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Computed Tomography Screening for Lung Diseases
among Asbestos-Exposed Workers



ACADEMIC DISSERTATION

To be presented, with the permission of
the Faculty of Medicine of the University of Tampere,
for public discussion in the Jarmo Visakorpi Auditorium,
of the Arvo Building, Lääkärintäti 1, Tampere,
on January 8th, 2010, at 12 o'clock.

UNIVERSITY OF TAMPERE

ACADEMIC DISSERTATION

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<http://granum.uta.fi>

Cover design by
Juha Siro

Acta Universitatis Tamperensis 1487
ISBN 978-951-44-7936-6 (print)
ISSN-L 1455-1616
ISSN 1455-1616

Acta Electronica Universitatis Tamperensis 922
ISBN 978-951-44-7937-3 (pdf)
ISSN 1456-954X
<http://acta.uta.fi>

Tampereen Yliopistopaino Oy – Juvenes Print
Tampere 2009

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1. List of original communications

This thesis is based on the following original articles, which are referred to in the text by the Roman numerals indicated below:

I Vierikko T, Järvenpää R, Autti T, Oksa P, Huuskonen M, Kaleva S, Laurikka J, Kajander S, Paakkola K, Saarelainen S, Salomaa ER, Tossavainen A, Tukiainen P, Uitti J and Vehmas T (2007): Chest CT screening of asbestos-exposed workers: lung lesions and incidental findings. *Eur Respir J* 29(1):78– 84.

II Vierikko T, Kivistö S, Järvenpää R, Uitti J, Oksa P, Virtema P and Vehmas T (2009): Psychological impact of computed tomography screening for lung cancer and occupational pulmonary disease among asbestos-exposed workers. *Eur J Cancer Prev* 18(3):203– 206.

III Vierikko T, Järvenpää R, Toivio P, Uitti J, Oksa P, Lindholm T and Vehmas T (2009): Clinical and HRCT screening of heavily asbestos-exposed workers. *Int Arch Occup Environ Health*, Epub ahead of print.

IV Vierikko T, Järvenpää R, Uitti J, Virtema P, Oksa P, Jaakkola MS, Autti T and Vehmas T (2008): The effects of secondhand smoke exposure on HRCT findings among asbestos-exposed workers. *Respir Med* 102(5):658– 664.

2. Abbreviations

B	regression coefficient
BMI	body mass index
CI	confidence interval or intervals
CT	computed tomography
CEI	cumulative exposure index
DL _{CO}	diffusing capacity
DL _{CO} /VA	specific diffusing capacity
ELCAP	Early Lung Cancer Action Project
FDG	fluorodeoxyglucose
FEV ₁	forced expiratory volume in 1 second
FIOH	Finnish Institute of Occupational Health
FNAB	fine needle aspiration biopsy
FVC	forced vital capacity
GGO	ground-glass opacity or opacities
HRCT	high-resolution computed tomography
HU	Hounsfield unit
ILO	International Labour Organization
MRI	magnetic resonance imaging
OR	odds ratio or ratios
PET	positron emission tomography
SD	standard deviation
SHS	secondhand smoke
TLC	total lung capacity
2 D	two-dimensional
3 D	three-dimensional

3. Abstract

Objectives: One objective of this research was to assess the use of computed tomography (CT) in screening for lung diseases among asbestos-exposed workers. The prerequisites for effective lung cancer screening were studied, and the psychological impact of the screening procedure was assessed. Another aim was to clarify the indications for screening with high-resolution computed tomography (HRCT) among asbestos-exposed workers and to study the effect of exposure to secondhand smoke (SHS, passive smoking) on HRCT images.

Materials and methods: Altogether 758 asbestos-exposed workers were invited to participate in the study, and 633 took part. HRCT was conducted on all of the participants to screen for occupational lung changes, while spiral CT was restricted to the smokers and ex-smokers (cessation within 10 years, n=180) to find lung cancer. HRCT images were assessed for lung fibrosis, emphysema, ground-glass opacities (GGO), and several other signs. The presence, number, and size of the lung nodules in CT were recorded, and they were examined further if needed. Finally the number of lung cancers was determined. All incidental findings (imaging abnormalities not related to the indication of the CT scan) were registered, and additional examinations were conducted if necessary. The participants gave a blood sample for laboratory analyses, and lung function tests were conducted. Occupational exposures, smoking habits, SHS exposure, and psychological items were inquired about via questionnaires.

Results: Altogether 83.5% of those invited participated in the CT examinations. Non-calcified lung nodules were found in the CT scans of 86 (13.6%) of the participants. Five lung cancers were confirmed histologically (0.8%). All them occurred among smokers or ex-smokers. Two cancers were in stage IA. Incidental findings were detected in 43.8% of the participants. Additional examinations due to incidental findings were needed for 41 (6.5%) of those screened. One incidental malignancy, mesothelioma of the pleura, was detected.

The screening was accepted well by the participants. The screening procedure itself or false positive results did not cause long-lasting adverse psychological reactions. On the contrary, health anxiety was lower after the screening. The intention to adhere to the trial was high (98%) among the workers, and the screening procedure or false-positive findings did not reduce it.

Interstitial HRCT abnormalities consistent with lung fibrosis were found in 88 (13.9%) of the 633 workers. Most (75.0%, n=66) of the detected fibrosis cases were mild. The magnitude of asbestos exposure showed an unexpected inverse relation ($p=0.009$) with fibrosis in the crude analyses. In multivariate analyses, age ($p<0.001$), ratio between forced expiratory volume in 1 second and forced vital capacity ($p=0.021$), and poor diffusing capacity ($p=0.001$) were associated with HRCT fibrosis, but the intensity of the asbestos exposure was not.

Total ($p=0.000$) and workplace ($p=0.001$) SHS exposures were significantly related to GGO in HRCT images. Suggestive positive relations ($p = 0.059$) were also detected between SHS exposure and irregular or linear opacities.

Conclusions: So far, whether CT screening helps to reduce lung cancer mortality is still unclear. Screening for lung cancer among asbestos-exposed workers can reveal early cases, but the large number of non-specific lung nodules and incidental findings that result in additional examinations would be a great challenge to health care. Positive smoking history can be used as an inclusion criterion when a decision is made about whether to screen asbestos-exposed persons or not. Screening is accepted well among these workers, and it does not induce adverse psychological effects that are permanent. Currently, asbestos-induced lung disease seems to be characterized by mild fibrosis. Age and lung function data can be used only to a limited extent in the selection of HRCT candidates with a high risk of fibrosis. The cross-sectional study design between asbestos exposure and fibrosis may suffer from selection and recall biases that blur this dose–response relationship. SHS exposure seems to induce adverse lung effects that can be detected in HRCT images, and GGO may be the primary finding in exposed persons.

Tiivistelmä

Tarkoitus: Tutkimuksen tarkoitus oli selvittää tietokonetomografian (CT) käyttöä asbestin aiheuttamien työperäisten keuhkosairauksien seulonnassa. Pyrkimyksenä oli tutkia tehokkaan keuhkosyöpäseulonnan edellytyksiä sekä seulonnan aiheuttamia psykologisia vaikutuksia. Lisäksi selvitettiin hienopiirtotietokonetomografian (HRCT) käyttöaiheita asbestille altistuneiden seurannassa sekä passiivisen tupakoinnin ja HRCT-kuvissa esiintyvien muutosten välisiä yhteyksiä.

Menetelmät: Tutkimukseen kutsuttiin 758 asbestille altistunutta työntekijää, joista 633 osallistui. Kaikille osallistujille tehtiin HRCT tutkimus. Spiraali-CT tehtiin tupakoitsijoille ja entisille tupakoitsijoille (alle 10 vuotta sitten lopettaneet, n=180) keuhkosyövän toteamiseksi. HRCT-kuvista luokiteltiin keuhkofibroosin, emfyseeman, mattalasimuutosten ja useiden muiden keuhkolöydösten esiintyminen. Havaituista keuhkotiivistymistä määriteltiin koko ja lukumäärä. Tarvittaessa tehtiin jatkotutkimuksia. Löydettyjen keuhkosyöpien lukumäärä kirjattiin. Myös sivulöydökset (joku muu löydös kuin keuhkotiivistymä) kirjattiin ja tehtiin tarvittavat jatkotutkimukset. Osallistujille tehtiin verikokeita ja keuhkofunktio tutkimuksia. Asbestille altistuminen, tupakointi-tavat, altistuminen passiiviselle tupakoinnille ja seulonnan psykologisia vaikutuksia kartoitettiin kyselylomakkeella.

Tulokset: Tutkimukseen osallistui suuri osa (83.5%) kutsutuista. Tutkituista 86:lla (13.6%) oli keuhkotiivistymiä. Keuhkosyöpiä löytyi viisi (0.8%), kaikki nykyisiltä tai entisiltä tupakoitsijoilta. Kaksi syövästä oli luokkaa IA. Sivulöydöksiä oli 43.8%:lla osallistujista, ja näistä yksi oli pahanlaatuinen, mesotelioma. Sivulöydösten takia lisätutkimuksia tehtiin 41:lle, eli 6.5%:lle osallistujista. Osallistujat hyväksyivät seulonnan hyvin. Itse seulonta tai väärät positiiviset löydökset eivät aiheuttaneet epäsuotuisia psykologisia vaikutuksia. Päinvastoin ahdistuneisuus laski seulonnan aikana. Suurin osa (98%) aikoi osallistua jatkossakin

seulontatutkimuksiin, ja aikomus oli yhtä suuri niillä, jotka olivat saaneet väärän positiivisen tuloksen.

Tutkituista 88:lla (13.9%) löydettiin HRCT-menetelmällä asbestoosiasteinen keuhkofibroosi ja suurin osa (75%, n=66) löydettyistä fibrooseista oli lieviä. Asbestille altistumisen määrässä ja keuhkofibroosissa löytyi yllättävä käänteinen yhteys vakioimattomissa tilasto analyyseissä (p=0.009). Vakioiduissa analyyseissä ikä (p<0.001), FEV₁/FVC (p=0.021) ja alentunut diffuusiokapasiteetti (p=0.001) olivat yhteydessä keuhkofibroosiin, mutta asbestille altistumisen määrä ei ollut.

Kumulatiivinen (p=0.000) ja työssä tapahtunut (p=0.001) altistuminen passiiviselle tupakoinnille olivat yhteydessä mattalasimuutoksiin HRCT:ssä. Positiivista yhteyttä (p=0.059) oli myös havaittavissa passiiviselle tupakoinnille altistumisen ja keuhkojen juostemaisten muutoksien välillä.

Yhteenveto: Vielä ei ole näyttöä siitä, vähentääkö CT seulonta keuhkosityöpäkuolleisuutta. Keuhkosityöpäseulonnalla voidaan löytää aikaisen vaiheen syöpiä asbestille altistuneilla työntekijöillä, mutta suuri määrä epäspesifisiä keuhkotiiivistymiä ja sivulöydöksiä, jotka tarvitsevat jatkotutkimuksia, aiheuttaa huomattavia haasteita terveydenhuollolle. Jos asbestille altistuneille suositellaan jatkossa keuhkosityöpäseulontaa, tulisi erityisesti nykyiset ja entiset tupakoitsijat sisällyttää seulonnan piiriin. Tämä suuren riskin ryhmä hyväksyi seulonnan hyvin, eikä seulonta aiheuttanut epäsuotuisia psykologisia vaikutuksia. Asbesti-altistuksen aiheuttama keuhkofibroosi näyttäisi nykyisin olevan pääosin lievää. Ikää ja keuhkofunktio tuloksia voidaan käyttää hyväksi vain valikoiduissa tapauksissa rajattaessa HRCT-tutkimukseen otettavia potilaita. Tällaisessa poikkileiketutkimuksessa, joka tutkii asbestialtistuksen ja keuhkofibroosin välisiä yhteyksiä, voi olla valikoitumis- ja muistamis-harhoja. Tässä tutkimuksessa löytyi viitteitä siitä, että altistuminen passiiviselle tupakoinnille voi aiheuttaa keuhkoihin mattalasimuutoksia, jotka voivat näkyä HRCT kuvissa.

4. Introduction

Asbestos is a term for a group of fibrous silicate minerals that are durable, fire resistant, and good electrical and heat insulators. Because of these properties, asbestos has been widely used throughout the world.

Exposure to asbestos is known to cause abnormalities of the pleura and the lungs (Lemen et al. 1980). The former include local areas of thickening of the parietal pleura (pleural plaques), exudates, thickening and scarring of visceral pleura, and malignant mesothelioma. In the lungs, asbestos exposure may cause diffuse interstitial fibrosis (asbestosis) and lung cancer (Browne 1994). A latency period between the first exposure and the clinical disease range from 10 to more than 40 years (Seidman et al. 1979, Selikoff et al. 1980).

The peak use of asbestos in the world occurred in the mid-1970s. Evidence of the adverse effects of asbestos exposure has resulted in the banning of asbestos in many countries, and its use has fallen ever since. Despite the dramatic decline in the use of asbestos in industrialized countries after the 1970s, it is still widely used in developing countries (Consensus report 2000).

In Finland the use of asbestos was banned in 1993. It has been estimated that about 200 000 employees were exposed to asbestos before that year (Asbestos Committee 1990). Much of the used material still exists in buildings, and, during renovation, repair and demolition, exposure to asbestos is still possible.

Due to their long latency period, asbestos-induced diseases still occur, and health examinations should continue although the exposure has ceased (International Labour Organization 1986). In Finland health examinations are obligatory for asbestos-exposed workers. Most severe asbestos-associated lung diseases are diagnosed with the use of clinical examinations, lung function tests, and chest radiography, but these examinations are of limited value in the assessment of early pathological changes. Chest radiography is not sensitive to subtle lung fibrosis or early lung cancer, especially when disturbing pleural abnormalities are present. Computed tomography (CT) allows the early identification of the adverse

pulmonary effects of asbestos exposure and is useful in the diagnosis of both malignant and non-malignant diseases.

There is increasing worldwide interest in screening for lung cancer with spiral CT. Since symptoms often do not appear before the disease is advanced and therefore the prognosis is poor, screening for lung cancer is an appealing option. Catching the disease in an early, curable stage is the purpose of any screening. So far, no conclusive evidence exists of lung cancer screening with respect to a decrease in mortality. Survival in lung cancer may be improved by screening when coupled with earlier intervention, but screening has also certain limitations. One of them is the high rate of nodule detection, which results in additional examinations. Cancer screening may also produce adverse psychological effects, especially with respect to false positive findings (Lampic et al. 2003, Brett et al. 2005). This problem could offset the potential benefits of screening and deter participants from attending subsequent screening rounds (Brett and Austoker 2001, Ford et al. 2003, Taylor et al. 2004). A screening program cannot be successful unless the screening and the subsequent diagnostic examinations after a positive finding are tolerated well, and the willingness to participate is high. Data on the psychological consequences of screening and surveillance programs for asbestos-exposed workers or CT screening programs for lung cancer are limited.

High-resolution CT (HRCT) is used to detect asbestos-related lung fibrosis, especially when chest radiography is equivocal. HRCT is often used as a supplementary examination, but its status in the screening and periodical surveillance of exposed workers is still unclear.

Smoking has been common among asbestos-exposed workers (Hammond et al. 1979, Oksa et al. 1994, Koskinen et al. 2002). It can produce detectable abnormalities in HRCT images (Remy-Jardin et al. 1993b) and thus interfere with the diagnostics of occupational lung disease. Whether secondhand smoke (SHS) is able to induce such changes is not known. HRCT readers should be able to recognize the kind of changes other simultaneous exposures, such as SHS, can induce. Exposure to SHS has also been an independent work-related health problem.

In this study Finnish workers exposed heavily to asbestos were screened for lung diseases with CT, and the psychological impact of the screening procedure was assessed.

5. Review of the literature

5.1 Asbestos and asbestos exposure

The term asbestos refers to a group of naturally occurring, fibrous silicate minerals (actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite) that are good thermal and electrical insulators. They are also durable, strong, and flexible. Because of these features, asbestos has been widely used in industry, typically in thermal insulation and fire protection. Its commercial use has resulted in a wide distribution of asbestos in the environment.

After the beginning of the 20th century, the industrial use of asbestos became widespread. During the late 1960s and 1970s, the accumulating evidence of health problems associated with asbestos exposure led to a reduction in its use. The world production of asbestos fibers reached its maximum in 1977, being 4 800 000 tons per year, decreasing to an annual 2 200 000 tons in 2003 (Virta 2006). The European Union banned asbestos use in most applications by its members in 2005 (Commission of European Communities 1999).

In Finland the use of asbestos peaked in the 1960–1970s (Figure 1). The first restrictions concerning asbestos use were issued in 1976, as the use of crocidolite and spraying as a work method were prohibited. In 1993 the use of asbestos products was banned, and strict regulations were applied to the renovation and inspection of old buildings (Huuskonen et al. 1995). Because of the long latency of asbestos-induced diseases, the highest incidence of these diseases is expected to occur in the early 2000s. In 2004, an estimated 50 000–60 000 asbestos-exposed workers were still alive (Nordman et al. 2006).

Asbestos (anthophyllite in Finland) miners, asbestos sprayers, and other insulators represent populations with the highest average asbestos-exposure levels in the past. Nevertheless, the bulk of the asbestos epidemic has resulted from exposure during the use and handling of asbestos products in construction, shipyards, car

repair, and industrial maintenance work. In such instances, exposure has been common, but usually not continuously heavy (Asbestos Committee 1990).

Still more than 300 000 buildings contain over 200 000 tons of asbestos in Finland (Huuskonen and Rantanen 2006). Today the exposure is supposed to be low, but construction workers may still occasionally be exposed at dismantling sites that have not been managed according to existing regulations or if the technique used for removal is inadequate (Riala and Riipinen 1998).

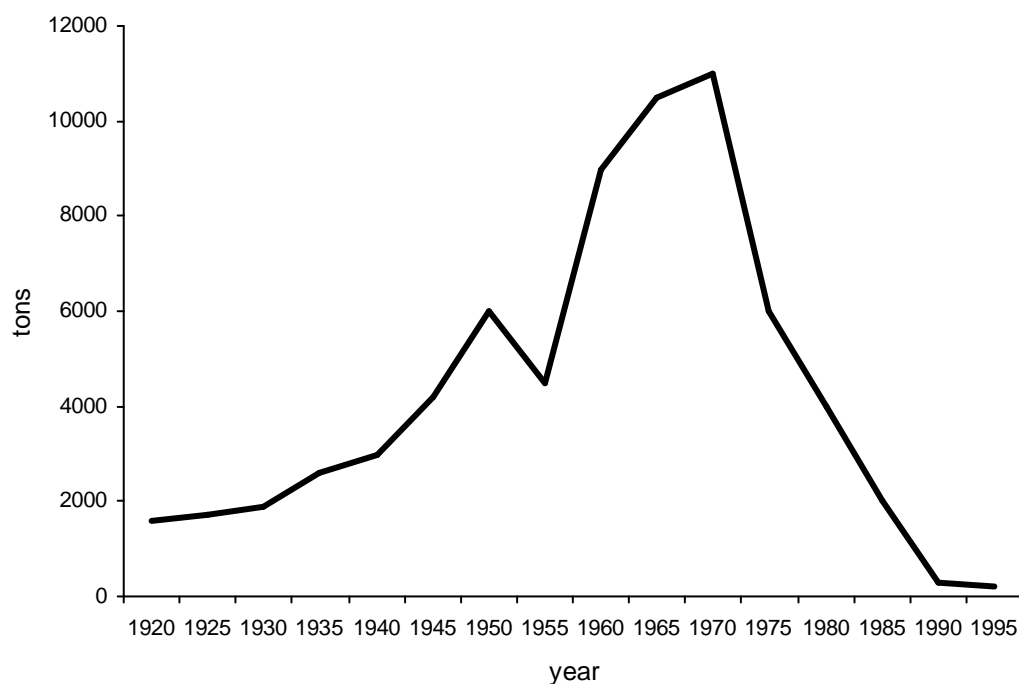


Figure 1. Asbestos consumption in Finland 1920–1995 (tons per year).
(Courtesy to Antti Tossavainen, Finnish Institute of Occupational Health)

Although the use of asbestos is declining in developed countries, it is widely used elsewhere. In 2003, world consumption was estimated to be 2 110 000 tons, being about 45% of the level in 1980. Relatively few countries in Asia, Middle East, South America, and the former Soviet Union remained as the leading users of asbestos

(Figure 2). These eight countries accounted for 82% of the world's apparent consumption in 2003, and consumption increased in most of these countries between 2000 and 2003 (Virta 2006).

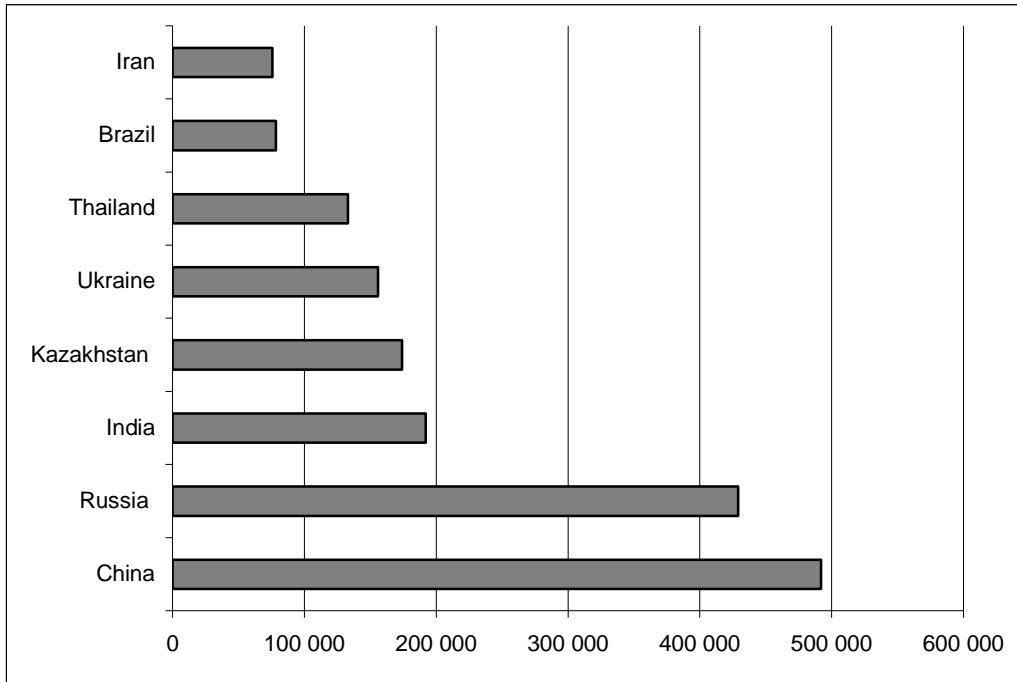


Figure 2. Estimated asbestos consumption (in tons) in eight leading consumer countries in 2003.

In 2007, 2 200 000 tons of asbestos were still produced (Figure 3), Russia being the most important producer in the world with approximately 925 000 tons (Virta 2009, British geological survey 2009). Thus, even if asbestos has caused health hazards in the industrialized world in the past, and in the beginning of 20th century, it is likely to cause even more in the future in developing countries, where the capacity to produce and use it is high but the mechanisms for prevention and control may not be developed.

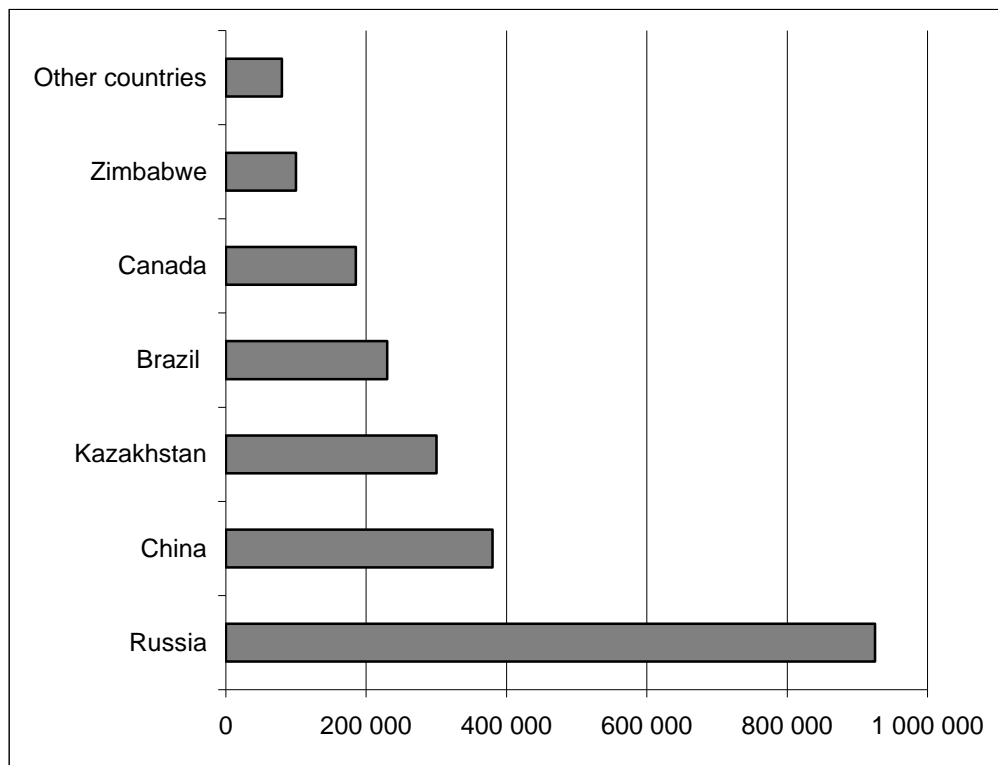


Figure 3. World asbestos productions in 2007 (in tons).

5.2 Asbestos-related diseases

The World Health Organization's International Agency for Research on Cancer has classified asbestos as carcinogenic to humans with sufficient evidence concerning the lung, mesothelioma, larynx, and ovary and limited evidence concerning cancer of the colorectum, pharynx, and stomach (Special report 2009). In addition, asbestos causes lung fibrosis (asbestosis), pleural plaques, diffuse pleural thickening, and exudative pleurisy (Lemen et al. 1980, Browne 1994). More recently, an association has been described between retroperitoneal fibrosis and asbestos (Uibu et al. 2004). In the present research, special attention was given to asbestos-related lung diseases.

5.2.1 Lung fibrosis and emphysema

The first cases of asbestos-associated lung fibrosis were described in the early 1900s, and the term “asbestosis” was presented by Cooke in 1927. Asbestosis is diffuse, interstitial fibrosis caused by the retention of inhaled asbestos fibers (Browne 1994). The progression of asbestosis is independent of continuing exposure; once a dose of asbestos sufficient to initiate the disease has been retained in the lungs, the process of fibrosis continues despite the removal of the exposure (Sluis-Cremer and Hnizdo 1989). In the earliest stages of disease, histological fibrosis concentrates in the respiratory bronchioles and then spreads to the alveolar septa (Craighead 1982). Fibrosis generally affects subpleural areas first and is the most prominent in the lower lobes posteriorly. When it progresses, it can cause honeycombing and shrinkage of the lungs. The manifest fibrosis results in restrictive lung disease (Gaensler et al. 1972), with decreased forced vital capacity (FVC), total lung capacity (TLC), and diffusing capacity (DL_{CO}). However, in the early stages of asbestosis, lung function may be normal (Aberle et al. 1988, Begin et al. 1993, Neri et al. 1994). The most important clinical signs are dyspnea, cough, and crepitating rales, but they are not specific to asbestosis (Becklake 1976). Classic clinical asbestosis is caused by long-term (10–20 years), moderate or heavy exposure, but even short-term exposure, if sufficiently intense, can result in asbestosis (Seidman et al. 1979). The disease is dose-related, and typically there is a long latency of decades between exposure and detected abnormality (Becklake 1976, Selikoff et al. 1980). The latency between the beginning of exposure and disease is at least 10 to 20 years, but it can be over 40 years (Selikoff and Hammond 1978, Selikoff et al. 1980). Recently a direct relationship has been demonstrated between the national consumption of asbestos in 1960–1969 in 33 countries and the number of deaths caused by asbestosis in 2000–2004 (Lin et al. 2007).

The prevalence of asbestosis is associated with time since first exposure, occupational group, duration of or cumulative exposure to asbestos, depending on the study (Becklake 1976, Neri et al. 1994, Algranti et al. 2001, Huuskonen et al. 2001, Ohar et al. 2004, Paris et al. 2004, Paris et al. 2008, Mastrangelo et al. 2009).

Asbestosis is generally diagnosed by clinical criteria without tissue examination. While asbestosis possesses no pathognomonic clinical, physiological, or radiological features, the criteria include a sufficient and reliable history of exposure

and an appropriate latency period between the exposure and the detection of the disease (Hillerdal 1997). An important criterion is the presence of diffuse lung fibrosis in chest radiography or more recently in HRCT (Shipley 1992). In addition, diffuse interstitial fibrosis due to other causes should be excluded.

Emphysematous changes of the lung are a common consequence of chronic cigarette smoking. Occupational exposure to silica has been shown to cause emphysema in addition to silicosis (Weill et al. 1994, Begin et al. 1995), and emphysema has also been found to be associated with coal workers pneumoconiosis (Parkes 1994). Inhaled asbestos fibers are known to cause pulmonary fibrosis, but their role in emphysema is unclear. Studies suggest that emphysema plays an important role in respiratory disability among asbestos-exposed persons (Sue et al. 1985, Staples et al. 1989, Begin et al. 1995, Piirilä et al. 2005). An increased prevalence of emphysema in both non-smoking and smoking workers who had been exposed to asbestos has been shown (Begin et al. 1995). In the study of asbestos-exposed workers, emphysema was the most common when the workers had asbestosis or were heavily exposed (Huuskonen et al. 2004).

5.2.2 Lung cancer

5.2.2.1 *Risk factors*

The risk of developing lung cancer varies across the population, and several risk factors can be identified. The incidence of lung cancer increases with age. In Finland, less than 3% of all new cases surface clinically in persons under the age of 50 years (Finnish Cancer Registry 2007). The biggest single risk factor is cigarette smoking, contributing to 85%–90% of all lung cancer cases (Doll and Hill 1956, Doll et al. 1994, van Klaveren et al. 2002, Alberg et al. 2007). Other risk factors include exposure to asbestos and other occupational carcinogens, radon, air pollution, and genetic susceptibility (Albin et al. 1999, Driscoll et al. 2005, Alberg et al. 2007). All types of asbestos can cause lung cancer, and it is the most common asbestos-induced neoplasm (Selikoff et al. 1964, Selikoff et al. 1980). Asbestos-induced lung cancer does not differ from non-asbestos lung cancer in location or histology. The causal association between asbestos exposure and lung cancer is well

accepted and exhibits a dose–response relationship at occupational exposure levels (Browne 1994). The risk of carcinoma is very low or undetectably low for the first 10 years after exposure to asbestos, but it gradually increases and is highest after more than 30 years (Selikoff et al. 1980, Karjalainen 1994, Oksa 1998). There is evidence, that exposure to low doses will not only produce fewer cancers, but also possibly longer latency times than high doses (Seidman et al. 1979). Worldwide, asbestos may account for an estimated 100 000–140 000 lung cancer deaths per year and contribute to nearly 5% to 7% of all lung cancers (LaDou 2004, Tossavainen 2004). In Finland, the average annual number of lung cancers registered as occupational diseases was 80 between 1997 and 2002 (Huuskonen and Rantanen 2006).

Asbestos can cause lung cancer in non-smokers (Lee 2001), but the risk is greater among asbestos-exposed smokers, being even 20 to 50 times higher than in a normal population (Hammond et al. 1979). The increase in lung cancer risk is proportionate to the degree of exposure to asbestos and the number of smoked cigarettes (Vainio and Boffetta 1994).

Workers with asbestosis and the progression of asbestosis also have an increased risk of lung cancer (Hughes and Weill 1991, Hillerdahl and Henderson 1997, Oksa et al. 1998, Karjalainen et al. 1999, Koskinen et al. 2002). In a Finnish study, asbestosis patients had a tenfold relative risk of lung cancer when compared with an unexposed population (Oksa et al. 1997). In a study of 17 000 construction workers, the standardized incidence ratio for the risk among those who had radiographic asbestosis was 2.4 (Koskinen et al. 2002). Of workers with progressive asbestosis, 46% developed lung cancer, whereas only 9% of the workers with stable asbestosis developed cancer (Oksa et al. 1998).

5.2.2.2 *Incidence and prognosis*

Lung cancer is the most common cancer in the world (Parkin 2001, Parkin et al. 2005, Kamangar et al. 2006). In 2002, there were 1.35 million new cases, representing 12.4% of all new cancers (Parkin et al. 2005). In Finland, lung cancer remains more common among men than among women, despite the falling incidence for men in recent years (Figure 4). In Finland, lung cancer is the second

most common cancer among men after prostate cancer, with 1542 new cases (11.3% of all) diagnosed in 2006. In 2006, it was the fourth most common cancer among women, with 627 (4.8%) new cases (Finnish Cancer Registry 2007).

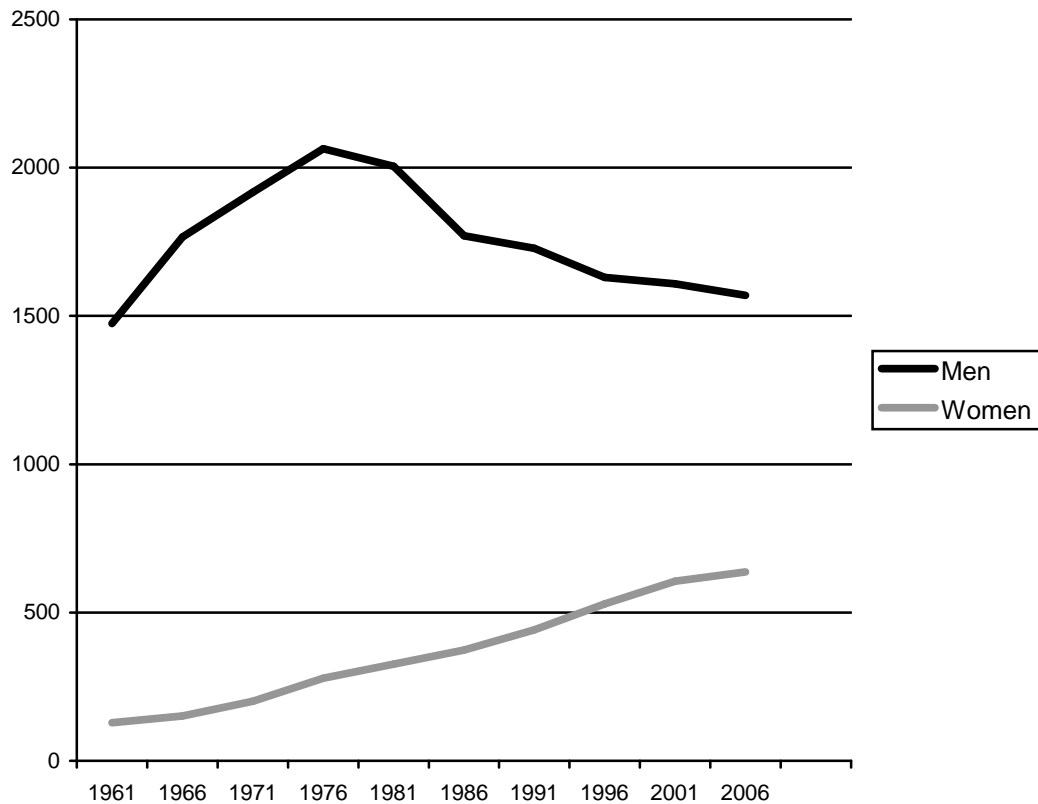


Figure 4. Lung cancer incidence in Finland in 1961–2006. (Finnish Cancer Registry 2007)

The high frequency of diagnoses, combined with the poor survival rate, makes lung cancer the most fatal cancer in the world (Levi et al. 1999, Jemal et al. 2003, Alberg et al. 2005, Ferlay et al. 2007, Jemal et al. 2007). In 2002, it was the most common cause of death from cancer, with 1.18 million deaths, or 17.6% of the world total (Parkin et al. 2005). In Finland, it is the leading cause of cancer death among men, with 1467 (25.4%) deaths in 2006, and the second most common among women (544, 10.6%) (Finnish Cancer Registry 2007).

Despite advances in the treatment of lung cancer, the overall prognosis remains poor, approximately 15% of affected patients surviving 5 years after the diagnosis (Fleehinger et al. 1992, Nesbitt et al. 1995, Mountain 1997, Jemal et al. 2007). Survival varies substantially with the clinical stage of the tumor at diagnosis. Among those with surgically treated early lung cancer, defined as stage IA or IB disease (local disease, with no nodal or distant metastases), the 5-year survival rate ranges between 63% and 76% in different studies, while for advanced disease the survival is less than 10% (Melamed et al. 1984, Fleehinger et al. 1992, Shah et al. 1996, Mountain 1997, Naruke et al. 1997, van Rens et al. 2000). Long-term survival with untreated stage I lung cancer is uncommon, the 5-year survival being 6% (Raz et al. 2007). Usually, lung cancer does not cause symptoms early. Thus it is diagnosed late, and over 50% of the patients show symptoms due to advanced local or metastatic disease that is incurable (Jett 1993). The principal hope for curative treatment remains in surgical resection, which requires tumors to be recognized early, before the local invasion or remote spread of the disease (Fleehinger et al. 1992). Therefore, the early detection by screening could be a method of choice with which to improve the prognosis of lung cancer.

5.3 Imaging of lung diseases

5.3.1 Plain chest radiography

Chest radiography has traditionally been the most used diagnostic tool in the initial evaluation for asbestos-related lung diseases due to its low cost, low radiation level, and wide availability. The earliest abnormalities associated with asbestosis are found in the lower zones of the lungs near the costophrenic angles. As asbestosis progresses, linear and irregular opacities become thicker and spread to middle or upper zones (Parker 1997). In established fibrosis, chest radiography is a valuable diagnostic tool, but it is not a sensitive test for early lung fibrosis. It has been shown that diffuse interstitial fibrosis may be evident in 18% to 26% of persons undergoing a pathological examination of lung tissue even when chest radiography appears normal (Gaensler et al. 1972, Kipen et al. 1987, Rockoff and Schwartz 1988).

It is estimated that pulmonary nodules of less than 6 mm can only occasionally be found in chest radiographs unless they are calcified, and lesions measuring 6–10 mm are detected in only 50% of cases (Brogdon et al. 1983). Even nodules larger than 10 mm may be missed in chest radiographs (Austin et al. 1992, Sone et al. 2000). A large portion of the lung may be concealed by the overlying thoracic spine, diaphragm, and mediastinal structures, and this concealment makes the detection of lung nodules, and hence early lung cancers, difficult in these regions (Brogdon et al. 1983). In addition, the contrast capability of chest radiography is too poor to allow an interpreter's detection of the very low nodular density caused by small tumors (Sone et al. 2000). For asbestos-exposed workers, chest radiographs may be even more challenging to interpret due to possible pleural abnormalities (Geftter and Conant 1988).

The introduction of systems involving dual-energy subtraction digital chest radiography has substantially increased the ability to detect nodules. This technique provides a markedly enhanced contrast resolution, especially in previously difficult-to-evaluate regions of the lung, including behind the heart and below the diaphragm level (Ravin and Chotas 1997). It is also possible, by use of both single- and dual-exposure techniques, to vary radiation exposure (kilovolt peak) and thereby facilitate detection of non-calcified nodules (Uemura et al. 2005). As the use of these newer techniques becomes more widespread in clinical practice, it is possible that fewer lung nodules will escape detection.

5.3.2 CT

5.3.2.1 *Spiral CT*

The development of CT has greatly improved the imaging of the chest (Costello et al 1991, Remy-Jardin et al.1993c, Garvey and Hanlon 2002). In comparison with chest radiography, CT has the potential to detect pulmonary nodules as small as 1–2 mm due to the high contrast between nodule and aerated lung, as well as the lack of superimposition (Davis 1991, Paranjpe and Bergin 1994). As a result, small lung cancers can be detected with greater sensitivity (Kaneko et al. 1996, Sone et al. 1998, Henschke et al. 1999). In a baseline lung cancer screening study, 1000

participants were studied with spiral CT and chest radiography (Henschke et al. 1999). CT located non-calcified nodules in 233 of the participants, while chest radiography depicted nodules in only 68 persons. Lung cancer was found with CT in 27 cases versus 7 with radiography. Of the CT-detected cancers, 88% were stage I.

Spiral CT allows rapid acquisition of a large volume of image data so that in one single breathhold the whole lung can be scanned. In 1998, multislice CT scanners were introduced. This development led to a further reduction in overall scan times and high-level image quality (Fuchs et al. 2000). These systems have 4 to 64 detector rows that acquire multiple image slices during each rotation of the X-ray tube. In a single breathhold, images of a smaller than 1-mm slice thickness through the chest can be obtained. With faster image acquisition times, fewer movement artifacts are also produced (Garvey and Hanlon 2002). These advances with multiplanar reformation have further improved the ability of spiral CT to detect and characterize lung nodules, many of them smaller than 5 mm.

5.3.2.2 *HRCT*

HRCT is a dedicated computer tomography method based on imaging with thin slices (1–2 mm) and sharp image reconstruction algorithms (Mayo et al. 1987). The slices are usually taken in 1- to 3-cm intervals. HRCT is more sensitive than chest radiography and spiral CT in depicting fine morphological alterations in the lungs (Aberle et al. 1988, Gamsu and Klein 1989, Staples et al. 1989, Remy-Jardin et al. 1991). It has been increasingly used for the early recognition of asbestos-related lung fibrosis (Gamsu et al. 1989, Akira et al. 1991, Oksa et al. 1994). In asbestos-exposed workers with normal chest radiographs, HRCT found abnormalities suggestive of asbestosis in 34% (Staples et al. 1989). In a study of Finnish asbestos sprayers, 9 of 12 (75%) had fibrosis in HRCT images, whereas the chest radiographs were normal (Oksa et al. 1994).

With HRCT, typical findings of asbestosis are those of fibrosis, namely, interlobular septal thickening, curvilinear subpleural lines, nodular opacities, ground-glass opacities (GGO), parenchymal bands, and honeycombing (Akira et al. 1990, Gamsu et al. 1995, Kraus et al. 1996). The distribution and types of HRCT findings are not specific to asbestosis but tend to differ from those seen, for

instance, in idiopathic interstitial fibrosis (Al Jarad et al. 1992a). In asbestosis, subpleural curvilinear lines and band-like opacities in the lower zones are more common, while GGO and cystic shadows, which extend to the upper thirds of the lung fields, favor idiopathic fibrosis.

Although the superior sensitivity of HRCT over plain radiography has been shown, chest radiography remains the main radiological tool due to its lower radiation exposure, lower cost, and better availability. CT is reserved for problem solving, such as clarifying pleural thickening and equivocal findings in chest radiographs (Aberle and Balmes 1991).

There is still no internationally accepted and widely used CT classification equivalent to the classification of the International Labour Organization (ILO) for plain radiographs, although some have been proposed (Al Jarad et al. 1992b, Gamsu et al. 1995, Kraus et al. 1996, Huuskonen et al. 2001, Kusaka 2005). In the proposals, methods of semi-quantitative scoring, grading, and coding are described.

5.4 Lung cancer screening

Lung cancer is the most common cancer in many countries, and, because most patients are diagnosed in late stages, it is also the most lethal. Screening would be an appealing option with which to improve the prognosis. The primary objective of cancer screening is to reduce mortality, which is usually measurable only after several years of follow-up. Mortality should be assessed preferably by means of a randomized controlled trial with a balanced distribution of confounding factors (Hakama 1991). Randomized controlled trials are underway to observe the possible mortality benefit of lung cancer screening with CT (Gohagan et al. 2005, Henschke et al. 2006, Bach et al. 2007, Infante et al. 2008), but no final results are yet available.

The potential of screening also has to be carefully weighed against its costs and expected screening-related morbidity. There is a wide variation in the magnitude of the cost-effectiveness ratios between the studies that have researched the cost-effectiveness of lung cancer screening (Black et al. 2006). The calculated cost per life-years gained varies from USD 2500 to USD 90 022, and the cost per quality-

adjusted life year ranges from USD 19 500 to USD 2 322 700 in a fully established program.

The public health importance and various interests are also reflected in the scientific polemic raised in connection with the study carried out by the Early Lung Cancer Action Project (ELCAP), the transparency of information concerning the patents held by the researchers, and the funding offered by tobacco companies (Chustecka 2008, Henschke and Yankelevitz 2008, Moy 2008).

It has been recommended that the screening of high-risk groups, such as asbestos-exposed workers, should be studied (Consensus report 2000), but, so far, routine spiral CT screening for lung cancer has not been recommended (Jett and Midthun 2005, Swensen et al. 2005, Gleeson 2006, Bach et al. 2007).

5.4.1 Prerequisites for effective screening

There are several prerequisites for successful screening. The best-known list was published by Wilson and Jungner in 1968 as follows:

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable for the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy about whom to treat as patients.
9. The cost of the case finding (including diagnosis and the treatment of patients diagnosed) should be economically balanced in relation to the possible expenditure on medical care as whole.
10. The case finding should be a continuing process and not a “once and for all” project.

In lung cancer screening, many of the criteria seem to be fulfilled. Lung cancer is an important health problem, with a relatively high incidence and a very high mortality to incidence ratio. There is agreement about the appropriate treatment for different stages of lung cancer, surgery being the curative option for localized disease (Mountain 1997). In developed countries diagnostic methods and treatment possibilities are available, and there is agreement about who should be treated. The recognizable latency period of lung cancer is represented by a small lung nodule, which can be identified by chest radiography or CT. CT is sensitive for small lung nodules and thus early-stage lung cancer, but it cannot reliably distinguish between benign and malignant nodules. Therefore, the screening program must absorb the costs of many false positive results. High coverage of the target population is of great importance for screening as a part of public health policy, since it forms an important determinant of program sensitivity and thus is a prerequisite for effectiveness (Hakama et al. 2007). To achieve high attendance, the screening test and also the entire screening program should be accepted by the population. In lung cancer screening, the acceptance should also cover the subsequent diagnostic examinations after a positive finding. This subject has been studied very little.

Screening with chest radiography has been found to be associated with the earlier detection of and improved 5-year survival from lung cancer (Salomaa et al. 1998). However, prior randomized controlled studies of lung cancer screening with chest radiography have not shown a reduction in mortality (Levin et al. 1982, Fontana et al. 1986, Kubik and Polak 1986). The trials showed significantly increased detection of early lung cancer, resectability, and 5-year survivorship in the study group compared with those of the control groups. Yet the trials did not demonstrate the reduction of disease-specific lung cancer mortality (Strauss et al. 1997, Marcus et al. 2000). Further analyses have emphasized the problems with the study design (Strauss 2002, Manser et al. 2004). The reporting of survival in lung cancer screening is also subject to various biases, including lead time, length time, and overdiagnosis bias (Black 2000, Patz et al. 2001, Marcus et al. 2006).

Lead time bias means that cases detected through screening are diagnosed earlier and the patients live longer from the time of diagnosis, even if death is ultimately not delayed as compared with the time of death in an unscreened population. Length bias results from the failure to control for the rate of disease progression. It is possible that screening will detect disproportionate numbers of less aggressive,

slow-growing tumors compared with those that are not detected at screening and are revealed clinically. Overdiagnosis can be defined as the detection of cancer that will not lead to death, or which would not otherwise have been diagnosed during a lifetime.

Even though all the prerequisites of a successful screening program are fulfilled, a decision to screen is likely to be affected by local economics and political conditions.

5.4.2 Lung cancer screening with CT

With the advent of new technology and the introduction of low-dose spiral CT, new hopes for lung cancer screening have been raised. In Japan, mass screening programs with spiral CT have been active since the mid-1990s (Kaneko et al. 1996, Sone et al. 1998, Nawa et al. 2002), and many studies were launched in the following years in Western countries (Henschke et al. 1999, Garg et al. 2002, Swensen et al. 2002, Tiitola et al. 2002, Pastorino et al. 2003, Diederich et al. 2004, Gohagan et al. 2004, MacRedmond et al. 2004, Bastarrika et al. 2005, Callol et al. 2007, Cilli et al. 2007, Das et al. 2007, Fasola et al. 2007, Mastrangelo et al. 2008). These studies have shown that screening with spiral CT allows the detection of a high proportion of early-stage lung cancers. The lung cancer detection rate ranges between 0.2% and 4.3% at baseline in different CT studies, and in most of them the detected cancers have been stage I tumors (Table 1). In repeat screenings, the cancer detection rates have been 0.1–1.1% per year (Nawa et al. 2002, Pastorino et al. 2003).

One of the major limitations of CT screening is the relatively high false positive rate. In the ELCAP study, 233 (23%) of the 1000 participants were found to have one to six non-calcified nodules in their CT scans, but only 27 of these nodules proved to be malignant (Henschke et al. 1999). The number of non-specific lung nodules in baseline screening ranges from 5.1% to 51% (Table 1), and annual screening may detect new nodules in 3.4%–14% of participants (Swensen et al. 2003, Henschke et al. 2006). There may be several explanations for the wide range of the number of lung nodules found. One may be the different prevalences of granulomatous infections in different endemic areas (Swensen et al. 2002). But, as

Swensen et al. point out, despite a high false-positive rate in their study, only two of the eight benign lesions excised were granulomas. Another explanation may be the variability in imaging techniques, since the studies that have used a smaller collimation of 5 mm or less have reported the highest rate of non-calcified nodules (Swensen et al. 2002, Diederich et al. 2002). The definition of a positive CT examination also varies. Some studies use the definition of a detected nodule of any size, in other studies a threshold size of 3–8 mm has been used (Table 1). Two Japanese studies used a subjective rating system in which the radiologists determined the likelihood of cancer without specifying what features of the CT examination made cancer more likely (Kaneko et al. 1996, Sone et al. 1998). Several background variables have also been studied to predict the existence of lung nodules, but no helpful variables have been found to avoid false-positive findings (Vehmas 2008).

Table 1. Overview of the baseline results on screening studies for lung cancer.

Reference (first author, year)	Screened number	Positive screen (% of participants)	Number of lung cancers (% of participants)	Number of stage I cancers (% of cancers)	Nodule size threshold for a positive scan	CT collimation
Bastarrika, 2005	911	131 (14.4%)	12 (1.3%)	11 (91.7%)	5 mm	8 mm
Callol, 2007	466	98 (21.0%)	1 (0.2%)	1 (100%)	5 mm	10 mm
Cilli, 2007	374	132 (35.3%)	9 (2.4%)	3 (33.3%)	Any size	8 mm
Das, 2007	187	73 (39.0%)	8 (4.3%)	5 (62.5%)	6 mm	1 mm
Diederich, 2002	817	350 (42.8%)	11 (1.3%)	7 (63.6%)	Any size	5 mm
Fasola, 2007	1045	460 (44.0%)	9 (0.9%)	8 (88.9%)	Any size	5 mm
Garg, 2002	92	30 (32.6%)	2 (2.1%)	1 (50.0%)	Any size	5 mm
Gohagan, 2004	1586	325 (20.5%)	30 (1.9%)	16 (53.3%)	3 mm	5 mm
Henschke, 1999	1000	233 (23.3%)	27 (2.7%)	23 (85.2%)	Any size	5 mm
Infante, 2008	1276	199 (15.6%)	28 (2.2%)	16 (57.1%)	Any size	5 mm
Kaneko, 1996	1369	351 (25.6%)	15 (1.0%)	14 (93.3%)	5mm	10 mm
MacRedmond, 2004	449	93 (20.7%)	2 (0.4%)	1 (50.0%)	Any size	10mm
Mastrangelo, 2008	1119	242 (21.6%)	5 (0.4%)	1 (20.0%)	Any size	NR
Nawa, 2002	7956	541 (6.8%)	36 (0.5%)	31 (86.1%)	8 mm	10 mm
Pastorino, 2003	1035	199 (19.2%)	11 (1.1%)	6 (54.5%)	Any size	10 mm
Sone, 1998	5483	279 (5.1%)	19 (0.3%)	16 (84.2%)	Any size	10 mm
Swensen, 2002	1520	782 (51.4%)	22 (1.4%)	14 (63.6%)	Any size	5 mm
Tiitola, 2002	602	111 (18.4%)	5 (0.8%)	0 (0%)	5 mm	10 mm
Vierikko, 2007	633	86 (13.6%)	5 (0.8%)	2 (40.0%)	Any size	10 mm/ 30 mm
Total	27 920	4715 (16.9%)	257 (0.9%)	176 (68.5%)		

NR=not adequately reported.

The differential diagnosis of pulmonary nodules, particularly when small, may be challenging (Winer-Muram 2006). Such nodules are poorly characterized by imaging tests and are difficult to biopsy. Of nodules smaller than 1 cm, 64%–92% have been found to be benign (Zerhouni et al. 1986, Henschke et al. 1999). The diagnostic work-up should find small lung cancers as early as possible, and unnecessary invasive procedures due to benign nodules should be avoided. Such nodules present a great challenge not only for medical staff, but also for patients, who often need to be followed for months or even for years with repeat CT scans. Sometimes more-invasive procedures involving potential iatrogenic hazards are needed, for example, fine-needle aspiration biopsies, bronchoscopies, or even thoracotomies. In different studies, biopsies have been carried out for 3%–27% of screen-positive participants (Henschke et al. 1999, Pastorino et al. 2003, Black et al. 2006). The management of positive screening CT varies between screening studies, but generally it involves either follow-up by further CT to observe for a change in size or a recommendation for a biopsy (Black et al. 2006). Not all recommendations are followed, depending on physician or participant choice. The high false positive rate represents a public health burden for screening in terms of costs and medical complications at follow-up, as well as possible emotional stress. A high false-positive rate is a consistent feature of studies involving CT screening for lung cancer, and it may prove to be a major limitation of CT screening in the future.

5.4.3 Incidental findings

An incidental finding is defined as an imaging abnormality not related to the indication of the CT scan. In the whole-body screening of 1192 participants, 86% had at least one abnormal finding, and 37% received a recommendation for further evaluation (Furtado et al. 2005). As expected, the older persons had more findings than the younger ones. Of the participants older than 70 years, 99% had abnormal findings, and, for those younger than 40 years, the corresponding figure was 43%. Abdominal findings were the most common (80%), and thoracic findings were the least common (49%), but the difference in the recommendation for further evaluation was smaller (49.7% and 44.5%, respectively). In chest CT scanning, incidental findings can be detected both in the thorax and in the upper abdomen,

while part of the upper abdomen is usually in the scanning area. In a project carried out by the Mayo Clinic to screen for lung cancer using spiral CT, 14% of the participants had incidental non-pulmonary findings that were deemed to be significant, and 6.7% of them were malignant (Swensen et al. 2002). After 3 years of scanning, 696 additional CT findings had been identified that were judged to be clinically important, and 16 of them were cancers other than of the lung (Swensen et al. 2003). In another study screening for lung cancer, incidental findings were reported for as many as 61.5% of the population, and significant findings were found for 49.2% (MacRedmond et al. 2004). The most common findings were emphysema (29%) and coronary artery calcification (14.3%). The findings were considered clinically important if they required further evaluation or had substantive clinical implications. The definition for the clinical significance of incidental findings differs, mostly concerning whether a recommendation for follow-up is issued. Even when follow-up guidelines exist, as in the case of pulmonary nodules (MacMahon et al. 2005), the variation is substantial. In studies screening for coronary artery disease, the difference in the number of nodules recommended for additional investigation ranged from 0.44% to 20.2% (Jacobs et al. 2008). The further study and treatment of such findings may provide a health benefit, but they can also lead to a series of unnecessary examinations, with extra radiation exposure, costs, anxiety, and morbidity. On the other hand, the importance of some incidental findings, such as coronary calcifications, as independent risk factors is not yet fully known.

5.4.4 Radiation dose

As the use of CT for screening purposes increases, attention should also be paid to the radiation dose (Shrimpton et al. 1991, Maher et al. 2004). The effective dose from a standard spiral CT of the chest ranges from 3 to 27 mSv, whereas that of chest radiography is 0.06–0.25 mSv (Diederich and Lenzen 2000, STUK 2009). There is little radiation absorption in the chest and a big difference in radiation absorption between the soft-tissue density lung nodules and aerated lung. Therefore, CT enables the reliable detection of nodules even with low radiation exposure (Gartenschläger et al. 1998, Rusinek et al. 1998). It is possible to decrease the tube

current from the standard 140 mA to 10–50 mA (Naidich et al. 1990, Henschke et al. 1999, Itoh et al. 2000). In programs screening for lung cancer, low settings have been used for the tube current, and the resulting radiation dose of low-dose CT is lower, 0.3–0.65 mSv, than in standard-dose spiral CT (Diederich and Lentzen 2000, Swensen et al. 2002, Maher et al. 2004).

Although the dose from a single low-dose CT examination is low, annual screening would increase the dose, and thus the risk of radiation-induced lung cancer associated with such repeated screening may not be negligible. If the dose-to-risk ratio is considered to be linear, the estimated death risk ratio caused by radiation is 1/10 000 men and 1/17 000 women screened (Roto et al. 2000). A screen-detected lung nodule may lead to one or more additional diagnostic CT examinations and thus increase the dose. It has been estimated that a mortality benefit of more than 5% would be needed to outweigh the potential radiation risks of annual CT screening (Brenner 2004).

5.5 Lung nodule differential diagnosis

Several methods can be used to separate benign lung lesions from malignant ones. There is a significant amount of literature available on the predictive factors for malignancy in lung nodules (Shaham and Guralnik 2000). By entering nodule characteristics (size, edge, location, type of calcifications) and patient risk factors (age, smoking, prior history of cancer) in the web-based questionnaire (www.chestx-ray.com/SPN/SPNProb.html), the probability that a lung nodule is malignant can be provided (Swensen et al. 1997). Despite this decision algorithm, the invasive procedure of benign lesions may occur for over 50% of the lung nodules detected (Cardillo et al. 2003).

5.5.1 Morphology

The morphological characteristics of small nodules can be visualized by CT with thin (approximately 1 mm) slices through the target nodule. Then the contours and type of nodule opacity can be evaluated. Data on screen-detected nodules have shown that the risk of malignancy is 20%–58% for nodules with smooth edges

(Zerhouni et al. 1986, Swensen et al. 1997, Takashima et al. 2003, Wahidi et al. 2007). For nodules with irregular, lobulated, or spiculated borders, the risk of malignancy has been found to be 33%–100%. Lung nodules may appear to be completely solid, pure GGO, or a mixture of the two (semi-solid). In two studies, most (73% and 59%) of the pure GGO were malignant (Takashima et al. 2003, Li et al. 2004). In another study, the percentage was lower, being 18% (Henschke et al. 2002). The likelihood of malignancy was 49%–63% for semi-solid lesions, but it was much lower, 7%–9%, for solid nodules (Henschke et al. 2002, Li et al. 2004). Although there is a trend towards a lower incidence of malignancy for smooth and solid nodules, no firm conclusions can be drawn because of the wide overlap.

5.5.2 Growth rate

A comparison of a current imaging examination with previous ones is necessary for an assessment of the growth rate of a pulmonary nodule. The growth rate is calculated in terms of “doubling time”, which refers to doubling in volume. In other words, a 26% ($=\sqrt[3]{2}$) increase in diameter corresponds to one doubling. The growth rate of lung cancer has been estimated with the use of chest radiography, and most of the reported doubling times have been shown to be between 1 and 16 months (Garland et al. 1963). However, shorter and longer doubling times have also been reported (Garland et al. 1963, Chahnian 1972, Winer-Muram et al. 2002, Takashima et al. 2003). In studies screening for lung cancer, the median doubling time of small cancers has been estimated to be between 160 and 180 days (Usuda et al. 1994, Winer-Muram et al. 2002). There is, however, a wide variation. In one study, 22% of the tumors had a volume doubling time of 465 days or more (Winer-Muram et al. 2002). When the nodule opacity was classified as GGO, semi-solid, or solid, the mean doubling times were 813, 457, and 149 days, respectively (Hasegawa et al. 2000).

The absence of detectable growth over a 2-year period has been widely accepted as an evidence of benignity. An article by Yankelevitz and Henschke (1997) questioned the scientific basis of this concept. The investigators traced the concept to articles published by Good and Wilson in 1958 and found that, according to the original data, the predictive value of benignity was only 65%. Nevertheless, the lack

of detectable growth of a pulmonary nodule implies at least a very long doubling time, which is associated with a high likelihood of benignity (Revel et al. 2004b). Even in the cases that are malignant, the lung cancers with longer doubling times tend to have a better prognosis (Weiss 1974, Mizuno et al. 1984). Small nodules are generally monitored by means of serial CT examinations to determine their growth. When a nodule shows growth, it should be biopsied or resected. However there seems to be no recommendation on the minimum growth rate for a nodule to be considered malignant.

Revel et al. has studied the reliability of two-dimensional (2D) measurement in the CT of pulmonary nodules (2004a). In that study, three radiologists each made three consecutive measurements of each nodule found, and the best intra-reader variability was 1.32 mm. If a 5-mm nodule doubles its volume, the diameter will increase by only 1.3 mm, a value that is the same as the detected intra-reader variability. In addition, some malignant nodules grow asymmetrically (Yankelevitz et al. 2000). These findings mean that the growth of a lung nodule may be missed in 2D measurements.

The observed lack reliability for 2D measurement favors the use of volumetric measurements performed with direct software calculations in the case of small nodules. If three-dimensional (3D) measurement techniques are used, the growth rate can be more reliably estimated (Yankelevitz et al. 2000, Kostis et al. 2004, Revel et al. 2004b). In an analysis of 54 nodules, a software 3D analysis yielded repeatable estimates for 96% of the nodules examined (Revel et al. 2004b). In addition, the intra- and inter-reader variability was very small. There are possible pitfalls in this technique, however. An increase in motion artifacts was found with decreasing nodule size, and this increase may affect the growth analysis (Kostis et al. 2004). Semi-solid and GGO nodules pose special challenges to the analysis of growth, while the delineation of the nodule boundaries may be difficult (Henschke et al. 2002).

5.5.3 Enhancement at CT

Dynamic CT with contrast enhancement may be useful in determining the malignancy of lung nodules. Nodule-enhancement CT is performed under the premise that neoplastic lesion, with its increased vascularity, will be enhanced when imaged with intravenous contrast material. Lesions that are enhanced greater than 15 Hounsfield units (HU) from the unenhanced level to peak contrast enhancement are considered likely malignant, whereas those that are enhanced less than 15 HU are considered likely benign (Swensen et al. 2000). In a multicenter study, 550 lung nodules ranging 5 to 40 mm in size were studied, and the sensitivity was 98% when enhancement greater than 15 HU was used as a marker for malignancy (Swensen et al. 2000). In addition, benign lesions like histoplasmosis, sarcoidosis, hamartoma, granuloma, and foreign body reaction may be enhanced more than 15 HU and therefore give a false positive result (Swensen et al. 2000, Christensen et al. 2006). In practice, nodules smaller than 10 mm cannot be reliably assessed with contrast enhancement, and the specificity of this technique is only about 60% (Swensen et al. 2000, Yi et al. 2004). With a relatively low cost and a high general availability, contrast enhancement CT may be a feasible method in the first diagnostic procedure when the objective is to avoid misclassifying malignant lesions as benign. The low enhancing nodules are more likely to be managed with observation than with intervention. However, the poor specificity can lead to increased overall costs and greater morbidity due to unnecessary biopsies and other thoracic surgical interventions.

5.5.4 Positron emission tomography

Positron emission tomography (PET) with glucose analog 18-fluorodeoxyglucose (FDG) detects the elevated glucose metabolism that is often present in malignancy (Gould et al. 2001). Studies have shown a sensitivity of 92%–96% and a specificity of 77%–90% with the use of FDG–PET in the diagnostic workup of pulmonary nodules (Lowe et al. 1998, Gould et al. 2001). However, the sensitivity and specificity of the method declines when the nodule is less than 1 cm, and false-negative results can occur (Goldsmith and Kostakoglu 2000, Lindell et al. 2005). This result is due to the limited spatial resolution of PET scanners and the relatively

weak metabolic signal produced by some tumors, such as bronchioloalveolar carcinoma and carcinoids (Lowe et al. 1998, Goldsmith and Kostakoglu 2000, Lindell et al. 2005). Few data exist for nodules smaller than 1 cm. In a review of 1474 pulmonary lesions of any size, only 8 nodules were less than 1 cm in diameter—3 true positive, 2 true negative, and 3 false negative cases (Gould et al. 2001). One study screening for lung cancer evaluated FDG–PET in nodule work-up (Bastarrika et al. 2005). There were 12 nonsmall-cell lung cancers, of which 4 were negative in a PET study (size range 8–11.5 mm). They concluded that FDG–PET may reduce unnecessary invasive procedures, but the negative nodules should be still followed up with CT. There are also benign pulmonary lesions like active granulomatous disease, other infections, and benign tumors with high metabolic rates resulting in false positive PET scans (Lewis et al. 1994, Lowe et al. 1998, Christensen et al. 2006). The American College of Chest Physicians currently recommends against the use of PET for patients with nodules that measure less than 8 mm in diameter (Gould et al. 2007). However, PET may be useful in detecting mediastinal and distal metastases when the diagnosis of lung cancer has been established (Lewis et al. 1994, Libby et al. 2004).

5.5.5 Biopsy

For nodules that have clinical and imaging features of malignancy, a tissue sample is required. To obtain tissue from a nodule, video-assisted thoracoscopic or open surgical biopsy may be performed. A less invasive method with which to gain a diagnosis is CT-guided fine-needle aspiration biopsy (FNAB). FNAB may have a sensitivity of 86.1% and a specificity of 98.8% in the diagnosis of malignancy (Lacasse et al. 1999). However, for nodules of 5–7 mm in diameter, the sensitivity may be only 50% (Wallace et al. 2002). The diagnostic accuracy depends not only on the nodule size and location, but also on the experience of the operator, the skill of the pathologist, and the techniques and equipment used. When non-specific benignity is diagnosed, further evaluation is required (Westcott et al. 1997). The lesion may be malignant, but a false-negative sample may have been obtained outside the nodule or from a necrotic area. A CT follow-up is needed, and, if further growth occurs, a repeat biopsy or resection is indicated. FNAB is an invasive

procedure, and complications can occur, the most common being pneumothorax and hemorrhage (Westcott et al. 1997, Wallace et al. 2002). Pneumothorax can occur in 25% of patients, but only 7% of them will eventually need a chest tube (Lacasse et al. 1999).

5.6 Psychological impact of screening

To date, only minimal knowledge is available regarding the psychological impact of screening and surveillance programs examining asbestos-exposed workers or CT-scan screening programs for lung cancer (Meyerowitz et al. 1989, Schnoll et al. 2003, van den Bergh et al. 2008). Most published studies of asbestos-exposed workers have focused on the psychological consequences due to the notification of health risks resulting from occupational exposure (Meyerowitz et al. 1989, Lowinger 1990). The attitudes of the public towards screening will be important in ensuring good participation in a screening program and adherence to a screening protocol.

The attitudes towards lung cancer screening have been studied among smokers. A survey among 172 current and former smokers found that 62% expressed an interest in CT screening for lung cancer (Schnoll et al. 2003). On the other hand, a study among 2001 persons showed that smokers were less likely than non-smokers to consider CT screening (Silvestri et al. 2007). A higher level of perceived risk has been found to be associated with a greater interest in screening (Schnoll et al. 2003, Hahn et al. 2006). In addition, the greater worry and distress caused by knowledge of the health risks of asbestos exposure have been found to be associated with a greater likelihood of attending a medical screening program (Meyerowitz et al. 1989).

Trial adherence refers to the number of participants attending subsequent screening tests. Achieving a high rate of attendance for screening is essential for the effective implementation of the screening program, while reduced attendance may decrease the sensitivity of the program (Hakama et al. 2007). In mammography screening studies, a previous false-positive result may enhance subsequent adherence (Burman et al. 1999, Lipkus et al. 2000). In two studies screening for lung cancer with chest radiography, the effect of false-positive findings has differed

(Ford et al. 2003, Taylor et al. 2004). In both studies, trial adherence was poorer among those who had received previous false-positive results. Adherence in lung cancer screening by CT has also been retrospectively studied (Montes et al. 2007). In that study, a trial adherence of 65% was achieved. The participants with lung nodules were more adherent than those without, but the effect of false-positive findings was not determined. The adherence was better among those who had to travel less than 200 km to the referral center. Former smokers and women were also more adherent than current smokers and men. In studies screening for lung cancer, the number of participants has fallen with each successive year. In a Japanese study, 1369 attended the baseline study, but only 184 attended the fourth screening (Kaneko et al. 1996). In a study with five annual screenings, only 24 of 817 participants attended all of the screenings (Diederich et al. 2004). The loss was due to death, the development of lung or some other cancer, funding limitations, refusals, and failures to return for annual screening on time. Progressive loss of participation in a series of repeat screenings can have an adverse impact on both the viability and cost-effectiveness of the program.

In addition to decreased mortality, the aim of any medical screening should be to increase the number of quality-adjusted life years. While the possible beneficial mortality effects of lung cancer screening are still unknown, negative side effects, including psychological ones, should be determined. In mammographic studies, the negative psychological impact of screening after a clear result has been minimal (Aro et al. 2000, Brett et al. 2005), or anxiety has been lower after the screening (Sutton et al. 1995, Swanson et al. 1996). In studies screening for lung cancer, spiral CT can detect false-positive findings in up to 50% of the participants at baseline (Swensen et al. 2002). False-positive test results may cause anxiety and lead to repeat CT studies or more invasive examinations (bronchoscopies, CT-guided lung biopsies, thoracoscopies), which may be at least uncomfortable or even painful, not to mention iatrogenic hazards. Repeat CT examinations may be easy for the participants, but the psychological anxiety may be high when the participants have to wait for answers, as in the study of van den Bergh et al. (2008), in which 46.4% of the respondents reported at least some discomfort while waiting for the baseline CT-scan results. Participants may exhibit a great deal of anxiety at being informed that they have had a positive screening result (Lipkus et al. 2000, McNaughton-Collins et al. 2004, Brett et al. 2005). In a study screening for prostate, lung,

colorectal, and ovarian cancer, cancer-related distress was temporarily increased by an abnormal screening result, the majority of these abnormal examinations being flexible sigmoidoscopies (Taylor et al. 2004). Health-related quality of life in CT screening for lung cancer has been the subject of one study (van den Bergh et al. 2008), which demonstrated no evidence of adverse effects on anxiety and distress due to CT screening for lung cancer. In addition, no negative impact was found after 6 months for persons with an indeterminate baseline CT result when they were compared with those with a negative result at baseline. However, the participants that needed more invasive examinations due to lung nodules were excluded from the questionnaire study.

5.7 Secondhand smoke

Since the 1980s, evidence has accumulated on the adverse health effects of secondhand smoke (SHS), also referred to as passive smoking, exposure to environmental tobacco smoke, and involuntary smoking. The adverse respiratory effects of SHS include lung cancer (Hackshaw 1998, Boffetta 2002), chronic respiratory symptoms (Pope and Xu 1993, Jaakkola et al. 1996, Jaakkola and Jaakkola 2002), lung function impairment (Masi et al. 1988, Rona and Chinn 1993, Xu and Li 1995), chronic obstructive pulmonary disease (Eisner et al. 2005), and asthma (Jaakkola et al. 2003). A meta-analysis by Boffetta (2002) found a 25% increased risk for lung cancer in association with marriage to a smoker, and workplace exposure to SHS was associated with a 17% increase.

Cigarette smoking is related to the development of emphysema and rare interstitial lung diseases, including desquamative interstitial pneumonia and respiratory bronchiolitis-associated interstitial lung disease (Katzenstein and Myers 1998, Ryu et al. 2001, Travis and King 2002). Respiratory bronchiolitis is an incidental histopathological finding in cigarette smokers (Niewoehner et al. 1974, Katzenstein and Myers 1998). When the condition is present as a form of interstitial lung disease with significant pulmonary symptoms, it is then described as respiratory bronchiolitis-associated interstitial lung disease (Holt et al. 1993). Desquamative interstitial pneumonia is considered to be a more extensive form of respiratory bronchiolitis-associated interstitial lung disease, and it seems likely that

these three entities represent the different ends of the spectrum of the same disease (Katzenstein and Myers 1998). In these entities, HRCT can be normal, but, when abnormalities are present, GGO, linear and reticular opacities, and small poorly defined nodules may be seen (Holt et al. 1993, Colby and Swensen 1996, Katzenstein and Myers 1998, Desai et al. 2003). They can be associated with the presence of centrilobular emphysema, and there is considerable overlap in the radiological findings (Colby 1998, Heyneman et al. 1999, Travis and King 2002).

For symptom-free smokers, HRCT has been shown to detect pathological lung changes such as emphysema, parenchymal micronodules, GGO, and bronchial wall thickening (Remy-Jardin et al. 1993b). These HRCT findings correlate with the same kind of pathological changes found in respiratory bronchiolitis and desquamative interstitial pneumonia (Remy-Jardin et al. 1993e). Even limited smoking (<10 pack-years) has been found to induce detectable HRCT abnormalities (Vehmas et al. 2003). This finding raises the question of whether SHS exposure alone can induce such changes. As pulmonary function tests often fail to identify the early stages of smoke-induced diseases, HRCT could prove to be a more sensitive clinical test. However, there are few data on the potential effects of SHS exposure on HRCT findings.

6. Aims of the study

The aim of this study was to assess the prerequisites for effective CT screening for lung cancer among asbestos-exposed workers. In addition, the role of HRCT in screening and surveillance was studied. Special attention was given to the effect of SHS exposure to HRCT images.

The detailed aims were as follows:

1. To find occult lung cancers among asbestos-exposed workers and to determine a high-risk group for screening purposes. The occurrence of incidental findings was also studied (Study I).
2. To study the acceptability of screening, health anxiety, and trial adherence among exposed workers. Special attention was given to the psychological impact of false-positive findings (Study II).
3. To characterize asbestosis today and to clarify the indications for HRCT and other health examinations in the surveillance of heavily exposed workers (Study III).
4. To determine whether the effects of SHS on lungs are detectable in HRCT images (Study IV).

7. Materials and methods

7.1 Study design

This cross-sectional study was carried out between January 2003 and December 2004. All of the asbestos-exposed workers (n=633) were screened for occupational lung diseases with the use of HRCT. Those who were current or ex-smokers (cessation within the last 10 years, N=180) were also screened for lung cancer with unenhanced low-dose spiral CT. To avoid unnecessary radiation exposure, spiral CT was scheduled only for this group because of its estimated higher risk for lung cancer. Those who were older than 70 years and presumed not to be operable were excluded from the spiral imaging (van Klaveren et al. 2002).

The protocol also included a questionnaire and a medical examination. Chest radiography, lung function, and laboratory tests were carried out during the first visit to the Finnish Institute of Occupational Health (FIOH). CT examinations were done within 1–2 months of this first visit.

7.2 Study population

The study population was collected from two groups. The first group (n=308) consisted of workers who participated in the Asbestos Screening Program of FIOH in 1990–1992 due to their occupational exposure (Huuskonen et al. 1995). From all those screened, persons were selected who were heavily exposed (i.e., whose expert-evaluated cumulative exposure was sufficient to cause lung fibrosis) and who lived in three geographic areas (Helsinki, Tampere and Turku and their surroundings). They had a calculated exposure index of 70 or more during a previous study (Koskinen et al. 2002). The other group (n=325) was formed from workers who had asbestosis or asbestos-related pleural findings and had visited the clinics of occupational medicine in Helsinki or Tampere for a clinical follow-up and were

willing to participate in the study. Their exposure was clinically estimated on the basis of their work history, and those with sufficient exposure to induce asbestosis were included. For the present study, an asbestos-exposure index was calculated for all of the participants on the basis of their responses to the questionnaire.

A total of 633 (83.5%) of the invited 758 workers attended the imaging study [627 men, 6 women, mean age 64.5 (range 45.3–86.9) years]. Altogether 372 were studied in Helsinki, 182 participated in Tampere, and 79 were from Turku.

Of the study group, 566 (89.4%) were construction workers, of which 264 were plumbers, the rest being industrial, real estate, or cleaning workers. There were 120 (19.0%) current smokers, 361 (57.0%) ex-smokers, 141 (22.3%) non-smokers, and 11 cases with lacking data on smoking. The age, smoking, SHS, and asbestos exposure of the participants are presented in Table 2.

Table 2. Age, smoking, secondhand smoke (SHS), and asbestos exposure of the participants.

Characteristic	N	Mean	SD	Median	Range
Age, years	633	64.5	6.8	64.8	45.3–86.9
Asbestos-exposure index	630	77.1	47.1	61.6	4.0–286.0
Duration of asbestos exposure, years	538	19.2	11.4	18.0	0.5–45.5
Latency ^a , years	538	41.6	7.4	42.0	14.0–62.0
Smoked pack-years	609	17.6	18.0	13.0	0.0–129.0
SHS exposure ^b	310	23.5	25.2	17.0	0–193.5

^a Time between onset of asbestos exposure and CT study.

^b Lifetime SHS exposure calculated in pack-years.

In Study II, the final statistical analyses were conducted for 310 participants (91 non-smokers and 219 ex-smokers) after the exclusion of the current smokers and those with missing information on SHS exposure.

In Study III the baseline psychological questionnaire was returned by 601 (94.9%) of the participants (all men). Both the baseline and follow-up questionnaire were returned by 457 (72.2%) participants. Of the false positive group, 62 (63.9%) also responded to the follow-up questionnaire.

Study IV was restricted to men (n=627, mean age 64.4, SD 6.7).

7.3 Imaging and image analysis

7.3.1 Radiography

Plain chest radiographs were taken in each center (Helsinki, Tampere, Turku). They were interpreted by a single reader (Tapio Vehmas in Helsinki and Turku, Ritva Järvenpää in Tampere) separately from the CT image analysis as a routine clinical procedure. Special attention was paid to possible lung shadows suggestive of a tumor.

7.3.2 CT

CT of the chest was performed with three different scanners: two-single slice scanners (Siemens Somatom Balance, Siemens Medical, Erlangen, Germany; Siemens Somatom Plus 4, Siemens Medical, Erlangen, Germany) in Helsinki and Tampere and one multislice scanner (GE Lightspeed 16 Advantage, GE Healthcare, Milwaukee, WI, USA) in Turku. Spiral CT images were obtained during a full inspiration in the supine position, from the lung apex to the costophrenic angle. The slice thickness was 10 mm with a 15-to-20-mm table feed. The imaging parameters were 110–120 kV and 36–110 mA. The images were reconstructed as 10-mm slices and printed as hard copies at window settings appropriate for viewing the lung parenchyma and soft tissues. In Tampere and Turku, the window width for lung parenchyma was 1500 HU, and the window level was –600 HU. In Helsinki, the

interpreters used the following two settings in the same session: 1200/–700, and 2000/–400 HU. The difference between the centers was due to the different settings used by the observer groups in their clinical practice.

HRCT images were exposed in the prone position and at full inspiration. The slice thickness was 1–1.25 mm, and slices were taken at 3-cm intervals (130–140 kV, 100–111 mA), from the lung apex to the costophrenic angle. The images were reconstructed with the use of a high spatial reconstruction algorithm and printed as hard copies using the same window settings as those use for spiral CT images.

7.3.3 Image analysis

The spiral CT and HRCT images were analyzed, and the findings were recorded by two radiologists in consensus (Tapio Vehmas and Taina Autti in Helsinki, and Ritva Järvenpää and Tuula Vierikko in both Tampere and Turku). The readers were aware that the participants had been exposed to asbestos, but they were blinded as to their medical data.

7.3.3.1 *Lung nodules and incidental findings*

The presence, number, and size of the lung nodules were recorded. If there was a benign type of calcification or fat in the nodule and the nodule was smaller than 20 mm in diameter, it was considered benign (Zerhouni et al. 1986, Henschke et al. 1999). A finding suspicious of lung cancer was any lung nodule that did not match these criteria and that had appeared or had increased in size since the possible previous examination.

Non-calcified lung nodules were examined further according a modification of the protocol used in the ELCAP study (Henschke et al. 1999). If the nodule was smaller than or equal to 5 mm in diameter, it was re-examined with spiral CT after 6 months and again after 12 months. The growth of these nodules was noted according to both visual assessment and measurement on screen. The slice thicknesses and imaging parameters were individually selected in these cases. For nodules 6–10 mm in diameter, the protocol recommended a thoracoscopic biopsy or a biopsy with CT guidance. Alternatively, the nodule was re-examined after 3

months, and, if needed, again after 6 and 12 months. When the nodules were smaller than or equal to 11 mm in diameter, a biopsy was recommended. All previous chest radiographs and CT images were reviewed when available.

All incidental CT findings were also registered. The radiologist informed the clinicians, who decided whether additional examinations were needed or not. Expert meetings were also used to solve problematic cases. The additional examinations due to lung nodules and incidental findings were conducted by FIOH, or the participants were sent to a hospital if needed.

7.3.3.2 *HRCT findings*

The HRCT images were assessed by the same readers who had read the spiral CT images. The lung abnormalities were recorded along with the thickening, calcification, and width of the pleura. For lung abnormalities, both a Finnish (Huuskonen et al. 2001) and an international scoring system (Kusaka et al. 2005) were used for the classification. These classification systems have been developed for quantifying HRCT abnormalities that have been described as occurring in asbestos-induced lung fibrosis.

In the Finnish system, the recorded abnormalities are as follows: septal thickening, subpleural lines, parenchymal bands (2–5cm), and honeycombing. These lung abnormalities were recorded and taken into account when interstitial fibrosis was classified by semi-quantitative scoring from 0 to 5 as follows:

1. Class 0: normal finding (normal finding by all criteria)
2. Class 1: subnormal finding (1–2 criteria sporadically for the lung periphery; no honeycombing)
3. Class 2: mild fibrosis (at least 2 criteria on both sides and in several slices from the lung periphery; no honeycombing)
4. Class 3: moderate fibrosis (several criteria, which extend deeper into the lung than in class 2; honeycombing as a general rule)
5. Class 4: severe fibrosis (several criteria or associated findings extending deep into the lung; honeycombing; lung architectural change)

6. Class 5: extreme fibrosis (extreme severe and various fibrotic changes; little normally aerated lung left).

If the readers could not match the findings exactly with any given fibrosis class, five subcategories (0.5, 1.5, 2.5, 3.5, 4.5) were used. In Finland, it has been agreed that class 2 (mild fibrosis) acts as a threshold for asbestosis.

Signs of centrilobular, paraseptal, and panlobular emphysema and bullae have been classified for both lungs separately using a similar scale from 0 to 5 without subcategories. A rough description of the pleural thickenings is made using two parameters (the greatest thickness in millimeters and the extent in square centimeters).

In the international system, both lungs are divided into three zones (upper, middle, and lower). Each of the six zones (three for each lung) are scored for each HRCT sign on a scale of 0 to 3. In this system 0 indicates no definitive abnormalities, 1 stands for mild abnormalities, 2 equals moderate abnormalities, and 3 represents severe abnormalities. The scores are then summed for both lungs. In the final score, zero indicates a normal finding, and the maximal score of 18 is the sum of the highest scores for each lung at three levels. The following main signs, as described in the Fleischner society recommendations (Austin et al. 1996), are evaluated as follows:

1. Well-defined rounded opacities, <10 mm in diameter (1 = abnormalities definitely present but few in number, 2 = numerous abnormalities, and 3 = abnormalities very numerous, normal anatomical lung structures poorly visible)
2. Irregular and/or linear opacities (1 = abnormalities definitely present but few in number, 2 = numerous abnormalities, and 3 = abnormalities very numerous, normal anatomical lung structures poorly visible)
3. Ground-glass opacities (GGO) (1 = focal, 2 = patchy, and 3 = diffuse)
4. Honeycombing (1 = extent of up to 10 mm, 2 = >10 mm to 30 mm, and 3 = > 30 mm in the subpleural parenchyma)
5. Emphysema (1 = up to 15%, 2 = between 15% and 30%, and 3 = >30% of the area of one zone).

In addition, the presence of several other radiological signs (yes or no) were noted, and those with a common occurrence ($n \geq 15$) were included as outcomes in the statistical analyses: bronchiectasis, bronchial wall thickening, suspicion of lung cancer, calcified granuloma, dependent opacity, parenchymal band, rounded atelectasis, subpleural curvilinear line, and tuberculosis. The scoring was conducted according to a published international system with standardized instructions and reference images (Kusaka et al. 2005).

7.4 Lung function tests

Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and the FEV_1/FVC ratio were obtained with spirometry (Vmax, Sensor Medics, USA; Medikro 940 Spirometer, Medikro, Finland). Single-breath diffusing capacity for carbon monoxide corrected for hemoglobin concentration (DL_{CO}), specific diffusing capacity corrected for hemoglobin concentration (DL_{CO} adjusted for alveolar volume, DL_{CO}/VA), and total lung capacity measured with helium (TLC) were measured using gas transfer equipment (Vmax, Sensor Medics, USA; Compact Transfer or Masterlab, Jaeger, Germany). All of the results of the lung function tests were expressed and analyzed as the percentage of the predicted value. In the analysis, the reference values were used to grade the ventilatory function on the basis of the distribution of values in the reference population (Viljanen 1982).

7.5 Questionnaires

An invitation letter provided general information about the study and explained the intention to screen for lung cancer with the use of CT, which differs from the standard health examinations of asbestos-exposed workers. A questionnaire for assessing background data (demographic characteristics, smoking status, smoked pack-years, respiratory symptoms, and diseases), occupational exposure, baseline psychological items, and SHS exposure was sent with the letter. The participants were asked to respond to the questionnaire before the medical examinations.

7.5.1 Occupational exposure

In the questionnaire, the participants were asked to provide detailed information on their occupational history. The questions were roughly the same as in the questionnaire of the Asbestos Screening Program in 1990–1992 (Huuskonen et al. 1995). The questionnaire covered a complete job title and industrial work history. The participants were asked to indicate their main work for each year during their career. The occupational assessment reviewed all their job positions. For occupations implying asbestos exposure, its duration was recorded. The asbestos exposure level associated with each job was assessed according to the calendar period of exposure and the typical reported task. To estimate cumulative asbestos exposure, an asbestos-exposure index for the work career until the screening visit was calculated by summing up the work years before and after the first regulation in 1976 concerning asbestos work in Finland, weighted by the respective estimated exposure levels (Koskinen et al. 2002). This index was calculated for all of the participants using only the information given in the questionnaire. If the information was completely missing, the index was taken from a previous study, made in 1990–1992, if available.

7.5.2 Psychological questionnaire

The psychological variables were based on the cognitive approach to the balance between health-related threat appraisal (health anxiety, health concern) and adaptive responses (Salkovskis et al. 2002).

The participants' awareness of the risks of asbestos exposure, perceived lung cancer risk, health anxiety, worry about lung cancer, views on the necessity of health screening asbestos-exposed workers, and trial adherence intention were assessed using the following scale: totally agree, somewhat agree, do not know, somewhat disagree, or totally disagree. The assessment was conducted via a questionnaire listing statements to which the participants were expected to respond.

The actual questions are listed below, first the four measures about health concern:

1. Awareness of the risks of asbestos exposure: “I am aware of the health risks that asbestos exposure can lead to.”
2. Perceived lung cancer risk: “The possibility that I might get lung cancer is quite small.”
3. Health anxiety was assessed using six items: “Participation in the screening adds to my sense of security,” “The invitation for the screening study makes me feel anxious,” “Waiting for screening results makes me feel nervous,” “This type of periodical screening study generates worry,” “Fear of the exacerbation of my illness worries me,” and “The examinations related to the study are unpleasant.” The five latter statements were reversed, and the items were summed into an overall score, the higher scores indicating greater anxiety.
4. Worry about lung cancer was assessed using two items: “The possibility that I will have cancer frightens me” and “I am worried about the possibility that I might have cancer.” The items were reversed and summed into an overall score, the higher scores indicating greater worry.

The variables measuring adaptive response follow:

1. Patients’ views concerning the necessity of the screening were assessed with three different statements: “It is necessary to screen the health of asbestos-exposed workers,” “My participation in the study is important to get new information on asbestos-induced diseases and their treatment,” and “Cancer should not be screened among healthy persons.”
2. Trial adherence intention was determined by: “I am willing to attend screening tests also in the future.” Trial adherence refers the number of participants attending subsequent screening tests.

7.5.3 SHS exposure

The information on SHS exposure was obtained with a questionnaire modified from the questionnaire used by the Finnish Environment and Asthma Study (Jaakkola et al. 2003). It included questions on an exposure matrix for SHS exposure. The SHS

exposure was self-reported, including both the past 12 months' exposure at work and at home and the lifetime exposure in the following 10 age periods: 0–1, 2–6, 7–15, 16–20, 21–30, 31–40, 41–50, 51–60, 61–70, and 71–80 years, exposure at home and at work. The number of cigarettes exposing the participant to SHS daily and the duration of exposure (in years) were reported for each age period. Cumulative exposure was calculated as SHS pack-years (one pack=20 cigarettes). For the statistical analyses, the age periods were summed to form a cumulative lifetime exposure index for the combined periods (0–80 years). The SHS questionnaire was returned by 310 non- or ex-smokers.

7.6 Statistical methods

The groups were generally compared using cross-tabulation and t-tests for normally distributed continuous variables and the Mann-Whitney U or Wilcoxon's test for skewly distributed continuous or ordinal variables. The differences between the categorical groups were also tested using cross-tabulation and the χ^2 -test or Fisher's exact test.

In Study II, the prescreening and postscreening psychological items were compared for the whole group and, further, for two subgroups (i.e., those with negative results and those with false positive results). The demographic and health variables [age, education (at least vocational training versus lower education), symptoms (cough, phlegm secretion, wheezing, dyspnea), marital status (unmarried, widow, divorced versus married or cohabiting), smoking status (current smoker, ex-smoker, non-smoker), smoked pack-years, years of asbestos exposure, and latency] were evaluated as potential predictors of the baseline psychological items and their change by using an analysis of covariance. The internal consistency of the question groups concerning health anxiety and worry about lung cancer was tested with Cronbach's alpha.

In Study III the principal variable of interest, interstitial lung fibrosis, was dichotomized either as indicating fibrosis (class 2 or more) or not fibrosis (classes 0 to 1.5) in the HRCT. For clinical reasons, the Finnish scoring system was used in the statistical analyses to differentiate between the fibrosis and no fibrosis groups, as it is the national classification system for asbestosis diagnostics today. The clinical,

laboratory, and lung function variables were then compared between the aforementioned groups (fibrosis or no fibrosis). The variables used were age, emphysema, pack-years, smoking status, potential image interpreter effect (1=RJ/TVi, 0=TA/TVe), body mass index (BMI, weight [kg]/height[m]²), duration of asbestos exposure, latency time since first exposure, the asbestos-exposure index, lung function, symptoms, and laboratory tests.

A logistic regression model was used to determine the variables independently associated with HRCT pulmonary fibrosis. With this model, all of the variables were tested that appeared to be separately associated with HRCT pulmonary fibrosis in the first analyses. All of the lung function variables were also tested because of their reported association with pulmonary fibrosis in the literature. All of the analyses were adjusted for age, smoking status (non-smoker, ex-smoker, or current smoker), BMI, the asbestos-exposure index, latency time since the first exposure, and interpreter group, by forcing the variables into every model. The adjusted variables were chosen from those used in the first analyses, but the overlapping (duration of asbestos exposure) or not significant variables (pack-years, laboratory tests, emphysema) were removed. For the determination of whether symptoms were related to asbestos exposure (independent variable), symptoms were used as outcome variables, each in turn, in the logistic regression models adjusted for age.

In Study IV, the current smokers were excluded from the SHS analysis. The observers' mean scores for the single HRCT signs formed the outcomes of interest. The exposures of interest were the past 12 months and the total cumulative SHS exposure index as a continuous variable. Home and work exposures were analyzed separately and combined. Multiple linear regressions were used to study the relations between SHS exposure and the radiological signs, with adjustment for age, the asbestos-exposure index, smoking status (ex-smoker versus non-smoker), potential image interpreter effect, BMI, and pack-years of active smoking for the ex-smokers. Due to the concern that co-linearity could distort the regression estimates, the variance inflation factors were determined for each model. Multiple logistic regressions with the same covariates were used for the binary radiological signs.

The following additional statistical procedures were also used to further clarify the relations:

1. Because the distributions of the radiological scores were skewed to the right and transformation did not correct the skewing, an ordinal regression was used as a confirmatory analysis method.
2. The analyses were carried out in a subgroup of non-smokers only.

The results are given as the regression coefficient (B) or as odds ratios (OR) and their 95% confidence intervals (95% CI) and p-values. The tests were performed with the SPSS (version 15.0, SPSS Inc., Illinois, United States) statistical software package.

7.7 Ethics

After receiving full information on the study, all of the participants gave their written informed consent. The study protocol was approved by the ethics committee of the Finnish Institute of Occupational Health (FIOH) and the local ethics committees at each participating hospital.

8. Results

8.1 Chest CT screening for lung cancer

8.1.1 Lung nodules

Non-calcified lung nodules were found in the CT scans of 86 (13.6%) of the participants (Figure 5).

Nodules were found in 45 (25%) of the CT/HRCT group and in 41 (9%) of the HRCT only group (CT/HRCT group: both HRCT and spiral CT were done, HRCT only group: only HRCT was undertaken). Of these 86 persons, 56 had a single pulmonary nodule, 18 had two nodules, and 12 had three or more nodules. The size of the biggest nodule was smaller than 5 mm for 30 participants, 6–10 mm in 36 participants and larger than 10 mm for 20 participants.

For 17 persons, nodules of similar size and location were also apparent in old CT scans, this finding confirmed the benign nature of those in the current scans. According to the imaging protocol, 61 persons with nodules were followed with CT. Within 1 year, 38 of them had one follow-up CT scan, 16 had two CT scans, and 7 had three scans. Altogether 37 persons were admitted directly to the hospital for examination because of lung nodules. The final decision about how to proceed with the nodules was individually decided by the referring physician. One PET scan was made during the diagnostic process, and, when positive, thoracotomy was undertaken revealing stage IIIB adenocarcinoma. Three CT-guided transthoracic fine-needle aspirations were made for lung nodules, and they revealed no malignancy, along with one biopsy of a pleural lesion guided by ultrasound that revealed mesothelioma. Two mediastinoscopies and 12 bronchoscopies were performed. Some repeated CT examinations were performed after hospital admission during the diagnostic process. Two thoracotomies were performed that revealed no malignancy. Two benign lung nodules were operated on. One was a 1.7-cm tuberculous nodule, and other was a 1-cm hamartoma.

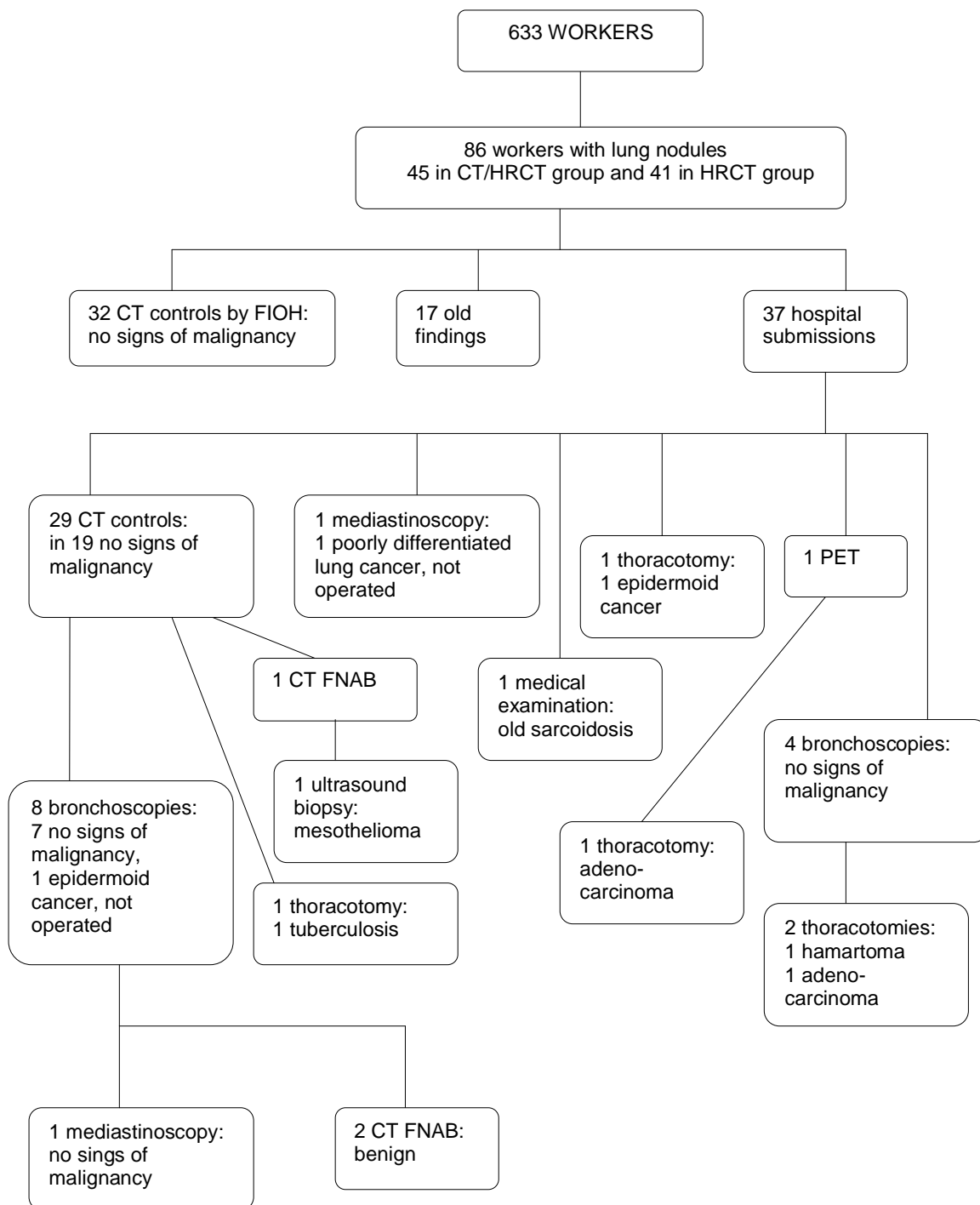


Figure 5. Flow chart of lung nodules. CT = computed tomography; FIOH = Finnish Institute of Occupational Health; FNAB = fine-needle aspiration biopsy; HRCT = high-resolution computed tomography, PET = positron emission tomography.

8.1.2 Lung cancers

Five lung cancers (0.8%) were confirmed histologically (Table 3). There were two adenocarcinomas, two squamous cell cancers, and one poorly differentiated lung carcinoma. Three cancers were operated on, two of which were stage IA. One patient was initially thought to have a stage IA cancer, but, at time of the surgery, it turned to be stage IIIB, giving a total of three stage IIIB cancers. Three of the five cancers were found in the group scheduled for HRCT only (all had stopped smoking more than 10 years earlier), and one of them was a curatively operated stage IA tumor. The chest radiography revealed only one cancer. All the lung cancers were found in patients who were smokers or ex-smokers.

Table 3. Characteristics of the patients with lung cancer.

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age, years	66	68	67	73	65
Asbestos-exposure index	105	47	44	73	25
Smoking status	Ex-smoker ^a	Ex-smoker ^b	Ex-smoker ^b	Ex-smoker ^b	Current smoker
Smoking, pack-years	43	10	10	29	13
Scheduled spiral CT	Yes	No	No	No	Yes
Tumor visible in chest radiography	No	No	Yes	No	No
Tumor size	1.9 cm	1.0 cm	4.0 cm and 2.8 cm	5.2 cm	3.0 cm
Histology	Squamous cell cancer	Adeno-carcinoma	Adeno-carcinoma	Squamous cell cancer	Poorly differentiated lung cancer
Tumor stage	IA	IA	IIIB	IIIB	IIIB
Therapy	Operation, curative	Operation, curative	Operation, not curative	Chemotherapy	Chemotherapy
Histology from	Operation	Operation	Operation	Bronchoscopy	Mediastinoscopy
Pleural plaques	Yes	Yes	Yes	Yes	Yes
Fibrosis score	1	1.5	1	2.5	1

^a Smoking cessation within the previous 10 years.

^b Smoking cessation more than 10 years earlier.

8.1.3 Incidental findings

Among the 633 screened persons, 343 incidental lesions were detected in 277 (43.8%) persons. Altogether 46 of the 343 lesions (13.4%) in 41 persons were examined further (Figure 6). Additional examinations were needed for 6.5% of those screened, and clinically important findings were regarded to exist for 0.8% (n=5).

Most of the incidental findings were coronary calcifications, cysts, or benign parenchymal scars or calcifications. Only the most evident coronary calcifications were recorded. Incidental findings resulted in 41 additional imaging procedures (ultrasound, CT, magnetic resonance imaging, urography), and 8 more invasive examinations (mediastinoscopy, bronchoscopy, thoracoscopy, biopsy). Seventeen thoracic findings (pleural effusions, mediastinal lymph nodes, tracheal nodule, etc) required additional examinations. Two patients with suspicious pleural nodules and effusions underwent thoracoscopy, but the histopathological diagnosis was fibrosis. Of the thoracic incidental findings, all but one proved to be benign. The one malignant was mesothelioma of the pleura, bringing the total number of malignancies to six (0.9%). Four of the 29 abdominal findings that required further evaluation were considered clinically significant (an adenoma producing aldosterone, thrombocytopenia detected in a person with splenomegalia, cirrhosis of the liver causing ascites, and ascites because of heart failure). Most of the findings that led to additional examinations proved to be benign lesions like cysts or adrenal incidentalomas. One liver biopsy was made for multiple hemangiomas.

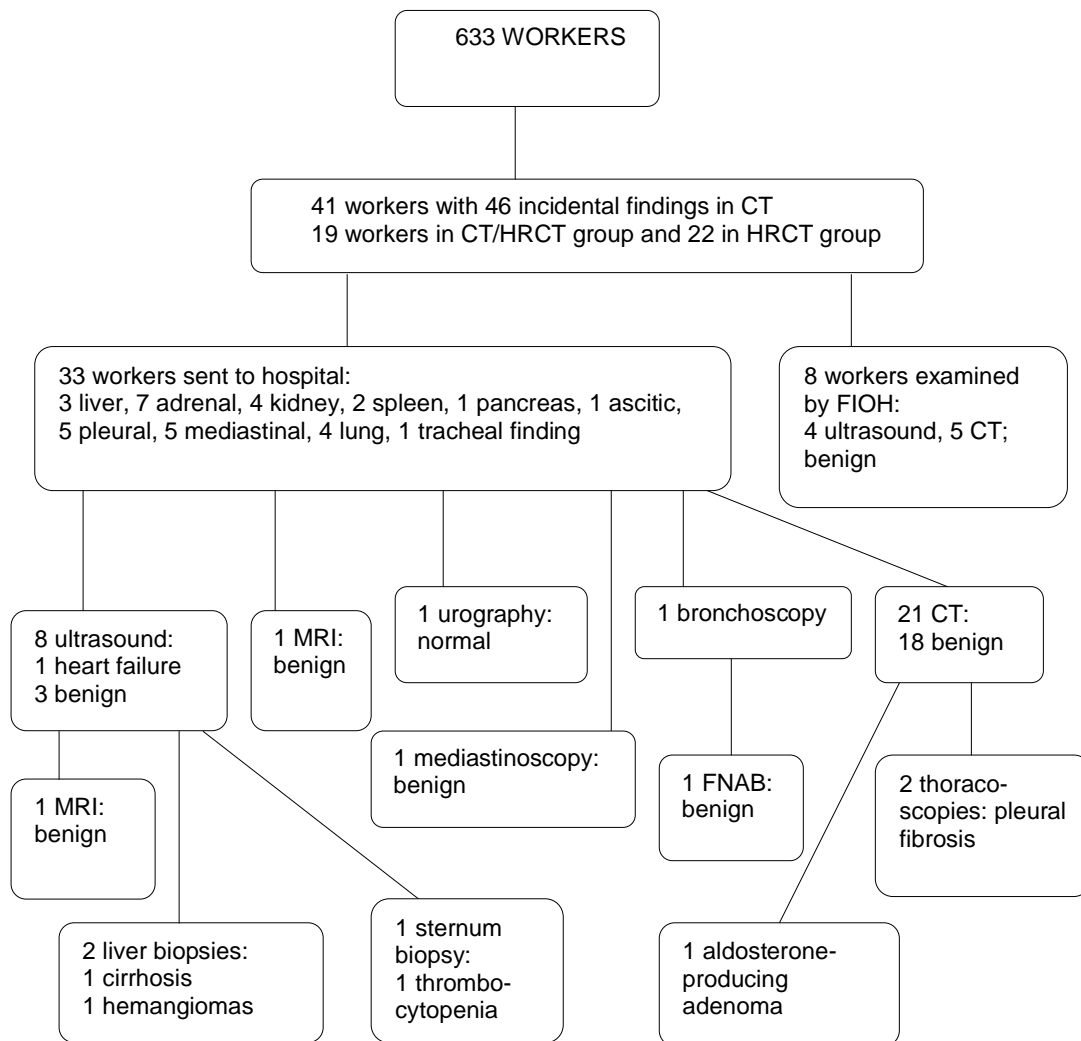


Figure 6. Incidental findings requiring additional examinations. CT=computed tomography; FIOH = Finnish Institute of Occupational Health; FNAB = fine-needle aspiration biopsy; HRCT = high-resolution CT; MRI = magnetic resonance imaging.

8.2 Psychological impact of screening for lung cancer

The baseline questionnaire was returned by 601 (94.9%) of the participants (all men, mean age 64.6 years, range 45.0–87.0). Both the baseline and follow-up questionnaires were returned by 457 (72.2%) persons. False-positive CT findings (lung nodules or incidental findings) that needed additional examinations and

revealed no cancer were found in 97 participants. Of this false-positive group, 62 (63.9%) also responded to the follow-up questionnaire. The participants who responded to both questionnaires were more often married or cohabiting ($p=0.008$) than those who only answered to the baseline questionnaire. No other demographic or health differences were detected between these groups.

8.2.1 Baseline results

None of the variables evaluated as potential predictors for the baseline psychological items had any significant effect on the items in the covariance models.

Most of the participants (99.6%) agreed totally or somewhat with the statement that health examinations of asbestos-exposed workers are necessary. Most (98.7%) also agreed that their participation in the study was generally important as a means of obtaining new information on asbestos-induced diseases and their treatment. The statement that cancer should not be screened among asymptomatic persons was supported by 11.3%.

Most of the workers (96.6%) were aware of the risks of asbestos exposure.

Trial adherence intention was high; 98.0% were ready to attend screening studies in the future.

In all, 34.2% thought that there was a possibility they may get lung cancer, and 36.8% considered such a possibility small. The results of the individual statements made in the baseline questionnaire are given in Table 4.

The mean score for health anxiety was 7.1 (scale 0–24). The mean score for worry about lung cancer was 3.0 (scale 0–8). High overall scores indicated greater health anxiety and greater worry about lung cancer. The internal consistency (Cronbach's alpha) for the health anxiety scale was 0.703, and for worry about lung cancer it was 0.768.

Table 4. Results of the baseline psychological questionnaire, individual questions.

Statement	Totally agree N (%)	Somewhat agree N (%)	Do not know N (%)	Somewhat disagree N (%)	Totally disagree N (%)	Total N
It is necessary to screen the health of asbestos-exposed workers	583 (97.3)	14 (2.3)	2 (0.3)	0	0	599
My participation in the study is important for obtaining new information on asbestos-induced diseases and their treatment	561 (94.3)	26 (4.4)	6 (1.0)	2 (0.3)	0	595
Cancer should not be screened among healthy persons	32 (5.5)	34 (5.8)	59 (10.1)	56 (9.6)	402 (69.0)	583
I am aware of the health risks that asbestos-exposure can lead to	538 (90.7)	35 (5.9)	11 (1.9)	7 (1.2)	2 (0.3)	593
The possibility that I might get lung cancer is small	86 (14.7)	129 (22.1)	169 (28.9)	131 (22.4)	69 (11.8)	584
I am willing to attend screening tests also in the future	546 (92.1)	35 (5.9)	9 (1.5)	3 (0.5)	0	593

%=% of total number.

8.2.2 Results of the longitudinal evaluation

The trial adherence intention remained high; 99.2% were ready to participate also in the future.

Across the group as a whole, health anxiety was significantly lower after the screening ($p < 0.001$). There were no significant changes in the other psychological items. Age, education, symptoms, marital status, smoking status, and smoked pack-years had no significant effect on the change in psychological items during the screening. High asbestos exposure was associated with reduced anxiety after the screening ($p = 0.003$).

Health anxiety was reduced in both the negative and the false-positive groups ($p < 0.001$ and $p = 0.027$, respectively). No significant difference in perceived lung cancer risk, trial adherence, or worry about lung cancer between the pre- and postscreening questionnaires was detected, either in the negative or in the false-positive group.

When the health anxiety statements were assessed separately, 43.4% of the participants totally or partly agreed that waiting for screening results made them feel nervous.

The results of the longitudinal evaluation of the psychological impact of lung cancer screening are given in Table 5.

Table 5. Longitudinal evaluation of the psychological impact of screening for lung cancer.

Item	N	Baseline Mean (SD)	Follow-up Mean (SD)	p-value ^a Wilcoxon signed ranks test, ^b t-test
Cancer should not be screened among healthy persons 0–4 ¹	442	0.66 (1.19)	0.66 (1.15)	0.953 ^a
Perceived lung cancer risk 0–4 ²	440	1.94 (1.20)	2.03 (1.22)	0.209 ^a
Trial adherence 0–4 ³	449	0.08 (0.33)	0.07 (0.30)	0.681 ^a
Worry about lung cancer 0–8 ⁴	435	2.97 (2.42)	3.13 (2.27)	0.135 ^b
Health anxiety, total 0–24 ⁵	419	6.74 (4.72)	5.82 (4.59)	< 0.001 ^b
Health anxiety in the negative group ⁶ 0–24 ⁵	354	6.64 (4.63)	5.73 (4.61)	<0.001 ^b
Health anxiety in the false positive group ⁷ 0–24 ⁵	62	7.63 (5.09)	6.42 (4.53)	0.027 ^b

¹ Lower scores indicate favorable opinion towards screening.

² Higher scores indicate higher perceived risk.

³ Lower scores indicate better trial adherence.

⁴ Higher scores indicate more worry.

⁵ Higher scores indicate greater health anxiety.

⁶ The participants who, after their CT scan, were told that no additional examinations were needed and that no lung cancer was found.

⁷ The participants who were told that their CT scan was positive and that they needed additional examinations, which however did not detect lung cancer.

8.3 Clinical and HRCT screening

8.3.1 Lung fibrosis and emphysema

Interstitial HRCT abnormalities consistent with lung fibrosis (i.e., fibrosis class 2 or more in the Finnish scoring system) were found for 88 (13.9%) of the 633 workers (fibrosis was found in 86 men and in 2 women). Of these, 66 (75.0%) were classified as class 2, 10 were between classes 2 and 3, 6 were in class 3, 4 were between classes 3 and 4, and 2 were in class 4, which is advanced fibrosis (Figure 7). In the HRCT images, any detectable emphysema (\geq score 0) was found for 143 (22.6%) persons. There was no significant difference in the amount of emphysema between the lung fibrosis (25/88, 28.4%) and no fibrosis (118/545, 21.7%) groups ($p=0.126$). In addition, the emphysema score was evenly distributed among the fibrosis and no fibrosis groups. The score was 1.1 for the fibrosis group and 1.1 for the no fibrosis group ($p=0.912$). Emphysema was not related to asbestos exposure.

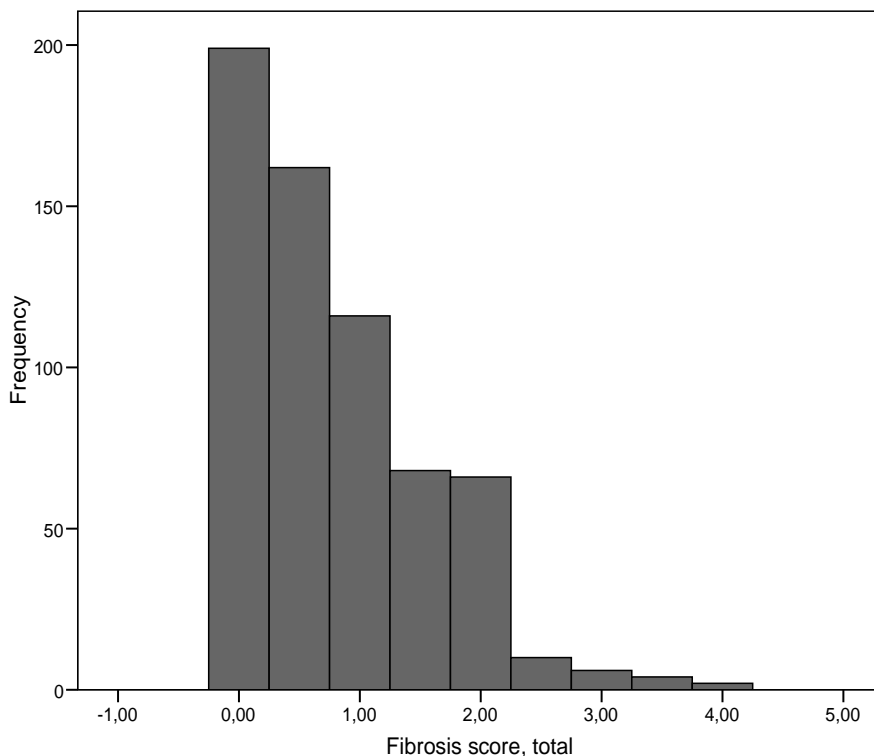


Figure 7. Lung fibrosis score for the HRCT images of the 633 screened participants.

8.3.2 Items associated with lung fibrosis

This study group consisted of 627 workers (with women excluded, n=6). In the comparison of the fibrosis and no fibrosis groups, the participants with fibrosis were older ($p < 0.001$) and had a slightly longer latency since first exposure ($p = 0.055$). No associations were noted between fibrosis and smoked pack-years or BMI, but there was an inverse relation between fibrosis and the asbestos-exposure index ($p = 0.009$) (Table 6). There were differences in smoking status, as there were more ex-smokers and fewer current smokers in the fibrosis group than in the no fibrosis group. In addition, there were differences between the fibrosis readings of both groups; the group in Helsinki had more fibrosis cases than did the Tampere group ($p = 0.003$).

Table 6. Demographic characteristics, smoking, and asbestos exposure of the 627 participants according to the pulmonary fibrosis determined by high-resolution computed tomography (HRCT).

Characteristics	All participants	HRCT fibrosis classes 0–1.5	HRCT fibrosis \geq class 2	p-value ^a
	Mean (SD) N=627	Mean (SD) N=541	Mean (SD) N=86	
Age	64.4 (6.7)	63.7 (6.4)	69.1 (6.9)	<0.001
Asbestos-exposure index	77.2 (47.2)	79.2 (47.2)	64.5 (45.6)	0.009
Latency, years	41.7 (7.5)	41.4 (7.6)	43.3 (6.7)	0.055
Duration of asbestos exposure, years	19.2 (11.5)	19.3 (11.5)	18.2 (11.7)	0.478
Pack-years	17.7 (18.1)	17.7 (18.4)	17.9 (15.5)	0.948
Smoking status				
Non-smoker	22.5%	23.3%	16.9%	<0.001
Ex-smoker	58.5%	55.5%	78.3%	
Current smoker	19.0%	21.2%	4.8%	
Emphysema, prevalence ^b	142 (22.6%)	117 (21.6%)	25 (29.1%)	0.126
Emphysema, score	1.1 (2.8)	1.1 (2.8)	1.2 (2.4)	0.854
Height (cm)	173.9 (6.4)	174.0 (6.5)	173.2 (5.8)	0.267
Weight (kg)	84.8 (13.8)	84.8 (14.1)	84.9 (12.3)	0.932
BMI	28.0 (4.2)	28.0 (4.3)	28.3 (3.6)	0.533

^a Comparison of the participants with and without HRCT fibrosis according to the t-test for continuous variables and the Pearson chi-square test for categorical variables.

^b The data are presented as n (%).

Decreased DL_{CO} (p<0.001) and DL_{CO}/VA (p<0.001) were associated with fibrosis, as was both dyspnea (p=0.028) and persistent cough (p=0.043). No significant relations were observed between fibrosis and the laboratory tests.

To identify factors independently associated with pulmonary fibrosis, multivariate analyses were performed. Older age was significantly associated (OR 1.14, 95% CI 1.09–1.21, p<0.001) with HRCT fibrosis, as were decreased DL_{CO}

(OR 0.97, 95% CI 0.95–0.98, $p < 0.001$), decreased DL_{CO}/VA (OR 0.97, 95% CI 0.95–0.99, $p = 0.001$), and increased FEV_1/FVC ratio (OR 1.04, 95% CI 1.00–1.07, $p = 0.034$). The asbestos-exposure index, laboratory tests, and symptoms did not show any significant relations to fibrosis. The results of the multivariate analysis are presented in Table 7.

Table 7. Comparison between the fibrosis and non-fibrosis groups; logistic regression.^a

Characteristic	OR (95% CI)	p-value
Age	1.14 (1.09–1.21)	<0.001
Asbestos-exposure index	1.00 (0.99–1.00)	0.433
Latency	1.02 (0.98–1.07)	0.271
FEV_1 , % of pred value	1.00 (0.99–1.02)	0.692
FVC, % of pred	0.99 (0.98–1.01)	0.476
FEV_1/FVC ratio, % of pred	1.04 (1.00–1.07)	0.034
DL_{CO} , % of pred	0.97 (0.95–0.98)	<0.001
DL_{CO}/VA , % of pred	0.97 (0.95–0.99)	0.001
TLC, % of pred	0.98 (0.96–1.01)	0.124
Dyspnea	1.47 (0.82–2.64)	0.197
Cough	1.69 (0.94–3.05)	0.081

^a Age, smoking status (current, ex, non), body mass index, reader effect, asbestos-exposure index, and latency period were adjusted for in the analyses.

pred=predicted value, FEV_1 = forced expiratory volume in 1 second, FVC= forced vital capacity, DL_{CO} = single breath diffusing capacity corrected for hemoglobin concentration, VA=alveolar volume, DL_{CO}/VA =specific diffusing capacity corrected for hemoglobin concentration, TLC=total lung capacity.

When the relations between the asbestos-exposure index and symptoms were tested, the index was inversely related to wheezing (OR1.00, 95% CI 0.99–1.00, $p=0.047$). Dyspnea, cough, and phlegm secretion showed the same kind of inverse trend, but no significant relationship to asbestos exposure.

8.4 Effects of SHS exposure

The comparison between the respondents (who had completed all of the SHS questions) and the non-respondents (with missing information) showed no major differences with respect to the background variables (age, asbestos-exposure index, BMI, and pack-years of active smoking for the ex-smokers), although the non-respondents were slightly older ($p=0.034$).

The lifetime SHS exposure of the respondents ranged between 0 and 193.5, the mean being 23.5 pack-years. The SHS exposures in the past 12 months ranged between 0 and 30 packs, with a mean of 0.43 packs.

In the multivariate regression analysis, both total SHS exposure in the past 12 months ($B=0.027$, 95% CI 0.000–0.054, $p=0.048$) and total lifetime SHS exposure ($B=0.005$, 95% CI 0.002–0.008, $p=0.000$) were significantly related to an increasing GGO score (Tables 8 and 9).

There was also a borderline significant effect of lifetime SHS exposure on irregular or linear opacities ($B=0.006$, 95% CI 0.000–0.013, $p=0.059$). The relations between the total SHS exposure and other HRCT signs were not statistically significant.

When SHS exposure at work and at home were studied separately, a relation was observed to GGO with both workplace SHS exposure in the past 12 months ($B=0.027$, 95% CI 0.000–0.054, $p=0.048$) and with the cumulative lifetime workplace exposure ($B=0.006$, 95% CI 0.003–0.009, $p=0.001$). Adjustment for the other type of SHS exposure in the models did not have much influence on the effect estimates, although thereafter the effects of recent exposure were no longer statistically significant. Both the home SHS exposure in the past 12 months and the lifetime home SHS exposure were also related to increased GGO, but these effects did not reach statistical significance. Home SHS exposure in the past 12 months was

also related to an increase in irregular or linear opacities (B=1.873, 95% 0.512–3.233, p=0.007) and honeycombing (B=1.100, 95% CI 0.675–1.524, p=0.000).

When the analyses were conducted for the subgroup of non-smokers, no significant associations were detected, probably due to the small sample size. The ordinal regression models confirmed the results by providing practically similar findings in all of the analyses. No collinearity problem was found when the variance inflation factors were determined. These factors ranged between 1.1 and 1.4.

Table 8. Effect of lifetime cumulative exposure to secondhand smoke (SHS) (pack-years) on the scores of the high-resolution computed tomography (HRCT) signs. (B=regression coefficient).

HRCT sign	Location	B ¹	95% CI	p-value	B ²	95% CI	p-value
Well-defined rounded opacity score	Work	-0.002	-0.005-0.000	0.105	0.000	-0.002-0.002	0.746
	Home	0.005	0.001-0.008	0.011	0.000	-0.002-0.002	0.972
	Total	0.000	-0.002-0.002	0.942	0.000	-0.002-0.002	0.754
Irregular or linear opacity score	Work	0.005	-0.003-0.014	0.217	0.003	-0.003-0.009	0.303
	Home	0.011	-0.001-0.023	0.082	0.006	-0.001-0.012	0.074
	Total	0.006	0.000-0.013	0.059	0.003	-0.003-0.009	0.306
Ground glass opacity score	Work	0.006	0.003-0.009	0.001	0.004	0.002-0.007	0.001
	Home	0.005	0.000-0.010	0.059	0.005	0.002-0.007	0.000
	Total	0.005	0.002-0.008	0.000	0.004	0.002-0.007	0.001
Honeycombing score	Work	0.001	-0.001-0.004	0.375	0.000	-0.002-0.001	0.528
	Home	0.003	-0.001-0.007	0.110	0.002	0.000-0.004	0.134
	Total	0.002	0.000-0.004	0.124	0.000	-0.002-0.001	0.521
Emphysema score	Work	-0.002	-0.013-0.009	0.724	-0.002	-0.010-0.005	0.536
	Home	-0.002	-0.019-0.014	0.775	-0.002	-0.011-0.007	0.651
	Total	-0.002	-0.011-0.007	0.669	-0.002	-0.010-0.005	0.535

¹Adjusted for the following confounders: age, asbestos-exposure index, smoking status (ex-smoker versus non-smoker), potential reader effect, body mass index, and pack-years of active smoking for ex-smokers.

²Adjusted for all of the mentioned confounders, as well as for SHS exposure in the past 12 months.

Table 9. Effect of exposure to secondhand smoke (SHS) (pack-years) in the past 12 months on the scores of the high-resolution computed tomography (HRCT) signs. (B=regression coefficient).

HRCT sign	Location	B ¹	95% CI	p-value	B ²	95% CI	p-value
Well-defined rounded opacity score	Work	0.000	-0.021–0.020	0.964	-0.001	-0.022–0.020	0.921
	Home	-0.065	-0.482–0.352	0.760	-0.065	-0.483–0.353	0.760
	Total	-0.001	-0.021–0.020	0.947	-0.001	-0.022–0.019	0.906
Irregular or linear opacity score	Work	-0.024	-0.081–0.032	0.399	-0.029	-0.087–0.028	0.315
	Home	1.873	0.512–3.233	0.007	1.847	0.491–3.202	0.008
	Total	-0.025	-0.082–0.032	0.389	-0.030	-0.087–0.028	0.308
Ground glass opacity score	Work	0.027	0.000–0.054	0.048	0.020	-0.007–0.047	0.151
	Home	0.066	-0.490–0.623	0.815	0.044	-0.501–0.588	0.875
	Total	0.027	0.000–0.054	0.048	0.020	-0.007–0.047	0.148
Honeycombing score	Work	0.000	-0.014–0.013	0.970	0.000	-0.013–0.014	0.945
	Home	1.100	0.675–1.524	0.000	1.093	0.669–1.517	0.000
	Total	0.000	-0.014–0.013	0.975	0.001	-0.013–0.014	0.940
Emphysema score	Work	0.011	-0.066–0.088	0.777	0.015	-0.063–0.094	0.702
	Home	-0.645	-2.482–1.192	0.490	-0.636	-2.477–1.204	0.497
	Total	0.010	-0.068–0.087	0.803	0.014	-0.065–0.093	0.727

¹ Adjusted for the following confounders: age, asbestos-exposure index, smoking status (ex-smoker versus non-smoker), potential reader effect, body mass index, and pack-years of active smoking for ex-smokers.

² Adjusted for all of the mentioned confounders, as well as for cumulative SHS exposure.

9. Discussion

9.1 Study population

The participants in this research were from three parts of the country and were primarily construction workers. They were identified from previous studies or they visited clinics of occupational medicine for a clinical follow-up. Thus they were typical Finnish asbestos-exposed workers of today. All of them had had at least one surveillance visit in the past, and therefore they had already had some experience with screening procedures. The participants were selected for this study while the pre-estimated asbestos exposure was high enough to be able to produce lung fibrosis or lung cancer.

The participation rate was high in the study; 83.5% of those invited took part in the CT study. This rate is slightly lower when compared with that of a previous CT screening study (93.8%) of Finnish asbestos-exposed workers (Tiitola et al. 2002), but better than that of German or Italian studies of asbestos-exposed workers, which had 59% and 58% participation rates, respectively (Das et al. 2007, Mastrangelo et al. 2008). Compared with experiences from cervical and breast cancer screening in Finland, a participation rate of more than 80% can be regarded as acceptable (Anttila and Nieminen 2000, Anttila et al. 2002). In the current research project, the high attendance rate may be explained by the fact that the participants' perception of the necessity for screening was high, and the respondents were well motivated to participate. This high motivation may have been due to the generally distributed information on the dangers concerning asbestos use.

High coverage of the target population is of great importance for screening as a part of public health policy since it forms an important determinant of program sensitivity and is a prerequisite for effectiveness (Hakama et al. 2007). A high participation rate also better enables the generalization of the results to a particular population.

9.2 Interpretation of the HRCT images

The scoring of the lung parenchymal signs was based on published guidelines and reference images. The images were read with two radiologists in consensus, and no inter-reader agreement was tested. The reader effect was not studied in detail because it had been previously reported for both the Finnish (Huuskonen et al. 2001) and international (Suganuma et al. 2009) systems. In the study of the Finnish system, good inter- and intra-observer agreements were achieved as regards the fibrosis score (Huuskonen et al. 2001). In the study that examined the international scoring system, the reader agreement was moderate to good for rounded opacities, irregular opacities, honeycombing, emphysema, and large opacities (Suganuma et al. 2009). GGO showed poor-to-fair agreement, but there were only two cases of GGO in that study. The optimal assessment of areas of GGO requires an awareness of the influence of window settings on the appearance of pulmonary structures and an analysis of lung attenuation. The use of low window settings can cause ground-glass appearance in normal parenchyma. The recommended choice for analyzing GGO and also other lung parenchymal abnormalities is a large window width (1000–2000 HU) and a high window level (–500 to –700 HU) (Remy-Jardin et al. 1993d, Primack et al. 1996).

There may be over- or under-detection of the abnormalities, as in any such study. However, if such misclassification is not related to the exposure status, it is random and leads to an underestimation of any true effects, rather than to any systematic bias. The interpreters had several years of experience in assessing HRCT images with the use of the window settings that they had used in their clinical practice. The settings were also in the recommended range. To control for any potential bias due to the two separate image reader teams, adjustment was made for this effect in the models of the statistical analyses.

9.3 Lung cancer screening

9.3.1 Prerequisites for effective lung cancer screening

When the prerequisites for effectively scanning for lung cancer are assessed, several steps of the screening process must be evaluated. The suitable risk population should be defined, and the screening test should be evaluated. Not only the CT itself should be evaluated as a suitable test, but also the entire screening process with its secondary examinations. CT has been widely studied for lung cancer screening, and its sensitivity exceeds that of chest radiography. The accuracy of CT for the detection of lung cancer is a complex issue, as all detected lung nodules should be studied as potential cancer. In this study, 94% of the detected nodules were benign, resulting in a high number of additional examinations. Incidental abnormalities were also common findings that required proper diagnostic workup and management. High coverage of the target population is of great importance for effective screening. If high attendance is to be achieved, the screening test and also the subsequent diagnostic examinations after a positive finding need to be accepted by the population.

In the next sections, these different aspects of prerequisites for effective cancer screening are discussed.

9.3.2 Lung cancer detection

Lung cancer was found in 0.8% of the participants, matching the results of other baseline screening trials (0.2%–4.3% [See Table 1 on page 30]). The percentage of stage I cancers (40%) was also in the range of most of the other baseline studies (20%–100%). The wide range of detected cancers may have been due to differences in smoking habits, age, and possibly occupational exposure. It was surprising that, in spite of both asbestos exposure and smoking among the participants, no more cancers were found. The median pack-years in four other studies (Henschke et al. 1999, Diederich et al. 2002, Swensen et al. 2002, MacRedmond et al. 2004) was 45, while the smoking history in the present study was lower (median 13 pack-years). The low risk is probably due to the fact that, in the material of this research, limited

tobacco smoking was compensated by an increased risk from asbestos exposure. It is also possible that false-negative cancers occurred in the group that was screened only with HRCT due to gaps between slices. There were lung cancers in 1.1% of the spiral CT group and in 0.7% of the HRCT group. The rate of false-negative cases is unknown, but this lack of knowledge may be corrected in the future with the use of the Finnish Cancer Register.

Only a few studies of lung cancer screening have been conducted among asbestos-exposed populations (Tiitola et al. 2002, Das et al. 2007, Fasola et al. 2007, Mastrangelo et al. 2008, Clin et al. 2009). In a German study, the lung cancer detection rate was higher, 4.3% (Das et al. 2007), than in the other studies (Table 10). This finding may be due to the slightly older age, heavier smoking, and possible asbestos exposures. The number of screened workers was as low as 187 in the Das study, and this low number made the estimation of cancer prevalence liable to error.

The time since the onset of asbestos exposure may also have influenced the result of the present research. Previously, researchers found that the effect of exposure peaked between 20 to 40 years after exposure (Selikoff et al. 1980, Hughes and Weill 1991, Hillerdahl and Henderson 1997). According to a more recent German study, the risk of lung cancer increases soon after the last asbestos exposure, and its maximum effect occurs 10–15 years after the exposure is received (Hauptmann et al. 2002). With this model, there could be a shorter latency period than previously assumed, especially for a high intensity of exposure. The average time from first exposure was 42 years for the participants of the present research. The most-exposed and susceptible workers could have died before the study. Of the participants, some had already entered screening programs, and some had undergone chest radiography during their clinical surveillance. In other words, the participants represented a selected population, somewhat resembling a diluted incidence group rather than a prevalence group. The cancer detection rate was, however, comparable with that of the other studies conducted among asbestos-exposed (Table 10).

Table 10. Baseline studies of lung cancer screening among asbestos-exposed persons.

Reference (First author, year)	N	Positive screen, number (%)	Lung cancers, number (%)	Stage I cancers, number (% of cancers)	Age, mean	Smoking, mean pack- years (% ^a)	Mean asbestos exposure years (CEI)	Latency, years since first exposure
Tiitola, 2002	602	111 (19%)	5 (0.8%)	0	63.0	24 (3%)	26 (NR)	NR
Das, 2007	187	73 (39%)	8 (4.3%)	5 (63%)	66.6	NR (1%)	30 (NR)	NR
Fasola, 2007	1045	460 (44%)	9 (0.8%)	8 (89%)	58.0	18.5 (34%)	30 (NR)	32
Vierikko, 2007	633	86 (14%)	5 (0.8%)	2 (40%)	64.5	17.2 (22%)	19 (77)	42
Mastrangelo, 2008	1119	242 (22%)	5 (0.4%)	1 (20%)	57.1	NR (35%)	18 (123)	34
Clin, 2009	972	NR	13 (1.4%)	NR	61.3	NR (32%)	NR	NR
Total	4558		45 (0.9%)		61.8			

CEI= cumulative asbestos-exposure index; NR= not reported.

%=% of participants

%^a=non-smokers, % of participants

The cessation of smoking among asbestos-exposed workers has been shown to be associated with a decreased risk of lung cancer, although the risk may never fall to the level of never smokers (Hammond et al. 1979, Reid et al. 2006). The present research included only the current and ex-smokers (cessation within 10 years), persons who supposedly have a higher risk for lung cancer, in the spiral CT group. This step was taken in an attempt to clarify the inclusion criteria for the lung cancer screening. This grouping was not successful, however, because there were more detected cancers in the estimated lower risk group. In three cancer cases, smoking had ceased 19–40 years earlier. The criteria for the smoking history (current active smoker or ex-smoker with cessation within the last 10 years) used as part of the

study protocol may have been too strict for former workers with asbestos exposure. Probably all asbestos-exposed smokers and ex-smokers should be included if cancer screenings are recommended in the future. On the other hand, both groups in the study were too small for any definite conclusions to be drawn.

Only one of the detected cancers was visible in the chest radiographs, the missed tumors being 1 to 5 cm in diameter. The great amount of pleural findings in radiographs made the interpretation challenging, and this has also been the case earlier (Geftter and Conant 1988). The finding of the present research confirms the superior sensitivity of spiral CT in detecting lung lesions, and even HRCT was more sensitive in this population.

9.3.3 Differential diagnosis of lung nodules

Non-calcified lung nodules have been found in 5%–51% of the study populations in baseline screening studies (Table 1, page 30). One reason for the wide range may be the variability in imaging techniques. This possibility was also evident in the present study in that lung nodules were found in 25% of the spiral CT group and in 9% of the HRCT group, with 3-cm gaps between the images.

Another reason for the wide range of detected nodules may have been the variability in the definition of the positive finding of reported nodules between studies. In the baseline ELCAP study, most of the nodules found (58%) were less than 5 mm in diameter (Henschke et al. 2002). Data from baseline screening in three trials of low-dose CT showed that the probability of malignancy is extremely low (<1%) for nodules that are less than 5 mm in diameter (Swensen et al. 2002, Gohagan et al. 2004, Henschke et al. 2004). For nodules that are 5 to 9 mm in diameter, the prevalence of malignancy increases from 2.3% to 6% (Gohagan et al. 2004, Henschke et al. 2004). This finding has led to an updated definition for a positive nodule finding in ELCAP screening at the baseline level (Henschke et al. 2004). The positive finding in the baseline screening includes solid or partly solid non-calcified nodules 5 mm or more in diameter or non-solid non-calcified nodules 8 mm or more in diameter. With this updated definition, positive results have been shown for 13% of the participants at baseline and for 5% at annually repeated screenings (Henschke et al. 2006). The present research included lung nodules of

any size. Of the detected lung nodules, 35% were smaller than 5 mm, and none of them proved to be malignant. If the criteria for a positive scan at baseline were changed, the need for repeat examinations could be decreased.

The work-up for screening-detected lung nodules in this study was defined according a modification of the protocol used in the ELCAP study (Henschke et al. 1999). Still the management of nodules was diverse, and the number of hospitalizations and invasive investigations was high. There were 10 bronchoscopies, 1 mediastinoscopy, 2 thorascopies, and 3 fine-needle lung biopsies that did not reveal any malignancy. In addition, 2 thoracotomies for benign disease (40% of all) were undertaken. In the ELCAP study, 94% of the recommended biopsies resulted in a diagnosis of malignancy, and no lobectomies were performed for benign disease (Henschke 2005). In other studies of lung cancer screening, this type of result has been difficult to achieve (Diederich et al. 2002, Swensen et al. 2002, MacRedmond et al. 2004). In a study of asbestos-exposed workers, 52% of all invasive surgeries were performed for benign conditions (Fasola et al. 2007). The reason for such a high number may have been the lack of CT biopsies.

Although the screening protocol may be defined clearly, there may be diversity due to the different practices and resources of different hospitals. This diversity influences the degree to which bronchoscopy, thoracoscopy, CT-guided lung biopsy, and PET studies are used. The techniques are likely to vary also according to the tumor location and patient tolerance of the procedure. The multicenter nature of the screening and the many clinicians responsible for actions after the screening may have caused the diversity in the diagnostic workup of the present study.

If screening is recommended in the future, there should be strict criteria for positive scans (possibly 5 mm at baseline) and a well-defined postscreening diagnostic algorithm for investigating suspicious nodules. All of the available information on past CT scannings should be available when the screening study is evaluated in order to avoid unnecessary examinations. The repeated CT screenings for positive findings should be performed in the same screening center where the first CT was done to avoid delays and diversity in the diagnostic algorithm.

9.3.4 Incidental findings

The definition of the incidental findings and their significance varies. Of lung cancer screening trials, only three other studies have reported such findings (Jacobs et al. 2008). MacRedmond et al. (2004) reported significant findings for 49.2% of their lung cancer screening population; these findings led to many referrals to specialists in respiratory medicine, cardiology, and gastroenterology. It is not clear which findings were or should be considered significant. Swensen et al. (2002) detected significant findings for 14% of their participants, and 6.7% of the findings dealt with a malignancy. In that study, the imaging protocol included a wider scan range than other studies of lung cancer screening. In a more recent Dutch–Belgian study, 8% of the participants had possible clinically relevant incidental findings, but after further examination, only 1% of the participants did have a clinically relevant incidental finding (van de Wiel et al. 2007). The study group advised against the systematically searching for and reporting of such findings in studies of lung cancer screening. The finding of the current research was in line with the Dutch–Belgian study, as most of the findings proved to concern benign abnormalities and were of no clinical importance. One incidental malignancy, mesothelioma, was found, yet without clinical benefit, while no curative treatment was possible. Patients with incidental findings should be followed up with the use of register data to work out their significance. For example, an incidental aortic calcification found in plain chest radiography was found to be associated with a sixfold increased risk of cardiovascular death among men aged 45 years, independent of major cardiovascular risk factors (Witteman et al. 1986). Incidental findings may lead to decreased morbidity and mortality from other conditions and thus enhance the value of the screening procedure. On the other hand, they can also lead to a series of unnecessary examinations, which merely increase anxiety and the costs of health care.

9.3.5 Psychological impact

As evidenced also in the current research, lung cancer screening is associated with a high number of additional examinations due to lung nodules and incidental findings. Some of the additional examinations are repeat CT examinations, which may be

technically easy for the participants, but the psychological anxiety may be high as they wait for the answers. In the current research, 43.4% of the participants responded that waiting for screening results made them feel nervous. The same type of result was found in another trial, in which waiting for the baseline CT scan results was reported to be uncomfortable by 46.4% of the participants (van den Bergh et al. 2008). These findings emphasize the fact that minimizing the waiting time for the test result is essential. The CT scans should be read within a short period of time after the examination by a radiologist at the site, and the report, with possible new recommendations for additional examinations, should be sent without delay to the person.

In lung cancer screening studies among smokers, the number of participants has fallen with each successive year. At 2 years, the ELCAP had lost 65% of its initial participants (Henschke et al. 2001). In a study of five annual screenings, only 24 of 817 participants had undergone all screenings (Diederich et al. 2004). The only study among asbestos-exposed workers, which had annual CT screening, reported a much higher (97.2%) participation rate than studies among smokers without asbestos exposure (Clin et al. 2009). The results of the present research indicate a similar trial adherence, as 98% of the participants were ready to attend screening also in the future, possibly because the participants were well aware of the risks that asbestos exposure can cause and were therefore highly motivated. It has been shown that a higher perceived risk for lung cancer is associated with more interest and willingness to be screened (Schnoll et al. 2003, Hahn et al. 2006). In the current study, the perceived cancer risk (33.6%) was higher than in studies among smokers with no known asbestos exposure, for which the perceived risk has been 14%–23% (Silvestri et al. 2007, van den Bergh et al. 2009).

Interestingly, although baseline health anxiety was not significantly associated with any of the studied variables, the reduction in anxiety after the screening was associated with high asbestos exposure. Possibly the most exposed participants had denied their risk, and afterwards their relief was pronounced. Many people who seek cancer screening do so to obtain peace of mind or reassurance about cancer (Taylor et al. 2004). This behavior may explain why the worry about cancer did not change during the screening procedure, but health anxiety was reduced when the examinations showed clear results. Knowledge of the health risks of asbestos

exposure is something that the workers must live with, and screening may help reduce the associated anxiety.

The additional examinations due to positive findings may cause an increase in anxiety, and the trial adherence can be influenced. Trial adherence among participants in lung cancer screening trials has been assessed in studies in which lung cancer was screened with chest radiography (Ford et al. 2003, Taylor et al. 2004). In both studies, trial adherence was poorer among those who had received previous false-positive results. The findings of the current study differed, as no negative effect on trial adherence was found as a result of false-positive CT findings. The intention to participate in the future was equally high in both the negative and false-positive groups.

On the other hand, a single baseline screening was carried out that did not evaluate psychological behavior in repeat screenings. Trial adherence was evaluated only via a questionnaire and was thus based on intentions rather than on actual screening behavior. In addition, the sample was restricted to high-risk asbestos-exposed workers, and the results may not be generalizable to unexposed populations likely to have less fear of cancer.

Negative screening results should assuage anxiety about cancer. Anxiety has been sparsely studied in trials dealing with lung cancer screening. One study assessed health-related quality of life in CT screening for lung cancer, and no negative effects were found during the first 6 months after the screening procedure (van den Bergh et al. 2008). In mammographic studies, the negative psychological impact of screening has been minimal, or anxiety has been lower after screening (Sutton et al. 1995, Swanson et al. 1996, Aro et al. 2000, Brett et al. 2005). The results of the current research also indicated a decrease in anxiety. Whether a decrease in anxiety could encourage people to continue smoking or even to restart should be studied. In a study involving annual CT screening, smokers with abnormal CT findings from multiple CT screens were found to be less likely to smoke at the 3-year follow-up than those who did not receive any positive results (46% versus 20%) (Townsend et al. 2005). In the same study, current smokers that received multiple normal screening results were found to behave similarly to smokers who did not participate in the lung cancer screening.

There is a possibility that the prescreening anxiety levels were increased in the present study; this possibility indicates that the observed reduction in anxiety really

represents a return to the actual baseline level. This suggestion was countered by a sigmoidoscopy screening study in which the anxiety scores were not increased after the respondents had been given the screening information (Wardle et al. 1999). Moreover, the participants of the present study were well aware of the increased health risks of asbestos exposure before their enrollment in the screening. In a study among asbestos-exposed workers, the experienced distress was found to result from the asbestos exposure itself, rather than from the screening (Meyerowitz et al. 1989). In a study of lung cancer screening, asbestos-exposed persons experienced a higher cancer distress than did the controls at the baseline of the screening program (Maurel et al. 2009). While asbestos-exposed workers are well aware of the risks, medical surveys might enhance psychological well-being among people undergoing screening programs, as medical surveillance has been shown to reduce uncertainty about health status and increase a sense of control (Meyerowitz et al. 1989, Tan-Wilhelm et al. 2000).

The findings of the current research indicate that CT screening among asbestos-exposed workers does not produce excessive long-term anxiety or other negative psychological effects that could prevent participation in a future screening program.

9.4 HRCT screening for lung fibrosis

In the current study, lung fibrosis (Finnish HRCT fibrosis class ≥ 2) was found in 13.9% of the participants, and the detected lung fibrosis cases were mostly mild. The prevalence is lower than in studies of past decades, when even more than 30% were found to have signs of asbestosis (Selikoff et al. 1980), but it is in line with the results of some recent studies. A study of 18 211 sheet-metal workers examined between 1986 and 2004 showed fibrosis in 9.6% of the workers in chest radiography (Welch et al. 2007). In two French studies of 706 and 5545 asbestos-exposed workers, 6.8%–7.2% had CT findings compatible with fibrosis (Paris et al. 2004, Paris et al. 2009). In Brazilian former asbestos-cement workers, fibrosis was found in 8.9% with HRCT (Algranti et al. 2001). In a study carried out by Paris et al., 88% of the detected fibrosis cases were estimated to be mild (Paris et al. 2004). Asbestos exposure of today's workers is remote in time and more limited than earlier described (Meurman et al. 1974, Selikoff et al. 1980, Hughes and Weill 1991, Oksa

et al. 1994, Begin et al. 1995). The strengthened regulation in the late 1970s and 1980s and in 1993 probably had a positive health impact (exposure control) (Huuskonen et al. 1995). A mortality study among British asbestos workers showed evidence of lower risk of asbestos-related diseases among those who were first exposed recently (Harding et al. 2009). Because of the longer general life expectancy, the exposed have more time to develop asbestos-related pulmonary diseases, even after milder exposures. Therefore, the patterns of asbestos-induced lung fibrosis may differ from those encountered in past decades. The matter is further complicated by the fact that aging independently causes fibrotic changes in lungs. Another explanation is selection bias: the more diseased have died, have changed their occupation and have been lost from follow-up, or have been too ill to participate.

Dyspnea on exertion and dry cough are typical in patients with established asbestosis, but they are not always present. Even early-stage asbestosis may be related with dyspnea (Staples et al. 1989). When these symptoms were compared with lung fibrosis in the current study, both symptoms showed an association in crude analyses, but when the analyses were adjusted for other variables, no relations were found, probably due to the early stage of the fibrosis found. The same type of findings has occurred in other studies, in which signs of early fibrosis have been detected in symptomless workers (Neri et al. 1994, Paris et al. 2004).

When the relations between symptoms and asbestos exposure were tested in the current project, it was found that the (age-adjusted) asbestos-exposure index was inversely associated with wheezing. Other symptoms showed the same type of inverse trend, although there were no significant relations. All dust including asbestos is irritating and can cause respiratory symptoms. The observation of the current study may have been due to selection bias in the material in that workers suffering the most from dusts may have quit their work early. The most-resistant ones may have remained longer in asbestos work and participated in the study (healthy worker effect). These mechanisms could explain the apparent inverse relation between asbestos exposure and fibrosis.

Established asbestosis has been found to be associated mainly with restrictive respiratory impairment (Miller 1993). On the contrary, HRCT abnormalities consistent with early-stage asbestosis have been described for workers without any functional abnormalities (Aberle et al. 1988, Staples et al. 1989, Begin et al. 1993,

Neri et al. 1994). In addition, an obstructive pattern has been described for mild fibrosis, but, as fibrosis was determined by chest radiography, emphysema may have affected the results (Ohar et al. 2004). The results of the present research confirmed the presence of a restrictive pattern even for mild fibrosis, while the FEV₁/FVC ratio was increased in the fibrosis group.

Diffusing capacity is regarded as a sensitive measure of parenchymal disease in asbestosis (Aberle et al. 1988, Staples et al. 1989, Harkin et al. 1996, Wang et al. 2006). In a study of asbestos-exposed workers, a marked impairment of diffusing capacity was associated with combined fibrosis and emphysema, but not with pulmonary fibrosis (Piirilä et al. 2005). In the present study, emphysema was evenly distributed among the fibrosis and no fibrosis groups. The fibrosis group had impairment in gas exchange, a finding that confirms the sensitivity of diffusing capacity. Still the differences cannot be directly applied to the individual patient, as the measurements fell often within normal limits and the odds ratios between the groups were minor. This finding is not surprising since most (75%) of the fibrosis cases were mild (class 2).

Chest radiography has been shown to be insensitive to early lung fibrosis. HRCT is more sensitive but also causes more radiation exposure and is more expensive, and its availability may be limited. The role of HRCT in the screening and surveillance of asbestos-exposed workers is also not clear. Some authors recommend HRCT only for those who have radiological ILO abnormalities greater than 1/0 or pleural plaques (Consensus report 1997, Friedman et al. 1988). Others recommend HRCT in the presence of functional impairment (Oksa et al. 1994, Neri et al. 1996, Nordman et al. 2006), even when chest radiographs are normal. In France, systematic HRCT scanning at 6-year intervals has been recommended (Consensus report 1999). HRCT may also be carried out for differential diagnosing (Nordman et al. 2006). In the present research, an attempt was made to determine whether asbestos-induced pulmonary fibrosis can be predicted by factors like the age of the worker, the latency or amount of exposure, respiratory symptoms, and laboratory or lung function tests in that this information would aid the selection of candidates for HRCT. Only age and lung function data were found to be associated with fibrosis. Still no clear age or function cutoff point could be determined for when HRCT should be carried out. The study did not detect any new information

that would lead to a change in the current practices presented in a guidebook for surveillance in Finland (Nordman et al. 2006).

9.5 Asbestos exposure

In the current research project, the asbestos-exposure index showed an unexpected inverse association with lung fibrosis in the first analyses, and, in the multivariate analysis, the association was also inverse, but it was not significant. The determination of past asbestos exposure may be difficult, and thus the relations may vary between studies. Some studies have found no association between the duration of asbestos exposure and lung lesions (Aberle et al. 1988, Staples et al. 1989, Piirilä et al. 2005). In other studies, fibrosis has been found to be positively related to the duration or latency of asbestos exposure, cumulative exposure, or to certain occupational groups (Begin et al. 1993, Oksa et al. 1994, Neri et al. 1996, Algranti et al. 2001, Huuskonen et al. 2001, Paris et al. 2008, Mastrangelo et al. 2009). In a study of retired workers, HRCT fibrosis was positively associated with cumulative asbestos exposure, but not with the duration of exposure (Paris et al. 2004). A study of shipyard workers (Neri et al. 1996) showed that all of the workers had had similar occupations in the same factory, the most salient differentiating factor thus being the duration of employment. The current population seemed to be homogeneous in that 90% of the participants were construction workers, but the true individual exposure of the workers differed even within the same occupational group. There may have also been some selection bias in the study group since, for some of the participants, the inclusion criterion was only the presence of lung fibrosis and not the estimated exposure, whereas, for other workers, the inclusion criterion was a high calculated asbestos-exposure index without lung disease. Therefore workers with low exposure and no fibrosis were not included (except possibly some with plaques and no fibrosis). It is also possible that workers who were more aware of the risks may have protected themselves against the exposure. Workers were selected whose exposure was supposedly high, but still the calculated asbestos-exposure indices ranged from as low as 4 to as high as 286. The assessment of asbestos exposure in the present study was based on questionnaires only, and the accuracy may therefore be questionable. Especially difficult was the assessment of the intensity of indirect

exposure (bystander exposure). A study of Maurel et al. (2009) showed that asbestos-exposed workers underestimate the intensity of personal exposure when compared with a hygienist's assessment. This circumstance was probably true also in the present study. Some workers, especially the older ones, may have forgotten past exposures and may also have been poorly aware of their exposure history, and thus probably distorted the assessment (recall bias). When information is collected on exposure during the past several decades among the elderly, questionnaire data alone may be unreliable. Industrial hygiene measurements are rarely available, and the retrospective assessment of asbestos exposure is usually based on job-specific questionnaires and job-exposure matrices (Ahrens et al. 1993). Neither of these two methods is clearly better than the other (Orlowski et al. 1993), but some combination may provide sufficiently accurate estimates on exposure and could be used in clinical practice (Nam et al. 2005). Data collection should include an interview by an experienced interviewer, but, during the screening of extensive populations, such a practice may be challenging.

9.6 SHS exposure and HRCT findings

In the current research, it was assumed that SHS exposure may cause detectable pulmonary findings. The result, that SHS was related to GGO found in HRCT images, supports the premise. This seems to be the first study examining such relations.

GGO in HRCT images are defined as “hazy increased attenuation of the lung, but with preservation of bronchial and vascular margins” (Austin et al. 1996, Collins and Stern 1997). It is a non-specific finding and correlates histologically with the partial filling of air spaces, inflammatory or fibrotic interstitial thickening, partial collapse of alveoli, or increased capillary blood volume (Austin et al. 1996, Collins and Stern 1997). Numerous disease processes can result in GGO as the sole or dominant finding in CT scans of the lung, including extrinsic allergic alveolitis, alveolar proteinosis, pulmonary edema, and interstitial pneumonias (Collins and Stern 1997). In chronic diffuse lung diseases, GGO have been found to be a reliable indicator of inflammation in the absence of signs of fibrosis, a good prognostic

factor, and, in active diseases, it is usually reversible (Lee et al. 1992, Remy-Jardin et al. 1993a, Remy-Jardin et al. 1993d).

Remy-Jardin et al. (1993b) did not detect GGO in CT scans of 51 non-smokers. Vikgren et al. (2004) found GGO to be a part of smoking-induced disease. They showed that the extent of GGO progressed among smokers over a 6-year interval and that the occurrence of GGO was higher among ex-smokers than among never smokers.

SHS is composed of side-stream smoke (about 80%) and exhaled mainstream smoke with similar carcinogenic, toxic, and irritant chemicals as in mainstream smoke. Possibly GGO findings in the present study were related to the same kind of pathological changes as those noted for diseases related to active smoking. GGO may represent a mild form of respiratory bronchiolitis, respiratory bronchiolitis-associated interstitial lung disease, or desquamative interstitial pneumonia and the linear and irregular opacities could indicate mild fibrosis due to long-lasting exposure. In the present study, current smokers were excluded from the study population and ex-smoking was controlled in the multivariate analyses so that active smoking would not act as an explanatory factor in any findings related to SHS exposure.

One limitation of the study was the small number of non-smokers. Histopathological changes of respiratory bronchiolitis can persist after the cessation of smoking, but it is often resolved (Fraig et al. 2002). In a study of Fraig et al. respiratory bronchiolitis was found in all of the current smokers, but only in 49% of the ex-smokers. There is evidence that areas of GGO in proven cases of respiratory bronchiolitis-associated interstitial lung disease decrease after the cessation of smoking (Nakanishi et al. 2007). For all heavy smokers in the study by Nakanishi et al., the scores for GGO and centrilobular nodules decreased significantly after smoking ceased, while those for linear and reticular opacities and emphysema did not change. Smoking had ceased 15–52 months before the HRCT follow-up. In addition, in a longitudinal follow-up study of patients with smoker's lung, GGO attenuation was reduced in those who had stopped smoking (Remy-Jardin et al. 2002). In a HRCT follow-up of patients with respiratory bronchiolitis-associated interstitial lung disease and desquamative interstitial pneumonia, areas of GGO showed resolution after smoking cessation and treatment (Hartman et al. 1996, Park et al. 2002). The ex-smokers in the present study had stopped smoking 1 to 52 years

before the HRCT imaging (mean 25.0 years); therefore, according to the results of previous studies, it is likely that the respiratory bronchiolitis and GGO caused by previous active smoking had decreased or disappeared by the time of the present study.

The harmful effects of SHS on HRCT signs were found to be dependent on the dose, the average score increasing by 0.005 for each pack-year of exposure. Most of the participants of the present study were construction workers working mainly outdoors, and therefore their SHS exposure at work may have been diluted. This possibility, along with the limited sample size, may have influenced the ability of the study to detect any possible association between SHS and emphysema or other radiological signs.

The exposure assessment was based on self-report, which may have caused some random error. However, this was the best assessment method available as it had been hypothesized that long-term exposure is of biological relevance in the present study (Jaakkola and Jaakkola 1997). Currently there are no biomarkers for SHS exposure that would measure long-term exposure. In a study of Coultas et al. (1989) repeated self-reports of the duration (years) of exposure to SHS were reliable, while the reports on the amount of cigarettes smoked were somewhat less reliable. Another study showed good agreement between the participants' own questionnaire reports on SHS exposure and surrogate reports of most exposure measures (Cummings et al. 1989). The questionnaire allows exposure to be assessed for several periods of life retrospectively, when it is no longer possible to monitor the exposure with other methods.

The studied participants were not a random population sample, and the results cannot be extrapolated directly to the general population. In many countries, it is not considered ethically correct to expose healthy volunteers to X-rays for the purpose of studying CT signs due to mild exposure. Finding suitable study groups for assessing the impact of SHS exposure can therefore be difficult. The multivariate analyses of the present study were adjusted for asbestos exposure, previous smoking, and some other potential confounders to ensure that these factors would not bias the findings.

10. Summary and conclusions

In this thesis, the prerequisites for effective lung cancer screening were assessed. Furthermore, the role of HRCT in the screening and surveillance of asbestos-exposed workers was studied. Any lung findings due to exposure to SHS were of interest. The main findings and conclusions are as follows:

1. Spiral CT proved to be effective in detecting lung cancer among asbestos-exposed workers. Even HRCT was more sensitive than chest radiography among the participants with many confounding chest findings, but as an imaging method it is not adequate for lung cancer screening. The numerous false-positive lung nodules and incidental findings (imaging abnormality not related to the indication of the CT scan), requiring additional examinations, are a major concern for possible future screenings. Thus far, no conclusive evidence is available that indicates a relationship between lung cancer screening and a decrease in mortality. If lung cancer screening is recommended in the future, there should be strict criteria for positive scans and a well-defined postscreening diagnostic algorithm with which to study suspicious nodules. Repeat CT screenings for positive findings should be performed in the same screening center to avoid delays and a diversity in the diagnostic algorithm. A smoking cessation time of 10 years is too strict an inclusion criterion for the screening of asbestos-exposed persons.

2. Among the asbestos-exposed population used for the current research, the screening procedure was accepted well. Screening does not seem to produce excessive long-term anxiety or other negative psychological effects that could prevent future participation in a screening program. Trial adherence intention was also good in the case of a false-positive result.

3. Today, asbestos-induced lung disease seems to be characterized by mild fibrosis even in heavily exposed workers. Age and lung function data can be used only to a limited extent in the selection of imaging candidates possessing a high risk of fibrosis, and the study did not produce any new recommendations for the use of

HRCT in surveillance. This type of cross-sectional study may suffer from selection and recall biases that blur the dose–response relation between asbestos exposure and fibrosis.

4. SHS exposure was related with GGO, and this finding further supports previous evidence that SHS has adverse effects that can be detected in HRCT images of the lungs.

Acknowledgements

This study is based on work carried out at the Department of Clinical Radiology, Tampere University Hospital and the Finnish Institute of Occupational Health. I wish to express my gratitude to these organisations for offering the facilities and resources which enabled me to undertake this study.

I express my sincere thanks to:

My official supervisors Docents Ritva Järvenpää and Tapio Vehmas. They always found time to guide and advice me when needed. Their enthusiastic and supportive attitude throughout this project made it possible to bring the work to a successful conclusion. This thesis would never have been possible without them.

Docents Panu Oksa and Jukka Uitti for their help and expertise in asbestos-related issues and for their encouraging guidance and contribution during the entire work.

Professor Seppo Soimakallio, head of the Department of Clinical Radiology, for his valuable comments and for providing research friendly environment in the department.

The official referees Docents Antti Karjalainen and Ossi Korhola for their careful review and constructive comments, which greatly improved the quality of this thesis.

Pauliina Toivio MSc for her always patient and friendly help in statistical work.

All the co-authors of the original publications of this dissertation: Docents Seppo Saarelainen and Jari Laurikka from the Tampere University Hospital; Professor

Matti S. Huuskonen, Simo Kaleva MSc, Sirkku Kivistö MA, Tuula Lindholm MD, Katja Paakkola MD and Docent Antti Tossavainen from the Finnish Institute of Occupational Health; Professor Maritta S. Jaakkola from the Oulu University Hospital; Docent Eija-Riitta Salomaa and Sami Kajander MD from the Turku University Hospital; Docents Taina Autti and Pentti Tukiainen from the Helsinki University Central Hospital. It has been a privilege and a pleasure to cooperate with all of you.

Mrs Georgianna Oja for careful and swift revision of the English language of this thesis.

My colleagues and friends in the Tampere University Hospital for their positive attitude and support.

The personnel of all of the participating centers for their assistance with the data collection and radiological imaging.

and

All of the voluntary participants for attending the time-consuming studies.

The study was financially supported by the Tampere Tuberculosis Foundation and the Medical Research Fund of the Tampere University Hospital.

Most of all, I want to thank my beloved husband Jari for his constant support during the intensive periods of writing; and our children Roope, Peetu and Matias for bringing joy and cheerful challenge to my life. I express thanks to all my Family and Friends for being there. You are always in my heart.

Tuula Vierikko

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Original communications

Psychological impact of computed tomography screening for lung cancer and occupational pulmonary disease among asbestos-exposed workers

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The objective of this study was to investigate the psychological impact of screening for lung cancer and occupational pulmonary disease among asbestos-exposed workers. Altogether, 633 workers were screened with chest computed tomography (627 men, 6 women, mean age 64.5 years). Participants' views on the necessity of screening, awareness of asbestos-exposure risks, their perceived lung cancer risk, trial adherence intention, health anxiety, and worry about lung cancer were assessed. Health anxiety was reduced significantly after screening ($P < 0.001$). After 1 year, no significant long-term psychological differences were found between those who immediately received clear results and those who were submitted to additional examinations because of positive findings. In conclusion, computed tomography screening of pulmonary disease was well accepted and did not produce excessive long-term anxiety or other negative psychological effects,

which could prevent the participation in the future screening programs. *European Journal of Cancer Prevention* 18:203–206 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

European Journal of Cancer Prevention 2009, 18:203–206

Keywords: asbestos exposure, computed tomography, lung cancer, psychology, screening, trial adherence

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Received 23 September 2008 Accepted 22 January 2009

Introduction

Lung cancer remains the leading cause of death because of malignancy in the world (Levi *et al.*, 1999; Alberg *et al.*, 2005). There is an increasing interest worldwide toward screening for lung cancer with spiral computed tomography (CT). Spiral CT can locate small lung nodules and thus detect lung cancer at an early and curable stage (The International Early Lung Cancer Action Program Investigators, 2006). Any screening is supposed to increase quality-adjusted life years. A screening program cannot be successful unless the screening and the subsequent diagnostic examinations after positive findings are well tolerated and the willingness to participate is high. Cancer screening may produce anxiety itself or especially by its false-positive findings (Lampic *et al.*, 2003; Brett *et al.*, 2005). Extra anxiety could offset the potential benefits of screening (quality-adjusted life years) and deter participants from attending subsequent screening rounds (Brett and Austoker, 2001; Ford *et al.*, 2003; Taylor *et al.*, 2004). The potential psychological effects of lung cancer screening or the periodical surveillance programs of asbestos-exposed workers have received little attention.

The primary objective of the whole project was to assess the feasibility of lung cancer screening (Vierikko *et al.*, 2007)

and to image the potential occupational pulmonary and pleural diseases with CT. In this study, we investigated the psychological impact of lung cancer screening among this group of asbestos-exposed workers.

Methods

The study population was collected from three groups of Finnish asbestos-exposed workers. Workers in the first group participated in the asbestos screening program in 1990–1992 owing to their occupational exposure and had no diagnosed asbestos disease at that time (Huuskonen *et al.*, 1995).

The remaining two groups were formed from workers with asbestosis or with asbestos-related pleural findings visiting the wards of occupational medicine for a clinical follow-up and willing to participate in the study.

Of the 758 invited workers, 633 (83.5%) took part in the CT study. When the cancer patients ($n=6$) were excluded from the positive result group, 97 (15.3%) of the participants had a false-positive result. The baseline questionnaire was returned by 601 (94.9%) of the participants (all men). Their mean age was 64.6 years (range 45–87). Both the baseline and follow-up

questionnaires were returned by 457 (72.2%) participants. Out of the false-positive group, 62 (63.9%) participants also responded to the follow-up questionnaire.

In a baseline psychological questionnaire, participants' awareness of the risks of asbestos exposure, perceived lung cancer risk, health anxiety (Salkovskis *et al.*, 2002), worry about lung cancer, views on the necessity of health screening of asbestos-exposed workers, and trial adherence intention were assessed. The follow-up psychological questionnaire was sent 1 year after the study; by then, the possible additional examinations had been conducted and the participants knew the results. All participants were screened with high-resolution CT for occupational lung and pleural diseases, and the high-risk subgroup ($n=180$) of current and ex-smokers (cessation within the past 10 years) also were screened with spiral CT for lung cancer in the same session (Vierikko *et al.*, 2007). Noncalcified lung nodules of any size were considered positive findings and suspicious of lung cancer. In such cases, the study protocol recommended reexamination with spiral CT to detect growth, or alternatively a biopsy performed thoracoscopically or with CT guidance.

A false-positive result was defined as a positive CT scan prompting additional examinations that did not detect lung cancer. The result was negative when no additional examinations were needed and no lung cancer was found. After receiving complete information on the study, all participants gave their written informed consent. Ethics committee approvals of the study protocol have been obtained at all the participating centers in Finland.

Statistical analysis

Prescreening and postscreening psychological items were cross-tabulated. The items were then assessed with paired-samples *t*-test or Wilcoxon's paired test in the whole group and, further, in two subgroups: those with negative and those with false-positive results.

The demographic and health variables [age, education (at least vocational training vs. lower education), symptoms (cough, phlegm secretion, wheezing, dyspnea), marital status (unmarried, widowed, divorced vs. married, cohabiting), smoking status (current, ex-smoker, nonsmoker), smoked pack-years, years of asbestos exposure, and year of first exposure (indicating latency)] were evaluated as potential predictors of the baseline psychological items and their change by using analysis of covariance.

Results

The sample characteristics are given in Table 1. The results of the baseline questionnaire are given in Table 2. The great majority of the participants (99.6%) agreed totally or somewhat with the statement that health examinations of asbestos-exposed workers are necessary.

Table 1 Sample characteristics

	Responded only to baseline questionnaire (n=144)	Responded to both questionnaires (n=457)	Total (N=601)	P value
Age (years)				
Mean (SD)	64.2 (7.1)	64.7 (6.6)	64.6 (6.7)	0.526 ^a
Range	45–85	48–87	45–87	
Married or cohabiting, n (%)	104 (72.5)	379 (83.8)	483 (81.0)	0.008 ^b
Minimum of vocational training, n (%)	48 (35.3)	159 (35.7)	207 (35.6)	0.939 ^b
Smoked				
pack-years				
Mean (SD)	19.6 (18.9)	17.1 (17.9)	17.7 (18.2)	0.155 ^a
Range	0–100	1–129	0–129	
Current smoker, n (%)	31 (22.0)	79 (17.5)	110 (18.5)	0.487 ^b
Ex-smoker, n (%)	79 (56.0)	269 (59.5)	348 (58.7)	
Years of asbestos exposure				
Mean (SD)	18.4 (11.9)	19.2 (11.2)	19.2 (11.5)	0.512 ^a
Range	1–46	1–46	1–46	
First year of asbestos exposure				
Mean (SD)	1961 (7.1)	1962 (7.6)	1961 (7.5)	0.314 ^a
Range	1931–1979	1942–1989	1931–1989	
Dyspnea, n (%)	53 (38.7)	176 (40.1)	229 (39.8)	0.769 ^b
Cough, n (%)	35 (25.5)	144 (32.3)	179 (30.7)	0.135 ^b
Phlegm secretion, n (%)	63 (46.7)	218 (50.0)	281 (49.2)	0.498 ^b
Wheezing, n (%)	39 (28.5)	152 (34.2)	191 (32.8)	0.215 ^b

^aBy *t*-test.

^bBy χ^2 test.

The statement that cancer should not be screened in asymptomatic individuals was supported by 11.3% of the participants. Most of the workers (96.6%) were aware of the risks of asbestos exposure.

Trial adherence intention was high: 98% of the participants were ready to attend screening studies in the future. In total, 34.2% of the participants thought that they are at risk of lung cancer, and 36.8% considered such a possibility quite small. The mean score of health anxiety was 7.1 and the mean score of worry for lung cancer was 3. High overall scores indicated greater health anxiety (scale 0–24) and greater worry about lung cancer (scale 0–8). The longitudinal evaluation of the psychological impact of lung cancer screening is given in Table 3.

Across the group as a whole, health anxiety was significantly lower after screening ($P < 0.001$). High asbestos exposure especially was associated with reduced anxiety after the screening ($P = 0.003$). Health anxiety was reduced significantly in both the negative and the false-positive groups ($P < 0.001$ and $P = 0.027$, respectively). No significant difference in perceived lung cancer risk, trial adherence intention, or worry about lung cancer between prescreening and postscreening questionnaires was detected either in the negative or in the false-positive groups.

Table 2 Results of the baseline psychological questionnaire, individual questions

Question	Totally agree, n (% of total)	Somewhat agree, n (% of total)	Do not know, n (% of total)	Somewhat disagree, n (% of total)	Totally disagree, n (% of total)	Total N
It is necessary to screen the health of asbestos exposed workers	583 (97.3)	14 (2.3)	2 (0.3)	0	0	599
My participation in the study is important to get new information on asbestos-induced diseases and their treatment	561 (94.3)	26 (4.4)	6 (1.0)	2 (0.3)	0	595
Cancer should not be screened in healthy persons	32 (5.5)	34 (5.8)	59 (10.1)	56 (9.6)	402 (69.0)	583
I am aware of the health risks that asbestos-exposure can lead to	538 (90.7)	35 (5.9)	11 (1.9)	7 (1.2)	2 (0.3)	593
The possibility that I might get lung cancer is quite small	86 (14.7)	129 (22.1)	169 (28.9)	131 (22.4)	69 (11.8)	584
I am willing to attend screening tests also in the future	546 (92.1)	35 (5.9)	9 (1.5)	3 (0.5)	0	593

Table 3 Longitudinal evaluation of the psychological impact of screening

Item	Number of participants	Baseline, mean (SD) median	Follow-up, mean (SD) median	P value
Cancer should not be screened in healthy persons (scale 0–4) ^c	442	0.66 (1.19) 0	0.66 (1.15) 0	0.953 ^a
Perceived lung cancer risk (scale 0–4) ^d	440	1.94 (1.20) 2	2.03 (1.22) 2	0.209 ^a
Trial adherence (scale 0–4) ^e	449	0.08 (0.33) 0	0.07 (0.30) 0	0.681 ^a
Worry about lung cancer (scale 0–8) ^f	435	2.97 (2.42)	3.13 (2.27)	0.135 ^b
Health anxiety, total (scale 0–24) ^g	419	6.74 (4.72)	5.82 (4.59)	<0.001 ^b
Health anxiety in the negative group ^h (scale 0–24) ^e	354	6.64 (4.63)	5.73 (4.61)	<0.001 ^b
Health anxiety in the false-positive group ⁱ (scale 0–24) ^e	62	7.63 (5.09)	6.42 (4.53)	0.027 ^b

^aBy Wilcoxon's signed rank test.

^bBy *t*-test.

^cLower scores indicate favorable opinion toward screening.

^dHigher scores indicate higher perceived risk.

^eLower scores indicate better trial adherence.

^fHigher scores indicate higher worry.

^gHigher scores indicate greater health anxiety.

^hParticipants that received a result from computed tomography (CT) examinations that no additional examinations were needed and no lung cancer was found.

ⁱParticipants that received a positive CT scan result prompting additional examinations that did not detect lung cancer.

Discussion

The respondents were well motivated to participate. Screening does not seem to produce excessive long-term health anxiety and trial adherence intention was not affected by false-positive findings.

Spiral CT can detect early-stage lung cancers, but false-positive findings may be detected in up to 50% of the participants at baseline (Swensen *et al.*, 2002), which may cause anxiety and lead to repeat CT studies or to more invasive examinations. Health-related quality of life in CT screening for lung cancer has been studied (Van den Bergh *et al.*, 2008). The study showed no difference in health-related quality of life between the negative and false-positive groups after 6 months. We found no sign of psychological distress caused by false-positive findings after 1 year.

False-positive findings may also influence the subsequent test adherence. The effect of false-positive results on lung cancer chest radiograph screening has been studied (Ford *et al.*, 2003; Taylor *et al.*, 2004). In both studies, trial adherence was poorer among those who

had received previous false-positive results. In our study, a false-positive result did not negatively affect trial adherence intention.

Our results indicated a decrease in anxiety. Whether this could encourage participants to continue smoking or even to restart should be studied. Smokers with abnormal CT findings from multiple CT screens were found less likely to smoke at the 3-year follow-up than those who did not receive any positive results (46 vs. 20%) (Townsend *et al.*, 2005). In the same study, current smokers that received multiple normal screening results were found to behave similarly to smokers who did not participate in lung cancer screening.

Interestingly, the reduction in anxiety after the screening was associated with high asbestos exposure. Possibly, the most exposed participants had denied their risk and thereafter the relief was pronounced. Knowledge of the health risks of asbestos exposure is something that the workers must live with, and screening may help reduce this anxiety.

In this study, the perceived cancer risk (33.6%) was higher than that of 23.1% in a study by Silvestri *et al.* (2007). A higher level of perceived risk has been associated with a greater interest in screening (Schnoll *et al.*, 2003; Hahn *et al.*, 2006) and so has greater worry and distress caused by knowledge of the health risks of asbestos exposure (Meyerowitz *et al.*, 1989). This may explain the good trial adherence (83.5% of those invited) in our study and why the intention to adhere did not decrease in cases of a false-positive result.

We performed a single baseline screening but did not evaluate psychological behavior in repeat screenings. The psychological items were not assessed during the screening process either. Trial adherence was evaluated only through questionnaire, and is thus based on intentions rather than actual screening behavior. In addition, our sample was restricted to high-risk asbestos-exposed workers, and the results may not be generalized to unexposed populations likely to have a lesser fear of cancer.

Conclusion

Screening does not seem to produce excessive long-term anxiety or other negative psychological effects, which could prevent the future participation in the screening program. Trial adherence intention was good also in the case of a false-positive result.

Acknowledgements

This study was financially supported by the Tuberculosis foundation of Tampere and by the Competitive Research Funding of the Pirkanmaa Hospital District, Tampere University Hospital. The authors thank Hanna Liikala, MA, for linguistic revision of the manuscript.

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The effects of secondhand smoke exposure on HRCT findings among asbestos-exposed workers

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Received 20 September 2007; accepted 22 December 2007

Available online 8 February 2008

KEYWORDS

Bronchiolitis;
Tobacco smoke
pollution;
Tomography;
X-ray computed

Summary

Objectives: There is evidence suggesting that secondhand smoke (SHS) exposure is causally linked to adverse respiratory effects. We examined the relations between the exposure to SHS and radiological signs in chest high-resolution computed tomography (HRCT).

Methods: Asbestos-exposed workers ($n = 633$) were imaged with HRCT, primarily to investigate potential occupational lung disease. After excluding current smokers, the study population included 361 ex- and 141 never-smokers. They answered a questionnaire on occupational exposures, smoking habits and SHS exposure. HRCT images were assessed for emphysema, ground-glass, irregular/linear and rounded opacities, honeycombing and several other signs. Regression analyses were adjusted for asbestos exposure, ex-smoking, age, body mass index and potential reader effect.

Results: Due to missing data the multivariate analyses were restricted to 310 participants aged 47.5–87.0 years. Their lifetime SHS exposure ranged between 0 and 193.5 pack-years (mean 23.5), and exposure in the past 12 months 0–30 packs (0.43). Total ($B = 0.005$, 95% confidence intervals (95% CI) 0.002–0.008, $p = 0.000$) and workplace ($B = 0.006$, 95% CI 0.003–0.009, $p = 0.001$) cumulative SHS exposures were significantly related to ground-glass opacities. Total SHS exposure in the last 12 months ($B = 0.027$, 95% CI 0.000–0.054, $p = 0.048$) and workplace exposure ($B = 0.027$, 95% CI 0.000–0.054, $p = 0.048$) were also

Abbreviations: DIP, desquamative interstitial pneumonia; GGO, ground-glass opacity; HRCT, high-resolution computed tomography; HU, Hounsfield Unit; RB, respiratory bronchiolitis; RB-ILD, respiratory bronchiolitis-associated interstitial lung disease; SHS, secondhand smoke; VIF, variance inflation factor.

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significantly related to ground-glass opacities. Positive effects of SHS were also detected on irregular/linear opacities.

Conclusions: SHS exposure in the last 12 months and over lifetime significantly increases ground-glass opacity in HRCT, suggesting an early or subclinical desquamative interstitial pneumonia/respiratory bronchiolitis. This study further supports that SHS has adverse effects on the lungs that can be detected by X-ray methods.

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Introduction

Since the 1980s, evidence has accumulated on the adverse health effects of secondhand smoke (SHS), also called passive smoking, exposure to environmental tobacco smoke and involuntary smoking. The adverse respiratory effects of SHS include lung cancer,¹ chronic respiratory symptoms,^{2–4} lung function impairment,^{5–7} chronic obstructive pulmonary disease⁸ and asthma.⁹ However, there is little data on potential effects of SHS exposure on diseases of the lung parenchyma.

High-resolution computed tomography (HRCT) has been shown to detect pathological lung changes in symptom-free smokers with normal chest radiographies and normal lung function.¹⁰ Even limited smoking (<10 pack-years) has been found to induce detectable HRCT abnormalities.¹¹ This raises the question whether SHS exposure could induce such changes. As pulmonary function tests often fail to identify the early stages of smoke-induced diseases, HRCT could prove to be a more sensitive clinical test. According to our knowledge, the relations between SHS exposure and HRCT signs have not been studied before. This may be partly due to the ethical problems in imaging healthy individuals with ionizing radiation, unless there is a specific clinical indication to carry out such investigation.

We studied the effects of SHS exposure on several HRCT signs among asbestos-exposed workers, who were examined primarily for potential occupational lung diseases.¹²

Methods

Study design

The study was a cross-sectional multicentre study of 633 asbestos-exposed workers in three cities (Helsinki, Tampere and Turku) in Finland. All participants underwent an imaging with HRCT, and answered a questionnaire in 2003–2004.¹²

Study population

The study population included asbestos-exposed workers who visited the clinics of occupational medicine for a clinical follow-up or had participated in a previous asbestos screening programme at the Finnish Institute of Occupational Health in 1990–1992.¹³ Current smokers were excluded from the present analyses focusing on SHS exposure, so the final study population included 141 never- and 361 ex-smokers, altogether 502 non-smokers. Of them 310 (all men, aged 47.5–87.0 years, mean age 65) completed all questions

in the questionnaire, including a comprehensive matrix on SHS exposure.

All participants gave their written informed consent and the ethics committee approvals of the study protocol were obtained at all the participating centres.

Questionnaire

The self-administered questionnaire was modified from the Finnish Environment and Asthma Study questionnaire.⁹ It included questions on demographic characteristics, respiratory symptoms and diseases, smoking status and an exposure matrix on SHS exposure. Questions on other occupational exposures with focus on asbestos exposure were added to this questionnaire.

Imaging

We used three different scanners: two single-slice scanners, Siemens Somatom Balance (Siemens Medical, Erlangen, Germany) in Helsinki, Siemens Somatom Plus 4 (Siemens Medical) in Tampere, and one multislice scanner, GE Lightspeed 16 Advantage (GE Healthcare, Milwaukee, WI, USA) in Turku. HRCT images were obtained during a full inspiration in a prone position. The slice thickness was 1–1.25 mm. The slices were taken at 3-cm intervals from the lung apex to the costophrenic angle. The imaging parameters were 130–140 kV and 100–111 mA. The images were printed as hard copies at window settings appropriate for viewing the lung parenchyma. In Tampere and Turku the window width was 1500 Hounsfield Unit (HU) and window level –600 HU. In Helsinki the interpreters used two settings in the same session: 1200/–700, and 2000/–400 HU. The difference between centres was due to the fact that the observer groups were used to these different settings in their clinical practice.

Image analysis

The HRCT images were assessed by two radiologists in consensus (TVE and TA in Helsinki, and RJ and TVi in Tampere and Turku). The assessment was performed blinded to smoking habits and other exposure data of the participants. For the assessment both lungs were divided into three zones: upper, middle and lower. Each of the six zones was scored for each HRCT sign on a scale of 0–3: 0—no definitive abnormality, 1—mild, 2—moderate and 3—severe abnormality. These were then summed up for both lungs. Final score 0 indicated a normal finding and the maximal score was the sum of scores (0–3) for each lung at three levels. The

following main signs, as described in the Fleischner Society recommendations,¹⁴ were evaluated: (a) well-defined rounded opacities, <10 mm in diameter (1 = small opacities definitely present but few in number, 2 = numerous small opacities and 3 = small opacities very numerous, normal anatomical lung structures poorly visible, sum grade of six zones: 0–18); (b) irregular and/or linear opacities (1 = abnormalities definitely present but few in number, 2 = numerous abnormalities and 3 = abnormalities very numerous, normal anatomical lung structures poorly visible, sum grades 0–18); (c) ground-glass opacities (GGOs) (1 = focal, 2 = patchy and 3 = diffuse, sum grades 0–18); (d) honeycombing (1 = up to 10 mm, 2 = >10–30 mm extent in the subpleural parenchyma and 3 = >30 mm up to whole area, sum grades 0–18); and (e) emphysema (1 = up to 15%, 2 = between 15% and 30% and 3 = >30% of the area of one zone, sum grades 0–18). In addition, the presence of several other radiological signs (yes/no) were noted and those with a relatively frequent occurrence ($n \geq 15$) were included as outcomes in statistical analyses: bronchiectasis, bronchial wall thickening, suspicion of lung cancer, calcified granuloma, dependent opacity, parenchymal band, rounded atelectasis, subpleural curvilinear line and tuberculosis. The scoring was conducted according to a published international system with standardized instructions and reference images.¹⁵

Exposure assessment

The information on SHS exposure was obtained with a questionnaire. The SHS exposure was self-reported, including both the past 12 months' exposure at work and at home and a lifetime exposure in 10 age periods: 0–1, 2–6, 7–15, 16–20, 21–30, ..., 71–80 years, with separate reporting of exposure at home and at work. The number of cigarettes the subject was exposed to daily and the duration of exposure (in years) were reported for each age period. Cumulative exposure was calculated as SHS pack-years (one pack = 20 cigarettes). For statistical analyses the age periods were summed to form a cumulative lifetime exposure index for 0–80 years.

Confounders

Current smokers were excluded from the study population, so the population included only never-smokers and ex-smokers. A never-smoker was a person who had never smoked regularly, and an ex-smoker had stopped smoking at least 12 months ago. The amount of smoking was inquired and the pack-years estimated for ex-smokers. Smoking status was grouped into ex- and never smoking, and multivariate analyses adjusted for both smoking status and pack-years of ex-smokers. The duration and amount of the asbestos exposure were assessed, and asbestos-exposure index was calculated for adjustment in multivariate models.¹⁶

Statistical methods

The mean scores of the radiological signs formed the outcomes of interest. The exposures of interest were the

SHS exposure in the past 12 months and the total lifetime SHS exposure index as continuous variables. Home and work exposures were analysed separately and combined. Multiple linear regression was used to study the relations between SHS exposure and the radiological signs, adjusting for age, asbestos-exposure index, smoking status (ex-smoker vs. never smoker), potential image interpreter effect (1 = RJ/TVi, 0 = TA/TVe), body mass index (weight [kg]/height [m]²)¹⁷ and pack-years of active smoking for ex-smokers. Results are given as regression coefficients and 95% confidence intervals (95% CI). Due to the concern that collinearity could distort regression estimates, the variance inflation factors (VIF) were determined for each model. Multiple logistic regression with the same covariates was used for binary radiological signs.

Some additional statistical procedures were also used to further clarify the relations:

1. Because the distributions of the radiological scores were skewed to the right and transformation did not correct this, ordinal regression was used as a confirmatory analysis method.
2. The analyses were carried out in a subgroup of never-smokers only.

Results

The final statistical analyses were conducted in 310 participants (91 never-smokers and 219 ex-smokers). The characteristics of the study population are presented in Table 1.

The comparison between respondents (who had completed all SHS questions) and non-respondents (with missing information) showed no major differences, although the non-responders were slightly older.

The lifetime SHS exposure ranged between 0 and 193.5, with the mean of 23.5 pack-years. The SHS exposure in the past 12 months ranged between 0 and 30 packs, with the mean 0.43 packs.

In multivariate regression analysis, both total SHS exposure in the past 12 months ($B = 0.027$, 95% CI 0.000–0.054, $p = 0.048$) and total lifetime SHS exposures ($B = 0.005$, 95% CI 0.002–0.008, $p = 0.000$) were significantly related to increasing GGO (Figure 1) score (Tables 2 and 3).

There was also a borderline significant effect of lifetime SHS exposure on irregular and/or linear opacities ($B = 0.006$, 95% CI 0.000–0.013, $p = 0.059$). The relations between the total SHS exposure and other HRCT signs were not statistically significant.

When SHS at work and at home were studied separately, the relation with GGOs was observed with both workplace SHS exposure in the past 12 months ($B = 0.027$, 95% CI 0.000–0.054, $p = 0.048$) and cumulative lifetime workplace exposure ($B = 0.006$, 95% CI 0.003–0.009, $p = 0.001$). Adjustment for the other type of SHS exposure in the models did not influence much the effect estimates, although after that the effects of recent exposure were no more statistically significant. Both home SHS exposure in the past 12 months and lifetime home SHS exposure were also

Table 1 Characteristics of the study population including ex- and never-smokers.

Characteristics	Responders		Non-responders		All		<i>p</i> -Value*
	<i>N</i>	Mean/SD (range)	<i>N</i>	Mean/SD (range)	<i>N</i>	Mean/SD (range)	
Age, years	310	65.0/6.6 (47.5–87.0)	192	66.0/7.0 (45.0–85.0)	502	65.0/6.8 (45.0–87.0)	0.034
Pack-years	303	12.8/16.0 (0–129.0)	177	14.2/14.7 (0–70.0)	480	13.3/15.5 (0–129.0)	0.354
Cumulative pack-years of SHS exposure	310	23.5/25.2 (0–193.5)			310	23.5/25.2 (0–193.5)	
Body mass index (kg/m ²)	298	28.2/4.2 (20.1–47.5)	182	28.8/3.9 (19.7–43.6)	480	28.4/4.1 (19.7–47.5)	0.164
Asbestos-exposure index	310	79.1/48.8 (8.0–286.0)	191	71.3/44.4 (4.0–252.0)	501	76.1/47.3 (4.0–286.0)	0.069

Responders answered the secondhand smoke (SHS) exposure questions (*N* = 310).

**t*-Test for differences between responders and non-responders.



Figure 1 Ground-glass opacity in HRCT. Patchy areas indicate GGO (arrows).

related to increased GGOs, but these effects did not reach statistical significance. Home SHS exposure in the past 12 months was also related to increased irregular and/or linear opacities ($B = 1.873$, 95% 0.512–3.233, $p = 0.007$) and honeycombing ($B = 1.100$, 95% CI 0.675–1.524, $p = 0.000$).

When the analyses were conducted in the subgroup of never-smokers, no significant associations were detected, probably due to the small sample size. Ordinal regression models confirmed the results by providing practically similar findings in all analyses. No collinearity problem was found when VIFs were determined.

Discussion

The main finding in our study of 310 asbestos-exposed workers investigated with HRCT was a significant effect of both SHS exposure in the past 12 months and lifetime cumulative SHS exposure on GGOs. In addition, irregular/linear opacities showed a positive relation with SHS exposure. To our knowledge, this is the first study

investigating the effects of SHS exposure on chest HRCT signs.

The workplace exposure was significantly related to GGO both in the past 12 months and over lifetime. The effects on GGO related to home exposures were of similar magnitude, but did not reach statistical significance probably due to the small number of participants that reported exposure at home.

GGO in HRCT images is defined as 'hazy increased attenuation of lung, but with preservation of bronchial and vascular margins'.^{14,18} It is a non-specific finding and correlates histologically with partial filling of air spaces, inflammatory or fibrotic interstitial thickening, partial collapse of alveoli, or increased capillary blood volume.^{14,18} Numerous disease processes can result in GGO as the sole or dominant finding in CT scans of the lung, including extrinsic allergic alveolitis, alveolar proteinosis, pulmonary oedema, and interstitial pneumonias.¹⁸ In chronic diffuse lung diseases GGO has been found to be a reliable indicator of inflammation in the absence of signs of fibrosis, a good prognostic factor, and in active diseases it is usually reversible.^{19–21}

Remy-Jardin et al.¹⁰ did not detect GGO in CT scans of 51 non-smokers. A study of Vikgren et al.²² found GGO to be a part of smoking-induced disease. They showed that the progression in the extent of GGO was seen among smokers in a 6-year interval, but that the occurrence of GGO was higher among ex-smokers than among never-smokers. Septal lines were found in both never- and current smokers.

Respiratory bronchiolitis (RB) is a common incidental histopathologic finding in otherwise healthy cigarette smokers.²³ In rare cases the condition presents as a form of interstitial lung disease with significant pulmonary symptoms, and abnormal pulmonary function, when the entity is called respiratory bronchiolitis-associated interstitial lung disease (RB-ILD).^{24–26} Cigarette smoking has also been related to rare interstitial lung disease, named desquamative interstitial pneumonia (DIP).^{24,27,28} DIP is considered to be a more extensive form of RB-ILD and it seems likely that these entities represent different stages of

Table 2 Effect of secondhand smoke (SHS) (smoking rate in packs) in the past 12 months on the scores of high-resolution computed tomography (HRCT) signs.

HRCT sign	SHS exposure location	<i>B</i> [*]	95%		<i>p</i> -Value	<i>B</i> [†]	95%		<i>p</i> -Value
			Lower	Upper			Lower	Upper	
Well-defined rounded opacities	Work	0.000	-0.021	0.020	0.964	-0.001	-0.022	0.020	0.921
	Home	-0.065	-0.482	0.352	0.760	-0.065	-0.483	0.353	0.760
	Total	-0.001	-0.021	0.020	0.947	-0.001	-0.022	0.019	0.906
Irregular and/or linear opacities	Work	-0.024	-0.081	0.032	0.399	-0.029	-0.087	0.028	0.315
	Home	1.873	0.512	3.233	0.007	1.847	0.491	3.202	0.008
	Total	-0.025	-0.082	0.032	0.389	-0.030	-0.087	0.028	0.308
Ground-glass opacity grade	Work	0.027	0.000	0.054	0.048	0.020	-0.007	0.047	0.151
	Home	0.066	-0.490	0.623	0.815	0.044	-0.501	0.588	0.875
	Total	0.027	0.000	0.054	0.048	0.020	-0.007	0.047	0.148
Honeycombing grade	Work	0.000	-0.014	0.013	0.970	0.000	-0.013	0.014	0.945
	Home	1.100	0.675	1.524	0.000	1.093	0.669	1.517	0.000
	Total	0.000	-0.014	0.013	0.975	0.001	-0.013	0.014	0.940
Emphysema grade	Work	0.011	-0.066	0.088	0.777	0.015	-0.063	0.094	0.702
	Home	-0.645	-2.482	1.192	0.490	-0.636	-2.477	1.204	0.497
	Total	0.010	-0.068	0.087	0.803	0.014	-0.065	0.093	0.727

*Adjusted for the following confounders: age, asbestos-exposure index, smoking status (ex-smoker vs. never smoker), potential reader effect, body mass index, and pack-years of active smoking for ex-smokers.

†Adjusted for all confounders mentioned above and also for cumulative SHS exposure.

the same disease.^{24,27} In these diseases HRCT can sometimes be normal. When abnormalities are detected, the signs that may be seen include GGOs, linear and reticular opacities, and small poorly defined nodules.^{24,25,27,29–31} There is also considerable overlap in the radiologic and histopathologic findings of these entities.^{24,26} SHS is composed of side stream smoke (about 80%) and exhaled mainstream smoke with similar carcinogenic, toxic and irritant chemicals as are found in mainstream smoke. Our findings of the relation between SHS exposure and GGO could be caused by the same kind of pathological changes that are noted in active smokers. GGO might represent a mild form of RB, RB-ILD or DIP, and the linear/irregular opacities could indicate mild fibrosis due to long-lasting exposure. We excluded current smokers from our study population and controlled for ex-smoking in the multivariate analyses to ensure that active smoking could not explain our findings related to SHS exposure.

A limitation of our study was the small number of never-smokers. The histopathologic changes of RB can persist after cessation of smoking, but they often resolve.³² RB was found in all current smokers but only in 49% of ex-smokers. There is evidence that areas of GGO in proven RB-ILD cases decrease after smoking cessation.³³ In all heavy smokers in the study by Nakanishi et al. the scores for the GGO and centrilobular nodules decreased significantly after smoking cessation, while those for linear-reticular opacity and emphysema were not changed. The smoking cessation had occurred

15–52 months before the follow-up HRCT study. Also in a longitudinal follow-up study of patients with smoker's lung GGO attenuation was reduced in those who had stopped smoking.³⁴ On follow-up HRCT of patients with RB-ILD and DIP, areas of GGO showed resolution after smoking cessation and treatment.^{35,36} The ex-smokers in the present study had stopped smoking 1–52 years before the HRCT imaging (mean 25.0); so, based on the results from previous studies, it is likely that the RB and GGO caused by previous active smoking had reduced or disappeared by the time of our study.

The harmful effects of SHS on HRCT signs were found to be dependent on the dose, the average score increasing by 0.005 for each pack-year of exposure. Most of the participants of the present study were construction workers working mainly outdoors, which may have diluted their SHS exposure at work, and this, along with the limited sample size, may have influenced our ability to detect any possible association between SHS and emphysema or other radiological signs.

A limitation of our study is that only 310 out of 502 participants (61.8%) completed all the questions on SHS exposure. We compared the responders to those with missing information and found that there were no major differences in their background characteristics.

The exposure assessment was based on self-report, which may have caused some misclassification. However, this was the best assessment method available, as we hypothesized

Table 3 Effect of lifetime cumulative secondhand smoke exposure (SHS) (pack-years) on the scores of high-resolution computed tomography (HRCT) signs.

HRCT sign	SHS exposure location	B^*	95%		p -Value	B^\dagger	95%		p -Value
			Lower	Upper			Lower	Upper	
Well-defined rounded opacities	Work	-0.002	-0.005	0.000	0.105	0.000	-0.002	0.002	0.746
	Home	0.005	0.001	0.008	0.011	0.000	-0.002	0.002	0.972
	Total	0.000	-0.002	0.002	0.942	0.000	-0.002	0.002	0.754
Irregular and/or linear opacities	Work	0.005	-0.003	0.014	0.217	0.003	-0.003	0.009	0.303
	Home	0.011	-0.001	0.023	0.082	0.006	-0.001	0.012	0.074
	Total	0.006	0.000	0.013	0.059	0.003	-0.003	0.009	0.306
Ground-glass opacity grade	Work	0.006	0.003	0.009	0.001	0.004	0.002	0.007	0.001
	Home	0.005	0.000	0.010	0.059	0.005	0.002	0.007	0.000
	Total	0.005	0.002	0.008	0.000	0.004	0.002	0.007	0.001
Honeycombing grade	Work	0.001	-0.001	0.004	0.375	0.000	-0.002	0.001	0.528
	Home	0.003	-0.001	0.007	0.110	0.002	0.000	0.004	0.134
	Total	0.002	0.000	0.004	0.124	0.000	-0.002	0.001	0.521
Emphysema grade	Work	-0.002	-0.013	0.009	0.724	-0.002	-0.010	0.005	0.536
	Home	-0.002	-0.019	0.014	0.775	-0.002	-0.011	0.007	0.651
	Total	-0.002	-0.011	0.007	0.669	-0.002	-0.010	0.005	0.535

*Adjusted for the following confounders: age, asbestos-exposure index, smoking status (ex-smoker vs. never smoker), potential reader effect, body mass index, and pack-years of active smoking for ex-smokers.

†Adjusted for all confounders mentioned above and also for SHS exposure in the past 12 months.

that long-term exposure is of biological relevance in our study.³⁷ Currently there are no biomarkers for SHS exposure that would measure long-term exposure. In a study of Coultas et al.³⁸ repeated self-reports of the duration (years) of exposure to SHS were reliable, while the reports on the amount of cigarettes smoked were somewhat less reliable. Another study showed a good agreement between the subjects' own questionnaire reports on SHS exposure and surrogate reports of most exposure measures.³⁹ The questionnaire allows the exposure assessment on several periods of life retrospectively when it is no longer possible to monitor the exposure with other methods.

The studied participants were not a random population sample and the results cannot be extrapolated directly to the general population. In many countries it is not considered ethically correct to expose healthy volunteers with X-rays to study CT signs due to mild exposures. Finding suitable study groups for this purpose can therefore be difficult. Our multivariate analyses were adjusted for the asbestos exposure, previous smoking and other potential confounders to ensure that these do not explain our findings. In these multivariate analyses, ex-smoking was related to emphysema only and asbestos exposure was related to irregular/linear opacities only, which suggests that any major residual confounding by these factors is unlikely.

Our scoring of the lung parenchymal signs was mostly based on published guidelines and reference images. There might be over- or underdetection of the abnormalities as in any such study. However, if such misclassification is not

related to the exposure status (in this case the SHS exposure), it is random and leads to an underestimation of any true effects rather than to any systematic bias. The interpreters had several years of experience in assessing HRCT scans, using the window settings, of which they had had experience in clinical practice. To control for any potential bias due to the two separate image reader teams, we adjusted for this effect in the models.

Conclusions

Our study of asbestos-exposed workers showed that SHS exposure can induce processes in the lungs detected as GGO and linear/irregular opacities in HRCT. Such findings may be the early signs of RB or DIP. Thus our study supports previous evidence that SHS has adverse effects on the lungs that can be detected by objective radiological methods. Such effects of SHS exposure on HRCT should be investigated in larger samples with heavier exposure levels before making any definite conclusions, but identifying suitable study groups for this purpose may be challenging.

Conflict of Interest

No financial or other potential conflicts of interest exist among the authors.

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