based estimates of prevalence or incidence. PAF was estimated on the basis of the exposure distributions of the cases. This procedure was likely to overestimate the PAF in relation to asbestos exposure because men and older individuals with a higher frequency of asbestos exposure were over-represented. In the entire Finnish population, about 3% are slightly exposed to asbestos and 1% are heavily exposed.57 These figures would give population attributable fractions of 12% and 7%, respectively.

We could not identify any clear association between RPF and atherosclerotic cardiovascular diseases other than aortic aneurysm. Heavy smoking was a significant risk factor for RPF. This association may be related to the atherogeneity of cigarette smoke. On the other hand, smoking enhances free radical production and increases asbestos-induced inflammation.58 Smoking is also known to lead to a greater accumulation of asbestos fibres in airway mucosa.59 Therefore cigarette smoking may have an indirect fibrogenic effect.

Although previous abdominal surgery did not correlate with the disease, several cases had undergone extensive and complicated abdominal operations before RPF manifestation. However, we were not able to obtain equivalent detailed verified information on surgical procedures from the controls, and, consequently, the negative result does not rule out this clinically observed causative factor.

An additional finding is the similar historical background of RPF and mesothelioma. The first case of mesothelioma was published in 1947,60 1 year before Ormond’s report. The number of cases increased in the 1960s because of the increased use of asbestos in the 1930s and 1940s.61 Since the 1960s, RPF has also become more common, but this increase can also be explained by better diagnostic facilities.

If supported by results from other investigations, the classification of RPF as an occupational disease should be considered and occupational history should be included in the evaluation of these patients.

Contributors
P Roto was the initiator and co-ordinator of the study. T Uibu was responsible for the identification of patients, interviews, data collection, statistical analysis, and preparation of the article. P Oksa assessed asbestos exposure levels and acted as an expert consultant. A Auvinen was responsible for epidemiological design and planned the data analysis. E Honkanen, K Metsärinne, and H Saha participated in the identification of the RPF patients. J Unti acted as an expert consultant. All the investigators contributed to study design and writing of the manuscript.

Conflict of interest statement
None declared.

Acknowledgments
We thank Heini Huhtala and Pirjo Palmroos for their assistance with the statistical analysis, and Ritva Jarvenpää for reviewing the CT scans. This study was supported by the Tampere Tuberculosis Foundation, the Medical Research Fund of the Tampere University Hospital, and the Finnish Work Environment Fund.

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2 Ormond JR. Bilateral ureteral obstruction due to development and compression by an inflammatory retroperitoneal process. J Urol 1948; 59: 1072.

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21 Dodson RF, O'Sullivan MF, Brooks DR, Bruce JR. Asbestos content of omentum and mesentery in nonoccupationally exposed individuals. *Toxicol Ind Health* 2001; 17: 138–43.
Asbestos-related pleural and lung fibrosis in patients with retroperitoneal fibrosis
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* Corresponding author

Abstract

Background: Retroperitoneal fibrosis (RPF) is a rare fibroinflammatory disease that leads to hydronephrosis and renal failure. In a case-control study, we have recently shown that asbestos exposure was the most important risk factor for RPF in the Finnish population. The aim of this study was to evaluate the relation of asbestos exposure to radiologically confirmed lung and pleural fibrosis among patients with RPF.

Methods: Chest high-resolution computed tomography (HRCT) was performed on 16 unexposed and 22 asbestos-exposed RPF patients and 18 asbestos-exposed controls. Parietal pleural plaques (PPP), diffuse pleural thickening (DPT) and parenchymal fibrosis were scored separately.

Results: Most of the asbestos-exposed RPF patients and half of the asbestos-exposed controls had bilateral PPP, but only a few had lung fibrosis. Minor bilateral plaques were detected in two of the unexposed RPF patients, and none had lung fibrosis. DPT was most frequent and thickest in the asbestos-exposed RPF-patients. In three asbestos-exposed patients with RPF we observed exceptionally large pleural masses that were located anteriorly in the pleural space and continued into the anterior mediastinum.

Asbestos exposure was associated with DPT in comparisons between RPF patients and controls (case-control analysis) as well as among RPF patients (case-case analysis).

Conclusion: The most distinctive feature of the asbestos-exposed RPF patients was a thick DPT. An asbestos-related pleural finding was common in the asbestos-exposed RPF patients, but only a few of these patients had parenchymal lung fibrosis. RPF without asbestos exposure was not associated with pleural or lung fibrosis. The findings suggest a shared etiology for RPF and pleural fibrosis and furthermore possibly a similar pathogenetic mechanisms.
Background

Retroperitoneal fibrosis (RPF), or Ormond’s disease, is a rare condition with fibrosis covering the abdominal aorta and the ureters. The etiology of RPF is generally unknown. It has been proposed that approximately one-third of RPF cases develop secondarily to aortic aneurysm, abdominal infections or surgery and as a side effect of several drugs, especially methysergide and other ergot derivates [1-3]. Asbestos is known to cause diffuse pleural thickening (DPT) and parietal pleural plaques [4]. High-level asbestos exposure may lead to the development of clinically detectable lung fibrosis (asbestosis) [5]. We have recently shown that asbestos exposure is one of the most important single risk factors for RPF, accounting for approximately 20% of all RPF cases in the Finnish population [6,7]. The aim of this study was to determine whether RPF patients have pleural or lung fibrosis and to assess the relations between asbestos exposure and intrathoracic fibrotic changes in RPF patients. Furthermore we evaluated the susceptibility for pleural and lung fibrosis among asbestos-exposed RPF patients and asbestos-exposed controls.

Subjects and methods

Study population

This material was part of our case-control study including 43 persons with RPF and 179 randomly assigned controls matched for year of birth, gender and central hospital district in Finland [6]. The diagnosis of RPF required the presence of the typical clinical condition–fibrosing mass covering the abdominal aorta and other retroperitoneal structures–and either histological confirmation (35 of 43 persons) or a follow-up of at least 1 year in order to rule out retroperitoneal malignancies (8 of 43 persons).

All of the participants were interviewed for medical history and asbestos exposure. The cumulative exposure to asbestos dust was estimated using fiber-years (40-hour shift per week at an average dust level of 1 fiber/ml for 1 year) and graded as follows: no significant asbestos exposure; slight exposure (asbestos exposure <10 fiber-years) and moderate-to-high exposure (asbestos exposure ≥ 10 fiber-years). Exposure was assessed by an occupational health physician with special expertise in the evaluation of asbestos exposure, the physician was blinded in terms of the case-control status of the participants. The details of the data collection have been given in our previous report [6].

We asked all of the unexposed and exposed patients with RPF and the controls with moderate-to-high asbestos exposure to participate in a study evaluating pleural and lung fibrosis with chest high-resolution computed tomography (HRCT). The Ethics Committee of the Tampere University Hospital approved the study protocol.

Participation rate and demographic features

Altogether 38 (88%) of the patients with RPF and 18 (86%) of the asbestos-exposed controls were willing to participate. None of the 5 RPF patients who refused to participate in the HRCT study had notable asbestos exposure, which was also the main reason for their refusal.

The mean time since first asbestos exposure was 41.4 (SD 12.1) years for the RPF patients and 42.4 (8.9) years for the controls (Table 1).

Imaging

The HRCT was carried out in seven central hospitals. The HRCT scans consisted of 1-mm slices at 20-mm intervals from the first rib to the costophrenic angle in the prone position and with full inspiration. No contrast medium was used. The images were printed at two separate settings appropriate for viewing the lung parenchyma or the mediastinum and the pleura, the settings depending on the scanner used.

Image analysis

All of the images were reviewed by two experienced thoracic radiologists. The reviewers were blinded to all medical information except the participants’ names and identification numbers, which were printed on the films. The images were scored by consensus reading. Lung fibrosis, parietal pleural plaques and diffuse pleural thickening (DPT) were scored separately (additional files 1 and 2). The scoring was modified from our earlier classification systems [8,9]. Model images were not used, and the scoring was carried out in two sessions within one week.

Table 1: Demographic and exposure characteristics of the patients with retroperitoneal fibrosis and asbestos-exposed controls.

<table>
<thead>
<tr>
<th>RPF</th>
<th>Asbestos exposure</th>
<th>Gender men/woman</th>
<th>Age mean (SD)</th>
<th>Pack-years of smoking mean (SD)</th>
<th>Age at diagnosis of RPF mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
<td>9/7</td>
<td>61.9 (9.7)</td>
<td>20.4 (18.8)</td>
<td>55.5 (9.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>19/3</td>
<td>64.1 (9.4)</td>
<td>27.0 (17.4)</td>
<td>54.9 (8.0)</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>18/0</td>
<td>66.0 (7.7)</td>
<td>22.4 (27.1)</td>
<td>NA</td>
</tr>
</tbody>
</table>

(RPF = retroperitoneal fibrosis, NA = not applicable)
Measurements of the maximum DPT thickness were performed subsequently in one session. A definitely abnormal finding that could be related to asbestos exposure was rated class 1 for DPT (unilateral DPT <5 mm) and class 2 for pleural plaques (bilateral plaques on less than half of the slices) and lung fibrosis (at least 2 abnormal findings on both sides in several slices) (additional files 1 and 2).

Classification of the pleural abnormalities
Pleural plaques are discrete areas of fibrous tissue limited to the parietal pleura, whereas diffuse pleural thickening or visceral pleural fibrosis is much more widespread and usually extends into the costophrenic angles [10-12]. Pleural plaques were diagnosed as sharply defined thickenings located internally with respect to a visible rib segment in the chest walls, paravertebral regions, or on the diaphragmatic surfaces, with or without calcification. Pleural thickening was classified as DPT if it appeared as a smooth, uninterrupted density with ill-defined margins and with extension of more than one-fourth of the pleural surface. Parenchymal bands extending from the pleural thickening to the lung parenchyma, rounded atelectasis, and the involvement of the interlobar fissures was used to differentiate DPT from pleural plaques. Rounded atelectasis was defined as a round or oval mass abutting the pleural surface and associated with the curving of pulmonary vessels or bronchi into the edge of the lesion [11]. The maximum thickness of the DPT was measured from the slices transversal with the thoracic wall.

Statistical analysis
For the statistical analysis we combined the two asbestos-exposed RPF patient groups. The groups were compared using the Kruskal-Wallis and the Mann-Whitney tests, as appropriate. An ordinal logistic regression analysis was performed to assess the risk factors for DPT, pleural plaques and lung fibrosis in the asbestos-exposed patients and controls. The factors evaluated were the presence of RPF, age at the time of the HRCT, smoking in pack years, and the pleural plaque, DPT and lung fibrosis grade, as appropriate. The analysis was based on proportional odds (i.e. constant odds ratio across ordered categories of the response variable: odds of having a diagnostic score × or higher relative to having a score below ×). The outcome variable was the radiological finding categorized into four classes. The results of the ordinal logistic regression analysis therefore indicated susceptibility to the development of fibrotic changes, given asbestos exposure. Statistical significance was assessed using the likelihood ratio test. In addition, the susceptibility for asbestos-related pleural fibrosis among the RPF patients was evaluated in a case-case setting [13] using logistic regression analysis. All of the calculations were carried out with STATA 8.0 software (Stata Corporation, College station, TX, USA)

Results
Parietal pleural plaques
The unexposed RPF patients had only minor pleural plaques (≤ class 2), and the differences between this group and the asbestos-exposed groups were statistically significant (Figure 1, Table 2). More than 60% of the asbestos-exposed RPF patients and half of the exposed controls had bilateral pleural plaques (Figure 1, Table 2), and almost half of them had widespread plaques in class ≥ 3. The frequency and quantity of the pleural plaques were similar in both of the asbestos-exposed groups. There were no differences between the asbestos-exposed cases and controls with respect to susceptibility to the development of parietal pleural plaques in the ordinal logistic regression analysis. Out of the studied variables, only lung fibrosis was associated with parietal pleural plaques (OR 3.78, 95% CI 1.52–9.43). The grade of pleural plaques was not related to age, smoking history, or DPT grade (additional file 3). In the case-case analysis, the OR for pleural plaques related to asbestos was 12.2 (Table 3).

Diffuse pleural thickening
DPT occurred more frequently among the RPF patients with asbestos exposure than among the unexposed patients (P = 0.045). There were no differences between the asbestos-exposed RPF patients and controls (P = 0.190) and none of the differences between the three groups reached statistical significance (Figure 1, Table 2). Among the RPF patients, asbestos exposure increased the risk for both DPT and for all pleural fibrotic changes (Table 3).

The mean maximum thickness of DPT was 2.8 (SD 1.0) mm for the 4 unexposed RPF patients, 9.8 (SD 5.1) mm for the 12 exposed patients with RPF and 5.1 (SD 2.7) mm for the 7 exposed controls (Figure 2). The difference between the three groups was significant (P = 0.040), and a similar difference was found for contralateral pleural thickening (P = 0.048). The respective values for the contralateral DPT were 2 (SD 0) mm (3 subjects), 6.5 (SD 4.2) mm (10 subjects), and 2.8 (SD 1.0) mm (4 subjects) (Figure 2).

Rounded atelectasis was detected in one unexposed RPF patient (6%), one asbestos-exposed control (6%) and five asbestos-exposed RPF patients (22%), three of whom had bilateral findings. No statistical difference was noted (p = 0.182).

In the ordinal logistic regression analysis, the asbestos-exposed RPF patients had a nonsignificantly increased risk for the development of DPT when compared with that of the asbestos-exposed controls (OR 3.06, 95% CI 0.81–
11.56). Age at the time of the HRCT, smoking history, pleural plaques, and lung fibrosis grade had no influence on the development of DPT (additional file 3).

The four patients with RPF related to the previous use of ergotamine derivatives had no DPT.

### Pleural masses

We observed exceptionally large pleural masses in three asbestos-exposed patients with RPF. The uniform masses were located anteriorly in the pleural space and continued into the anterior mediastinum (Figure 3). The overall volumes of these masses clearly differed from the plaques and DPT found in the other persons. These unique fibrotic findings were omitted from the DPT thickness assessment, which was measured from the continuous dorsal fibrotic sheet.

### Lung fibrosis

There was no notable lung fibrosis in the unexposed RPF patients, but the three groups did not differ statistically in this respect (Figure 1, Table 2). One asbestos-exposed RPF patient had mild lung fibrosis (class 2), and two had moderate fibrotic changes (class 3), as did two controls. The exposed RPF patients were not more susceptible to lung fibrosis than the asbestos-exposed controls (OR 1.29, 95% CI 0.25–6.63). Lung fibrosis was associated with the occurrence of pleural plaques (OR 2.73, 95% CI 1.10–6.78). Age, smoking and DPT did not affect the development of lung fibrosis (additional file 3).

Most of the asbestos-exposed RPF patients with DPT also had bilateral pleural plaques and vice versa. One person had all three of the distinctive abnormal findings. The most typical findings of the asbestos-exposed controls were bilateral pleural plaques, and 1 subject from the control group had all three notable changes. Twelve (75%) of the unexposed RPF patients, six (27%) of the asbestos-exposed RPF patients and six (33%) of the asbestos-exposed controls did not have any of these changes.

---

**Figure 1**

*Diffuse pleural thickening, pleural plaques and lung fibrosis.* Proportion of persons with diffuse pleural thickening (DPT) (class $\geq 1$), bilateral parietal pleural plaques and lung fibrosis (class $\geq 2$) among the unexposed patients with retroperitoneal fibrosis (RPF), the asbestos-exposed patients with RPF and the asbestos-exposed controls. * Difference between three groups, ** Difference between the unexposed and exposed RPF patients $P = 0.045$.
Pleural fibrosis at the time of the RPF diagnosis

Using patient's medical files, we were able to evaluate the presence of pleural fibrosis in 14 out of 17 RPF asbestos-exposed patients having fibrosis in the current HRCT. At the time of the RPF diagnosis, eight of them had had fibrotic changes in their thoracic X-ray and 6 had not. The subjects having pleural fibrosis at the time of the RPF diagnosis had a higher mean score for both PPP (2.8 versus 1.5) and DPT (2.1 versus 1.0) compared with the ones who had developed pleural changes after the appearance of RPF. These differences were not of statistical significance.

Discussion

This study describes the association between RPF and asbestos-related lung diseases. We hope that our results help to identify persons who have developed RPF through occupational exposure to asbestos. Even though the findings of the current study alone are not enough to declare a causal association between asbestos exposure and RPF, they strengthen the validity of the results of our earlier case-control study and clarify the phenotype of asbestos-related RPF.

To our knowledge, the literature contains only three reports describing asbestos-related pleural findings in altogether five RPF patients [14-16]. In our study 16 out of 22 (73%) asbestos-exposed RPF patients had asbestos-related pleural pathology in their chest HRCT. The prevalence of pleural plaques, DPT and lung fibrosis found in the asbestos-exposed RPF patients was similar to that determined for the asbestos-exposed controls, but DPT was clearly more extensive in the asbestos-exposed RPF patients. Only a few RPF patients and controls with more than 10 fiber-years of asbestos exposure had asbestosis. It seems that the exposure level associated with the development of RPF is comparable to that associated with the

Table 2: Parietal pleural plaques, diffuse pleural thickening and lung fibrosis in the patients with retroperitoneal fibrosis (RPF) and the asbestos-exposed controls.

<table>
<thead>
<tr>
<th>Radiological finding</th>
<th>RPF without asbestos exposure</th>
<th>RPF with asbestos exposure</th>
<th>Controls with ≥ 10 fy of asbestos exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 16 % (N)</td>
<td>&lt;10 fy N = 13 % (N)</td>
<td>≥ 10 fy N = 9 % (N)</td>
</tr>
<tr>
<td>Pleural plaques</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>class 0</td>
<td>68.8 (11)</td>
<td>23.1 (3)</td>
<td>11.1 (1)</td>
</tr>
<tr>
<td>class 1</td>
<td>19.8 (3)</td>
<td>15.4 (2)</td>
<td>22.2 (2)</td>
</tr>
<tr>
<td>class 2</td>
<td>12.5 (2)</td>
<td>38.5 (5)</td>
<td>33.3 (3)</td>
</tr>
<tr>
<td>class 3–5</td>
<td>0 (0)</td>
<td>23.1 (3)</td>
<td>33.3 (3)</td>
</tr>
<tr>
<td>DPT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>class 0</td>
<td>75.0 (12)</td>
<td>46.2 (6)</td>
<td>44.4 (4)</td>
</tr>
<tr>
<td>class 1</td>
<td>6.3 (1)</td>
<td>0 (0)</td>
<td>11.1 (1)</td>
</tr>
<tr>
<td>class 2</td>
<td>18.8 (3)</td>
<td>23.1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>class 3</td>
<td>0 (0)</td>
<td>30.8 (4)</td>
<td>44.4 (4)</td>
</tr>
<tr>
<td>Lung fibrosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>class 0</td>
<td>87.5 (14)</td>
<td>69.2 (9)</td>
<td>66.7 (6)</td>
</tr>
<tr>
<td>class 1</td>
<td>12.5 (2)</td>
<td>15.4 (2)</td>
<td>22.2 (2)</td>
</tr>
<tr>
<td>class 2</td>
<td>0 (0)</td>
<td>7.7 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>class 3–5</td>
<td>0 (0)</td>
<td>7.7 (1)</td>
<td>11.1 (1)</td>
</tr>
</tbody>
</table>

(fy = fiber years, DPT = diffuse pleural thickening)

Pleural fibrosis at the time of the RPF diagnosis

Using patient's medical files, we were able to evaluate the presence of pleural fibrosis in 14 out of 17 RPF asbestos-exposed patients having fibrosis in the current HRCT. At the time of the RPF diagnosis, eight of them had had fibrotic changes in their thoracic X-ray and 6 had not. The subjects having pleural fibrosis at the time of the RPF diagnosis had a higher mean score for both PPP (2.8 versus 1.5) and DPT (2.1 versus 1.0) compared with the ones who had developed pleural changes after the appearance of RPF. These differences were not of statistical significance.

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To our knowledge, the literature contains only three reports describing asbestos-related pleural findings in altogether five RPF patients [14-16]. In our study 16 out of 22 (73%) asbestos-exposed RPF patients had asbestos-related pleural pathology in their chest HRCT. The prevalence of pleural plaques, DPT and lung fibrosis found in the asbestos-exposed RPF patients was similar to that determined for the asbestos-exposed controls, but DPT was clearly more extensive in the asbestos-exposed RPF patients. Only a few RPF patients and controls with more than 10 fiber-years of asbestos exposure had asbestosis. It seems that the exposure level associated with the development of RPF is comparable to that associated with the

Table 3: Pleural fibrosis consisting of bilateral parietal pleural plaques (PPP) and diffuse pleural thickening (DPT) in the patients with retroperitoneal fibrosis (RPF pts) regarding their asbestos exposure

<table>
<thead>
<tr>
<th>Pleural fibrosis</th>
<th>Unexposed RPF pts</th>
<th>Asbestos-exposed RPF pts</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>10</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>6</td>
<td>17</td>
<td>5.7 (1.4 – 23.4)</td>
</tr>
<tr>
<td>PPP -</td>
<td>14</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>PPP +</td>
<td>2</td>
<td>14</td>
<td>12.2 (2.2 – 68.2)</td>
</tr>
<tr>
<td>DPT -</td>
<td>12</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>DPT +</td>
<td>4</td>
<td>12</td>
<td>3.6 (0.9 – 14.7)</td>
</tr>
</tbody>
</table>

(OR = Odds ratio)
development of pleural fibrosis rather than to the high level of exposure that induces asbestosis.

On the basis of our results, it can be argued that RPF is an independent risk factor for pleural fibrosis. The results of the case-control setting (ordinal regression analysis, additional file 3) indicate that RPF patients are more prone towards the development of severe DPT than exposed control subjects. The small number of cases did not allow us to evaluate the interactions between asbestos and RPF. Pleural fibrosis was evident at the time of the RPF diagnosis in most of the cases. Asbestos exposure occurs mainly via the respiratory system, and pleural fibrosis is far more common than RPF. It has been estimated that there are approximately 200 000 asbestos-exposed people [17], 80 000 men with bilateral pleural plaques, and even more with DPT [18] and, according to our estimations, 70–100 patients with RPF in Finland. Taking into consideration these findings, we suggest that asbestos-exposed subjects with RPF develop concomitant pleural fibrosis because of their higher individual susceptibility for asbestos-induced fibrosis.

Parietal pleural plaques are considered pathognomonic for asbestos exposure, and hence they also serve as an indicator of past exposure [19]. The clear difference between the unexposed and exposed groups with a positive trend in the RPF subgroups with slight and moderate

Figure 2
Maximum thickness of diffuse pleural thickening. Maximum thickness of diffuse pleural thickening (DPT, black diamonds), and the respective values for the contralateral pleura (white diamonds), in the unexposed patients with retroperitoneal fibrosis (RPF), the asbestos-exposed patients with retroperitoneal fibrosis and the asbestos-exposed controls. The lines connect each individual's values. "0" indicates that no diffuse pleural thickening was detected.
pleurisy can occur earlier [27]. DPT can be induced by moderate asbestos exposure, and the amount of exposure required for the development of DPT is probably higher than for parietal pleural plaques [28]. Nine out of the eleven asbestos-exposed patients with RPF and bilateral DPT also had bilateral pleural plaques (class ≥2). Marked DPT masks parietal plaques, and some patients with class 2 plaques and thick DPT may, in fact, have had bilateral plaques of class 3.

Ergot drugs have been shown to cause pleural effusion and DPT [23]. This finding is particularly interesting because the use of ergotamine derivate is also a well known risk factor for RPF [29]. In our study, however, the persons having RPF in relation to the use of ergoline medication had no signs of DPT. The pleural effusion and DPT induced by asbestos and ergot drugs share common features, and the etiological diagnosis is difficult for persons with both exposures [30].

Three asbestos-exposed RPF patients had exceptionally large anterior pleural masses extending into the anterior mediastinum. All of them also had typical asbestos-related findings: widespread bilateral plaques in all three; dorsal DPT in two cases (Figure 3A and 3B) and fibrotic lesions fulfilling the criteria for asbestosis in one case (Figure 3C, not shown with the parenchymal settings). In all of these cases the pleural masses were visible in the chest X-rays taken at the time of the diagnosis of RPF. The coexistence of large masses in the pleural and retroperitoneal space suggests a common etiology, although there was no continuity between the mediastinal and retroperitoneal masses. In our experience, such changes are rarely found even in asbestos-exposed persons having other marked pleural pathology. Two similar cases having slight asbestos exposure and no other known risk factors for RPF have been recently reported in France [16]. It seems that asbestos can induce unusually severe fibrotic reaction in some susceptible individuals.

Our study showed that the frequency of asbestos-related lung fibrosis in RPF patients was not higher than that of
the asbestos-exposed controls. It has been widely accepted that the development of asbestosis requires high-level asbestos exposure, a minimum of 20–25 fiber-years [31]. Most of our patients and the controls had exposure of <20 fiber-years, and, therefore, the proportion of persons with asbestosis was low.

Although we propose that pleural and retroperitoneal fibrosis may both be caused by asbestos fibers, there are certain differences in the clinical picture of pleural fibrosis and RPF. RPF is usually symptomatic, causing poorly localized pain in the abdominal, flank, or back region. Symptoms and laboratory findings suggesting systemic inflammation—weight loss, fever and nausea, a clearly elevated erythrocyte sedimentation rate and anaemia—are frequently present [32]. DPT usually progresses slowly and is asymptomatic in many cases, and parietal plaques cause no symptoms. Only patients with acute asbestos pleurisy may have local and systemic symptoms and a moderately elevated erythrocyte sedimentation rate [27]. Corticosteroids usually have a dramatic effect on inflammation in RPF, and together with surgical management of ureteric obstruction are the mainstay treatment for RPF [33]. Corticosteroids have no role in the management of DPT, but may alleviate the symptoms of acute asbestos pleurisy.

Albeit our study population is one of the largest published sets of RPF patients in the literature, the numbers of participants in our study was still rather small. Therefore we combined the groups of RPF patients with slight and moderate-to-high asbestos exposure. This combined group of RPF patients had, on the average, less asbestos exposure than the control group with exposure of ≥ 10 fiber-years in all cases. The ordinal logistic regression modeling may, therefore, have underestimated the risk of pleural fibrosis in association with RPF.

On the basis of our epidemiologic work and our current study we propose the following criteria for the classification of RPF as an occupational disease: (i) occupational asbestos exposure of ≥ 10 fiber-years (OR 8.8) or (ii) occupational asbestos exposure of <10 fiber-years (OR 5.5) combined with bilateral pleural plaques or DPT or both pleural plaques and DPT. The presence of asbestosis (parenchymal fibrosis) should not to be required for the diagnosis of asbestos-related RPF. Asbestos-related RPF, like asbestos-related pleurisy, should be a diagnosis of exclusion. Nevertheless, asbestos-related pleural findings should be taken into account also in the presence of other risk factors, such as ergotamine medication or abdominal aortic aneurysm.

**Conclusion**

In conclusion, the majority of the asbestos-exposed patients with RPF had asbestos-related pleural fibrosis and it was more extensive than in the asbestos-exposed controls. Lung fibrosis was equally frequent among the asbestos-exposed RPF patients and the controls. RPF without asbestos exposure had no association with pleural or lung fibrosis.

The findings suggest a shared etiology for RPF and pleural fibrosis and possibly similar pathogenetic mechanisms in some subjects. All RPF patients should be evaluated for asbestos exposure, and lung HRCT should be performed if appropriate.

**Competing interests**
The authors declare that they have no competing interests.

**Authors’ contributions**
TU was responsible for the data collection, statistical analysis and preparation of the article; RJ and JH evaluated the CT scans; AA planned the data analysis; EH, KM and HS participated in the identification of the RPF patients. PR was the initiator of the study, JU acted as an expert consultant and PO evaluated the asbestos exposure. All of the investigators contributed to the study design and writing of the manuscript.

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References


Retroperitoneal and pleural fibrosis in an insulator working in power plants

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SUMMARY

We describe a case history of a former insulator who developed concomitant retroperitoneal and pleural fibrosis. In his work, the patient had been exposed on a daily basis to asbestos dust while demolishing and installing pipeline insulations. The heavy asbestos exposure was confirmed by a high level of asbestos content in his autopsy lung sample. We propose that both retroperitoneal fibrosis and diffuse pleural thickening were induced in our patient by an abundant amount of amphibole asbestos fibres found in his lung and retroperitoneal tissues.

CASE PRESENTATION

In 1979, a 52-year-old man with slowly progressing back and abdominal pain was admitted to our hospital. He had previously been healthy, had used no medication and had smoked for 10 pack-years. Laboratory tests showed elevated creatinine and erythrocyte sedimentation rates. The findings of the intravenous urography–bilateral hydronephrosis and medialisation of the ureters–suggested the rare fibroinflammatory disorder, retroperitoneal fibrosis (RPF). Laparotomy revealed a large fibrous mass that covered the ureters and the major abdominal vessels (fig 1C). The ureters were dissected from the fibrous mass and wrapped in the omentum to prevent restenosis. The renal function remained stable until 1990, when a relapse of RPF was treated with corticosteroids.
In 1989 the patient was referred because of suspicion of occupational lung disease. He had worked from 1952 to 1986 as an insulator in power plants. In his work, he was exposed to asbestos dust daily while demolishing old pipeline insulation and installing new insulation. His cumulative asbestos exposure was estimated to exceed 25 fibre-years, which is sufficient to induce asbestosis. Chest x-ray showed extensive bilateral fibrotic lesions (fig 1A), some of which were anticipated on the x-ray taken at the time of the RPF diagnosis. Asbestosis, bilateral pleural adhesions and parietal pleural plaques were diagnosed and accepted as occupational diseases. Occupational asbestos exposure was also proposed as the cause of RPF, but it was not accepted by the insurance company.
In 2002 the lung fibrosis was re-evaluated using chest high resolution computed tomography (HRCT). There was extensive bilateral diffuse pleural thickening (DPT) with rounded atelectasis (fig 1B), but the parenchymal fibrosis was only mild. DPT may cause substantial loss of lung function. During 14 years of follow-up, our patient’s vital capacity decreased from 2.8 litres (55% of normal) to 2.00 litres (47%) and diffusion capacity decreased from 77% to 61% of the expected normal value. He had moderate exertional dyspnoea and chronic productive cough.

In 2004 the patient developed unstable angina pectoris. He underwent coronary revascularisation that was complicated by postoperative stroke. Rehabilitation was difficult, interrupted by several episodes of cardiopulmonary failure, some aggravated by iatrogenic adrenal insufficiency. The patient developed chronic hypercapnia and died a year later through cardiorespiratory failure at the age of 79 years.

The medico-legal autopsy showed bilateral pleural plaques and widespread thickening and adhesions of the visceral pleura. The retroperitoneal structures were adherent and the abdominal aorta was intensely calcified. There was no continuity between the pleural and retroperitoneal fibrotic lesions. Histology showed fibrosis with inflammatory cell infiltration both in the pleural and retroperitoneal tissue. Unfortunately the lungs were not distended before sampling and reliable post mortem grading of the lung parenchymal fibrosis was not possible. There was a very high concentration of asbestos fibres in the lung parenchyma (59 million fibres/g) consistent with heavy asbestos exposure. The asbestos content of the abdominal lymph nodes and retroperitoneal fibrous tissue was also substantial and the same amphibole asbestos fibres were present (table 1). The cause of death was asbestos related lung disease, with atherosclerotic heart disease acting as a contributing condition.

Table 1 Asbestos fibres in tissue samples of the patient with retroperitoneal fibrosis

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Number of fibres detected</th>
<th>Asbestos content* 10^6 fibres/g of dry tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung parenchyma</td>
<td>18</td>
<td>59.00</td>
</tr>
<tr>
<td>Lymph node at the level of renal arteries</td>
<td>13</td>
<td>0.80</td>
</tr>
<tr>
<td>Lymph node behind the proximal end of the abdominal aorta</td>
<td>11</td>
<td>0.80</td>
</tr>
<tr>
<td>Retroperitoneal fibrosis mass, right side</td>
<td>0</td>
<td>0.14</td>
</tr>
<tr>
<td>Retroperitoneal fibrosis mass, left side</td>
<td>1</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*Asbestos fibres over 1 micrometre in length were detected using scanning transmission electron microscopy. The concentration of asbestos fibres is given according to the original dry weight of the samples.

DISCUSSION

At the time of diagnosis the patient did not have any other known risk factors for RPF than asbestos exposure (for example, ergotamine medication, abdominal aortic aneurysm, abdominal trauma or infection), and no signs of autoimmune disease were found during the follow-up. We propose that both RPF and DPT were induced in our patient by the abundant amount of amphibole asbestos fibres found in his lung and retroperitoneal tissues. This case also illustrates the progressive nature of asbestos induced DPT causing the lungs to "shrink" and leading to respiratory failure.
This is one of several patients with retroperitoneal fibrosis referred to our clinic of occupational medicine for suspicion of asbestos related lung disease. Using these cases, we have argued that there may be a causal relationship between occupational asbestos exposure and RPF, which was supported by our case–control study. There are no data indicating that non-occupational asbestos exposure would be associated with RPF. Recently, two cases of RPF and pleural fibrosis continuing into the mediastinum have been reported by Cottin et al. The asbestos exposure of these men appeared to be slight, but no other causative factors were found. In our unpublished series we have observed three similar asbestos exposed RPF patients with large pleural masses extending into the anterior mediastinum.

LEARNING POINTS

Retroperitoneal fibrosis (RPF) is a rare multi-aetiologic fibroinflammatory condition that causes hydronephrosis and renal failure. Asbestos fibres reach the retroperitoneal space and may induce retroperitoneal fibrosis. All RPF patients should be evaluated for asbestos exposure, and chest high resolution CT should be performed, if pleural or lung fibrosis is suspected on the chest x ray.

Competing interests: none.

Patient consent: Patient/guardian consent was obtained for publication.

REFERENCES


