A POPULATION-BASED STUDY OF LUNG CANCER AND BENIGN INTRATHORACIC TUMORS

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Abstract

A prospective population-based study was conducted to assess the incidence, diagnosis, histology, treatment and survival of lung cancer in northern Finland. The results were compared with those obtained in a similar survey 20 years earlier.

In a population of 440,000, altogether 602 lung cancer patients, 510 men and 92 women, were diagnosed during the years 1990-92, the annual incidence per 100,000 being 63 for males and 9.5 for females. Lung cancer was confirmed histologically in 381 cases (63%) and in addition, cytologically in 135 cases (23%). Squamous cell carcinoma was the most common histologic type (40%), the proportion of adenocarcinomas being 26%, small-cell carcinomas 24% and large cell carcinomas 4%. The age-standardized incidence of lung cancer had decreased significantly among males (from 87 to 63 per 100 000) compared to the situation 20 years earlier but increased among females (from 4.1 to 9.5), mainly due to adenocarcinoma.

The 5-year survival rate had improved during 20 years from 4% to 12% (p<0.001). The differences in survival between the histological types ($\chi^2_{\text{logrank}}=59.2$, $p<0.0001$), TNM stages ($\chi^2_{\text{logrank}}=199.6$, $p<0.001$), symptomatic stages ($\chi^2_{\text{logrank}}=120$, $p<0.001$) and treatments ($\chi^2_{\text{logrank}}=277$, $p<0.001$) were also significant. A total of 20% of the patients were operated on in the newer series of patients, the corresponding percentage in the earlier series being 16%. The 5-year survival of the patients who had been operated on had increased from 23% to 48%. The survival of patients with non-small-cell lung carcinoma had increased significantly, even though the patients were older now than earlier.

In seventy operated lung cancer patients, the histologic tumor types and grades were compared with the etiological factors of lung carcinoma, including cigarette smoking and asbestos exposure. A majority of the patients (93%) were smokers. The incidence of adenocarcinoma among non-smokers had remained the same, 50%. The accumulation of the p53 protein in lung carcinoma was associated with heavy smoking. Exposure to asbestos fibers either by a positive history or by a number of asbestos bodies (AB) in the histological sections of lung tissue was also associated with p53 accumulation.

Benign intrathoracic tumors are uncommon, and their occurrence in unselected populations is poorly defined. Thirty-six benign intrathoracic tumors were found. A histologic diagnosis was available for 24 (67%). Hamartoma was the most common benign lung tumor.

Keywords: histology, adenocarcinoma, survival, asbestos exposure
Acknowledgements

This study was carried out at the Department of Internal Medicine, Oulu University Hospital, and the former Päivärinne Hospital during the years 1990-98.

I express my deepest gratitude to my supervisor Professor Vuokko Kinnula, M.D., Ph.D., Pulmonary Medicine, whose optimistic enthusiasm, encouragement and support have been of an invaluable importance for the completion of this work.

I wish to express my sincere gratitude to Professor Antero Kesäniemi, M.D., Ph.D., Head of the Department of Internal Medicine, for his support and encouraging attitude towards research.

I owe my warmest thanks and respect to my other supervisor Associate Professor Esko Huhti, M.D., Ph.D., who suggested this topic to me. His unending support, overwhelming experience in epidemiological statistics and patience in guiding me in scientific writing and thinking made this thesis possible.

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I started to work with pulmonary medicine and especially with lung cancer patients at Päivärinne Hospital in year 1987. I wish to express my thanks to my colleagues and the staff of Ward 5 in Päivärinne Hospital for introducing me to the world of pulmonary medicine. Also I want to thank all patients who participated in my study.

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Oulu, May 1999

Riitta Mäkitaro
Abbreviations

AB      Asbestos body
CT      Computed tomography
NSCLC   Non-small-cell lung cancer
SCLC    Small-cell lung cancer
List of original papers

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


II Mäkitaro R, Pääkkö P, Huhti E, Bloigu R & Kinnula VL. Prospective population-based study on the survival of the patients with lung cancer. (submitted for publication)


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Original papers
1. Introduction

Lung cancer is a common malignancy among men and increasingly common among women in the industrialized countries throughout the world (Devesa et al 1987, Jensen et al 1990). It accounts for 21% of all cancer cases among males and 4% among females in the European Community (Jensen et al. 1990). Patients diagnosed with lung cancer are older now than a few decades ago (Coggon & Acheson 1983, Connolly et al. 1990), which may have an impact on diagnostic assessment, histology and treatment. Over the recent decades, there have been both geographical and temporal changes in the distribution of the histological subtypes of lung cancer (Beard et al 1988, Connolly et al 1990, Rennert et al 1991). However, most previous studies on lung cancer have been conducted on hospital series or patient registries without any pathological review of slides, and hence give deficient information on the incidence of the disease and its treatment. Many cases of lung cancer may remain undiagnosed, patients are not necessarily referred and differences in the treatment policy between centers cause further selection. Only a few prospective population-based studies are available in which the incidence and histology of lung cancer have been systematically assessed in terms of data obtained from national cancer registers (Nou et al 1979, Huhti et al 1980, Edinburgh Lung Cancer Group 1987).

Given that both diagnostic techniques and treatment modalities have improved, the prognosis of lung cancer patients may also have been improved. Fiberoptic bronchoscopy is routinely used to facilitate the diagnosis, and the increasingly accurate imaging methods enable better sampling procedures and more precise staging of tumors. Despite the recent major advances in biomedical technology however, the 5-year mortality rate of lung cancer still remains at 87-90%. Compared with many other malignant tumors, little progress in survival has been achieved; the 5-year survival for all cases of lung cancer was 6% in 1950-1954 and 13% in 1981-1987 (Beckett 1993). The treatment of choice for lung cancer, i.e. radical surgery, has remained the same, but the surgical techniques and postoperative treatments have improved. On the other hand, many clinical studies have addressed the effects of chemotherapy and combination therapy, especially in small-cell carcinoma and stage III diseases, and suggest that they prolong the survival of the patients (Wada et al 1996, Bonomi 1998, Bunn et al 1998). Many of these studies have, however, been conducted in centers with a particular interest in chemotherapy and in groups of patients with strictly defined inclusion criteria. Thus, these studies can be used in the
assessment of new chemotherapeutic agents, but they do not give information about the survival of lung cancer patients in general. Most of the population-based studies available are retrospective register- or hospital-based investigations (Connolly et al 1990, Watkin et al 1991, Fergusson et al 1996, Connolly et al 1997). These studies may only include a selected group of patients and often have low diagnostic accuracy in comparison with prospectively collected patient series.

Therefore, we conducted a population-based, prospective study to investigate the presentation, incidence, histology, surgical treatment and 5-year survival of all patients with lung cancer in a defined geographical area. Importantly, a similar survey had been conducted in this area during the years 1968-71, which is why the results of the present study could be compared with those obtained 20 years ago.

The lung cancer risk is strongly associated with exposure to cigarette smoking. However, only a fraction (10-20%) of lifetime smokers develop lung cancer, suggesting that genetic factors may also affect individual susceptibility to lung cancer. The development of cancer requires the accumulation of several mutations of different growth-regulatory genes in a single progenitor cell (Vogelstein & Kinzler 1993). Among these genes, the tumor suppressor gene p53 has a central role (Hollstein et al 1991). With the increasing knowledge of the functions of growth-regulatory genes, renewal of the p53 function by gene therapy experiments has been preliminarily used in the treatment of cancer (Roth et al 1996). This study was conducted in order to clarify the association between p53 accumulation and the etiologic factors of lung carcinoma, namely cigarette smoking and asbestos exposure.

Benign intrathoracic tumors are uncommon, and their occurrence in unselected populations is poorly defined. Most published data are case reports or retrospective results of surgical series (Bateson 1965, Toomes et al 1983, Mitsudomi et al 1990, Salminen 1990). The clinical problem related to benign tumors is to differentiate them from malignant lesions on chest x-rays. Despite the availability of modern clinical techniques, most intrathoracic tumors require thoracotomy before a histological diagnosis can be established (Oldham 1980). We reviewed prospectively all suspected intrathoracic tumors found during three years in a defined population in northern Finland, to investigate the clinical picture and prevalence of intrathoracic benign tumors.
2. Review of the literature

2.1. Lung cancer

2.1.1. Incidence

At the beginning of the 20th century, lung cancer was a rare disease, but now it is the most commonly diagnosed malignancy throughout the world (Hammar 1994). Lung cancer incidence and mortality have increased steadily over the past decades, and lung cancer is strongly associated with cigarette smoking. A lag phase of about 20 years exists between an increase in cigarette smoking in a particular population and a rise in deaths from lung cancer. Decreased smoking of cigarettes is associated epidemiologically with a declining incidence of lung cancer. In Finland, the lung cancer rates among men began to decline slowly in the early 1980s, but the rates among women are still increasing. About 1,700 new cases of lung cancer (42 per 100,000) are diagnosed annually among males in Finland, the age-standardized rates being 64 per 100,000 in the European Community and 71-80 per 100,000 in the USA, and the corresponding figures for females being 8.4, 8.2 and 25.8-42.9 (Finnish Cancer Registry 1997, Parkin et al. 1992, Zheng et al. 1994).

2.1.2. Risk factors

2.1.2.1. Smoking

The association between lung cancer and cigarette smoking was first reported in epidemiological studies almost 50 years ago (Wynder & Graham 1950, Doll & Hill 1952) and a dose-response relationship has been found repeatedly since then (Doll & Peto 1976). Doll and Peto correlated the smoking habits of over 34,000 British physicians with mortality from lung cancer over a period of 20 years and found a significant decline both in cigarette smoking and in mortality in this group in contrast to the general male population, in which neither mortality rates from lung cancer, nor tobacco consumption decreased. A
A study of over 10,000 Californian physicians (Enstrom 1983) and British female doctors (Doll et al. 1980) gave rise to similar conclusions. Cigarette smoking is the major cause of lung cancer, and investigators have concluded that smoking now accounts for 95% of lung cancers in developed countries (Doll & Peto 1981). The prevalence of smoking has been decreasing since about 1970, but has increased again since 1994, particularly among young people and women aged under 35 (Dobson et al. 1998, Statistics Finland 1998).

Exposure to environmental tobacco smoke (also called passive smoking) also causes lung cancer (Hackshaw et al. 1997). The increased risk was noted in a study of non-smoking wives of heavy smokers in Japan (Hirayama 1981). Numerous case-control studies (Correa et al. 1983, Garfinkel et al. 1985, Stockwell et al. 1992, Fontham et al. 1994, Kabat et al. 1995) and cohort surveys (Garfinkel 1981, Hirayama 1984, Cardenas et al. 1997) have consistently across studies, suggested a small but real risk for lung cancer among non-smokers exposed to the tobacco smoke of others. Also, according to those studies, there is a dose-response relation between a non-smoker’s risk of lung cancer and the number of cigarettes and years of exposure to smoke, which adds weight to the evidence that the association between environmental exposure and lung cancer is causal (Hackshaw et al. 1997).

2.1.2. Asbestos

Asbestos, a naturally occurring rock consisting of magnesium and calcium silicates, is one of the known causes of human cancer. Asbestos is the most common occupation-related cause of lung cancer, and the risk increases with cumulative exposure. Builders, plumbers, gas fitters, carpenters, electricians, metal plate workers and fitters constitute the largest high-risk groups. The annual production of asbestos increased until the 1970s and the worldwide annual production has still remained at 1 kg/yr per capita (Kogan & Polzik 1990). The role of asbestos as an occupational factor predisposing to lung cancer has been extensively investigated. According to epidemiological (Selikoff et al. 1979) and experimental (reviewed by Barrett et al. 1989) studies, asbestos is a carcinogen. Asbestos may induce chromosomal alterations, including chromosome loss, deletions and translocations (Lechner et al. 1985). In a study by Karjalainen et al. (1993), an etiological fraction of 19% was calculated for asbestos among the male Finnish lung cancer patients operated on in Helsinki. Nevertheless, accurate rates are difficult to determine, because the impacts of asbestos and cigarette smoke on the lung cancer are multiplicative (Berry et al. 1985), and most of the persons exposed to asbestos are cigarette smokers. According to Selikoff et al. (1968), there is a 5-fold increase in the incidence of lung cancer in non-smoking persons and a 61-fold increase in those who are both exposed to asbestos and cigarette smokers. The synergistic effect may be partly due to the inhibitory influence of cigarette smoke upon the clearance of asbestos (Churg et al. 1987). Environmental exposure to asbestos does not increase the risk of lung cancer (Camus et al. 1998).
2.1.2.3. Other risk factors

Radon is a naturally-occurring odorless radioactive gas which emanates from uranium naturally occurring in the soil. Radon decay products contribute to the lung cancer risk by forming deposits when inhaled and then damaging the respiratory system by the emission of x-rays. An elevation in the risk of lung cancer has been noted among uranium miners in Colorado and iron ore miners in Sweden (Archer et al. 1974, Radford & St Clair Renard 1984, Samet et al. 1984). Radon exposure may increase the risk of lung cancer among smokers threefold (Samet 1989). People who live in houses with high radon levels are more likely to develop lung cancer (Lubin & Boice 1997, Darby et al. 1998). There is a consistent pattern of increased lung cancer prevalence among the close relatives of lung cancer patients, even after adjustment for smoking habits (Shaw et al. 1991, Brownson et al. 1997). Family studies have shown a two- or three-fold risk for lung cancer among the non-smoking relatives of lung cancer patients compared with non-smokers without a family history of lung cancer (Sellers 1990). There are several studies which confirm that emphysema and chronic bronchitis are independent risk factors for lung cancer (Samet et al. 1986, Skillrud et al. 1986, Nomura et al. 1991). Also, there is an excess risk of lung cancer among patients with pulmonary fibrosis after corrections for age, gender and smoking (Turner-Warwick et al. 1980). Dietary factors appear to influence the lung cancer risk. Many studies have demonstrated that antioxidant vitamins decrease the lung cancer risk (Kvale et al. 1983, Ziegler 1989, Knekt et al. 1991), although the results of two randomized studies suggested an increased risk of lung cancer associated with the ingestion of beta carotene or other retinoids (The Alpha-Tocopherol, Beta Carotene Cancer Prevention Group 1994, Omenn et al. 1996). Other occupational exposures besides asbestos increase the incidence of lung cancer: uranium (in miners, Samet et al. 1984), arsenical fumes (Lee & Fraumeni 1964), nickel (Doll et al. 1977), metallic iron (Radford & St Clair Renard 1984), haloethers (such as dichloromethyl ether and chloromethyl methyl ether, McCallum et al. 1983, Gowers et al. 1993). The genetically determined ability to metabolize carcinogens may be one factor affecting the lung cancer risk (Pelkonen 1992). Molecular genetic factors might be most influential in stratifying risk of lung cancer (Shields & Harris 1993, Anttila et al. 1995, Raunio et al. 1995).

2.1.3. Screening

Prevalence screening studies comparing patients whose cancer was diagnosed on radiologic screening with those presenting symptomatically showed no difference in the 5-year survival rate of 5% versus 4.5% (Huhti et al. 1983). Four randomized, prospective controlled trials including 36,000 male smokers aged over 45 revealed no evidence to suggest that screening could reduce lung cancer mortality (Fontana et al. 1984, Frost et al. 1984, Melamed et al. 1984, Kubik & Polak 1986). The Memorial Sloan-Kettering Project (Flehinger et al. 1984, Melamed et al. 1984) and the John Hopkins Lung Project (Frost et al. 1984), which were specifically designed to evaluate the benefit of sputum cytology in screening, found no benefit from the addition of sputum cytology to annual radiographic screening. The Mayo Lung Project (Fontana et al. 1984) and the Czechoslovak study
(Kubik & Polak 1986, Kubik et al. 1990) addressed the effect of regular screening with chest radiography. In both of these studies, screening led to improvements in stage distribution, resectability and survival. However, the disease-specific mortality showed no improvements. Based on these studies, mass screening for lung cancer is not recommended. On the other hand, there was an increase in the cumulative incidence of lung cancer in the experimental group in these studies, which prevented significant improvements in survival from translating into corresponding reductions in mortality. The lead time bias and the length bias do not adequately account for the differences in cumulative incidence observed in these studies. There has been a re-evaluation of these trials and new studies with a more favorable attitude towards risk group screening (Strauss et al. 1997, Salomaa et al. 1998). One plausible explanation for the failure to demonstrate mortality differences in these studies might be population heterogeneity; the groups may not have been comparable with regard to risk factors other than smoking, such as radon exposure, presence of chronic obstructive lung disease, family history of cancer, dietary factors, or molecular genetic factors. There are also preliminary results for lung cancer screening by spiral CT with more accurate results and earlier detection compared with conventional chest radiography (Sone et al. 1998).

2.1.4. Diagnosis and staging

The most common symptoms of lung cancer, irrespective of tumor histology, are cough, weight loss, dyspnoea, chest pain and haemoptysis (Huhti et al. 1980, Chute et al. 1985). The first procedure for a person showing these symptoms is chest radiography. Computed tomography (CT) gives more detailed imaging of the chest tumor. The most important way to confirm the diagnosis is to establish the cytology or histology of the tumor. Sputum cytology can provide the diagnosis of lung cancer in as many as 40% of the cases, and the yield increases when multiple samples are used (Oswald et al. 1971). Flexible fiberoptic bronchoscopy is used to diagnose cancer with biopsy and brushing and also to make local staging. The overall diagnostic yield for lung cancer with fiberbronchoscopy is about 70% in the case of central lesions and over 90% when the lesion is visible bronchoscopically (Arroliga & Matthay 1993). Transbronchial needle aspiration can help to stage malignant disease in mediastinal lymph nodes, which, if positive, can preclude the need for further surgical staging (Harrow & Wang 1996). Transthoracic needle aspiration is the procedure of choice for sampling peripheral nodules (Salazar & Westcott 1993). Currently, most new lung cancers are only found after symptoms and signs reflect the occurrence of regional or distant metastases. In advanced lung cancer, the diagnosis may sometimes be confirmed simply from the histology of an enlarged peripheral lymph node or a distant metastasis. The search for metastatic disease requires a thorough history and physical examination, accompanied by appropriate laboratory testing. Two meta-analyses compared the results of clinical evaluation with those of routine head CT, abdominal CT, and radionuclide bone scans in patients with newly diagnosed lung cancer and indicated that if a comprehensive clinical evaluation was negative, the likelihood of finding metastatic disease in subsequent staging test was low (Hillers et al. 1994, Silvestri et al. 1995).
Precise and accurate staging is vital for the selection of effective treatment, for determining the prognosis and for making comparisons with other results. The TNM staging system for lung cancer was revised and unified with the earlier staging systems by the American Joint Committee on Cancer and the Union Internationale Contre le Cancer (UICC) in 1986, and included in the International Staging System for Lung Cancer (Table 1). The new TNM definitions and stage groupings were especially valuable, because they simultaneously yield prognostic information on the tumor and assist in the selection of therapy (Mountain 1986). The refinements in the staging system were published in 1997 with the new staging groups (Table 2) (Mountain 1997). Stage I was split into stage IA and IB because of the difference in 5-year survival. Secondly, stage II was divided into IIA and IIB, and the group of patients with T3N0M0 disease was moved into the IIB stage because of their better survival compared with the other groups in the stage III category. Additionally, the status of satellite tumors was clarified. For staging a chest tumor, it is considered essential to make a careful physical examination to detect distant metastases, and to use bronchofiberoscopy and either CT or mediastinoscopy or both to assess resectability (Fernando & Goldstraw 1990). Previously, mediastinal lymph nodes (N) were assessed by mediastinoscopy, whereas CT of the thorax is used for the clinical staging nowadays. CT evaluates the whole mediastinum including the lymph nodes which are not reached by mediastinoscopy, such as the aorto-pulmonary and inferior subcarinal nodes. On the other hand, CT has low specificity and sensitivity in the staging of lung cancer; when the size of the lymph node is used to determine malignancy, the sensitivity and specificity remain below 70% (Kerr et al. 1992, McLoud et al. 1992). A study by Medina Gallardo et al. showed that more than 60% of patients initially assessed as having N1 or N2 disease by using CT actually had N0 disease when assessed at thoracotomy. The authors of this study recommended careful sampling at thoracotomy as the method of choice for the correct evaluation of mediastinal lymph nodes in NSCLC (Medina Gallardo 1992). On the other hand, radical, systematic mediastinal lymphadenectomy compared with lymph node sampling with the resection of only suspicious lymph nodes results in a more detailed staging of the N2 region, which is of prognostic significance (Izbicki et al. 1995). However, the practice of perioperative staging used by cardiothoracic surgeons is often inadequate, and may overestimate the accuracy of preoperative evaluation (Tsang & Watson 1992). The more extensively a patient is investigated, the more likely there will be stage migration, with more patients being categorized as having an advanced stage and fewer patients being classified as having less advanced disease.
### a) Characteristics

#### Primary tumour (T)

<table>
<thead>
<tr>
<th>T0</th>
<th>No evidence of primary tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Tumour proven by the presence of malignant cells in bronchopulmonary secretions but not visualised roentgenographically or bronchoscopically, or any tumour that cannot be assessed as in a retreatment staging</td>
</tr>
<tr>
<td>T1S</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>A tumour that is 3.0 cm or less in greatest dimension surrounded by lung or visceral pleura, and without evidence of invasion proximal to a lobar bronchus at bronchoscopy</td>
</tr>
<tr>
<td>T2</td>
<td>A tumour more than 3.0 cm in greatest dimension, or a tumour of any size that either invades the visceral pleura or has associated atelectasis or obstructive pneumonitis extending to the hilar region. At bronchoscopy, the proximal extent of demonstrable tumour must be within a lobar bronchus or at least 2.0 cm distal to the carina. Any associated atelectasis or obstructive pneumonitis must involve less than an entire lung</td>
</tr>
<tr>
<td>T3</td>
<td>A tumour of any size with direct extension into the chest wall (including superior sulcus tumours), diaphragm, or the mediastinal pleura or pericardium without involving the heart, great vessels, trachea, oesophagus or vertebral body, or a tumour in the main bronchus within 2 cm of the carina without involving carina</td>
</tr>
<tr>
<td>T4</td>
<td>A tumour of any size with invasion of the mediastinum or involving the heart, great vessels, trachea, oesophagus or vertebral body or carina or presence of malignant pleural effusion</td>
</tr>
</tbody>
</table>

#### Nodal involvement (N)

<table>
<thead>
<tr>
<th>N0</th>
<th>No demonstrable metastasis to regional lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>Metastasis to lymph nodes in the peribronchial or the ipsilateral hilar region, or both, including direct extension</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis to ipsilateral mediastinal lymph nodes and subcarinal lymph nodes</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis to contralateral mediastinal lymph nodes, contralateral hilar lymph nodes, ipsilateral or contralateral scalene or supraclavicular lymph nodes</td>
</tr>
</tbody>
</table>

#### Distant metastasis (M)

<table>
<thead>
<tr>
<th>M0</th>
<th>No (known) distant metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>Distant metastasis present – specify site(s)</td>
</tr>
</tbody>
</table>

### b) Staging

<table>
<thead>
<tr>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage IIIA</th>
<th>Stage IIIB</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1N0M0</td>
<td>T2N0M0</td>
<td>T3N0M0</td>
<td>T1N0M1</td>
<td>T2N0M1</td>
</tr>
<tr>
<td>T2N0M0</td>
<td>T2N1M0</td>
<td>T3N1M0</td>
<td>T2N1M1</td>
<td>T1N1M1</td>
</tr>
</tbody>
</table>
Table 2. TNM definitions a) in the international staging system b) for lung cancer (1997).

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1N0M0</td>
<td>T2N0M0</td>
<td>T3N1M0</td>
</tr>
<tr>
<td>IB</td>
<td>T2N1M0</td>
<td>T3N2M0</td>
<td>T4N2M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T2N1M0</td>
<td>T3N2M0</td>
<td>T4N3M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T3N0M0</td>
<td>T3N1M0</td>
<td>any TNNM1</td>
</tr>
<tr>
<td>IIIA</td>
<td>T3N0M0</td>
<td>T3N1M0</td>
<td>any TNNM1</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3N0M0</td>
<td>T3N1M0</td>
<td>any TNNM1</td>
</tr>
<tr>
<td>IV</td>
<td>any TNNM1</td>
<td>any TNNM1</td>
<td>any TNNM1</td>
</tr>
</tbody>
</table>

a) Primary tumour (T)

- **T0**: No evidence of primary tumour
- **Tx**: Tumour proven by the presence of malignant cells in bronchopulmonary secretions but not visualised roentgenographically or bronchoscopically, or any tumour that cannot be assessed as in a retreatment staging
- **TIS**: Carcinoma *in situ*
- **T1**: A tumour that is 3.0 cm or less in greatest dimension surrounded by lung or visceral pleura, and without evidence of invasion proximal to a lobar bronchus at bronchoscopy *(ie, not in the main bronchus)*
- **T2**: A tumour more than 3.0 cm in greatest dimension, or a tumour of any size that either invades the visceral pleura or has associated atelectasis or obstructive pneumonitis extending to the hilar region. At bronchoscopy, the proximal extent of demonstrable tumour must be within a lobar bronchus or at least 2.0 cm distal to the carina. Any associated atelectasis or obstructive pneumonitis must involve less than an entire lung
- **T3**: A tumour of any size with direct extension into the chest wall (including superior sulcus tumours), diaphragm, or the mediastinal pleura or pericardium without involving the heart, great vessels, trachea, oesophagus or vertebral body, or a tumour in the main bronchus within 2 cm of the carina without involving carina
- **T4**: A tumour of any size with invasion of the mediastinum or involving the heart, great vessels, trachea, oesophagus or vertebral body or carina or presence of malignant pleural or pericardial effusion, or with satellite tumor nodule(s) within the ipsilateral primary-tumor lobe of the lung

b) Staging

- **N0**: No demonstrable metastasis to regional lymph nodes
- **N1**: Metastasis to lymph nodes in the peribronchial or the ipsilateral hilar region, or both, including direct extension
- **N2**: Metastasis to ipsilateral mediastinal lymph nodes and/or subcarinal lymph nodes
- **N3**: Metastasis to contralateral mediastinal lymph nodes, contralateral hilar lymph nodes, ipsilateral or contralateral scalene or supraclavicular lymph nodes

Distant metastasis (M)

- **M0**: No (known) distant metastasis
- **M1**: Distant metastasis present – specify site(s) •

*the uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is classified T1.

• Separate metastatic tumor nodule(s) in the ipsilateral nonprimary-tumor lobe(s) of the lung are classified M1.
2.1.5. Histologic types of lung cancer

The second edition of the WHO histologic typing of lung tumors, which was published 1981 (WHO 1981), is the most widely used. The classification is based on light-microscopic criteria. Common lung neoplasms are classified by the best-differentiated region of the tumor and graded by the most poorly differentiated area. Lung cancers are divided into two main groups on the basis of their histology and clinical features, namely small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC) (Table 3). Squamous cell carcinoma, adenocarcinoma, large cell undifferentiated carcinoma and small-cell carcinoma account for about 95% of all lung cancers. The proportions of the histologic cell types are markedly affected by the nature of the population studied. Over the recent decades, there have been both geographical and temporal changes in the distribution of histologic types of lung cancer. In 1977, Vincent and co-workers reported an increasing proportion of adenocarcinomas, which has become the leading lung cancer subtype in North America, while squamous cell carcinoma remains the most frequent subtype in Europe (El-Torky et al. 1990, Parkin & Sankaranarayanan 1994, Travis et al. 1994, Charloux et al. 1997). The percentage of adenocarcinoma is particularly high in the Far East, i.e. Hong Kong, Japan and Taiwan (Hirayama et al. 1981, Kung et al. 1984, Takise et al. 1988, Ko et al. 1997). Some surveys have failed to show this change: a study from the Tumor Register of New Mexico showed an increasing proportion of small-cell carcinomas rather than adenocarcinomas among the female population, but histologic diagnosis was only available in half of the cases (Butler et al. 1987). A study from Minnesota, USA, showed equal increases in all histologic cell types of bronchogenic carcinoma, and 96% of the cases had histologic confirmation and all the slides had been re-evaluated (Beard et al. 1988). The accuracy of hospital-reported pathological diagnoses of lung cancer varies within 50-80% between original and review diagnoses (Greenberg et al. 1984, Butler et al. 1987, Browson et al. 1995), and indicates the importance of pathological review of registry-reported lung cancer cases for large-scale etiological studies.
Non-small-cell lung cancer account for about 80% of all cases of lung cancer. Clinically detectable distant metastases are present in about two thirds of patients with SCLC at diagnosis, which is almost twofold compared to NSCLC patients. In the absence of treatment, tumor progression in SCLC is rapid, with a median survival of 2 to 4 months; untreated patients with NSCLC, on the other hand, even some with widespread metastatic disease, may, in rare instances, live for 5 years. Since about one third of patients with NSCLC have surgically resectable disease, surgery is the mainstay of potentially curative therapy for this disease. In SCLC, however, surgery is only rarely possible, since most patients have either locally advanced disease or distant metastases. Chemotherapy produces objective tumor responses in about 80% of patients with SCLC, while response rates in NSCLC are lower and much less often complete. Radiotherapy elicits responses in about 90% of patients with SCLC and in about one half of those with NSCLC. Thus, the therapeutic approaches to these groups of patients with lung cancer are different (Ihde 1995).
2.1.6.1. Non-small-cell lung cancer

Surgery. In 1933, Graham and Singer introduced the practice of surgical resection of lung cancer with a curative intent. A trial in 1963 (Morrison et al. 1963) showed surgery to be more effective than radiotherapy, but there are no recent reliable estimates of the increase in survival possibly attributable to surgery. Surgical techniques and postoperative treatment have improved over the years (Shah & Goldstraw 1995, Wada et al. 1996), and surgery has become the generally preferred treatment for stages I, II and a limited group of patients with stage IIIA disease, in which complete resection is feasible. Acceptance of the surgical procedure has been supported by the encouraging survival data. Five-year survival, which remains below 15% for lung cancer generally, exceeds 70% after resection of the T1N0 subgroup of stage I NSCLC (Mountain 1986, Naruke 1988). On the other hand, patients with stage I non-small cell lung cancer without surgery based on data collected in screening programs, had a 5-year survival of 2% (Flehinger et al. 1992). Surgery remains the main possibility to cure patients with squamous cell carcinoma, adenocarcinoma and large cell carcinoma (Mountain 1986, Naruke 1988), but it has little to offer in cases of small-cell cancer owing to the disseminated nature of this cancer type (Ihde 1995). Surgery for lung cancer carries a 5% overall operative mortality risk and causes significant morbidity (Romano & Mark 1992, Lederle & Niewoehner 1994). Surgery is appropriate for patients who are relatively fit, who have adequate respiratory capacity, and who have early-stage, histologically confirmed NSCLC. However, only a small part of all patients with lung cancer are operated on in many countries: about 10% in Scotland (Fergusson et al. 1996), 20% in the Netherlands (Damhuis et al. 1996), 25% in Spain (Mane et al. 1994) and 10% in the USA (Zagonel et al. 1994). In Finland, 20% of all lung cancer cases are treated surgically (Rainio et al. 1991).

Radiotherapy. Radiotherapy can be given at several points during the course of lung cancer: before, after or instead of surgery, at radical dosage to inoperable patients with limited disease, and as palliative therapy to inoperable patients either to the primary tumors or to symptomatic metastases. Radiotherapy has an indisputable palliative effect on many symptoms caused by lung tumors, including haemoptysis, pain, vena cava superior syndrome and partial or total atelectasis of the lung. A report on 50 elderly patients, with peripheral (T1-2N0) tumors given radical radiotherapy because of refusal of surgery or medical contraindications, showed a 2-year survival rate of 56% and a 5-year survival rate of 16%, which compared favorably with a non-randomized surgical group of 86 patients over 70 years of age with 48% and 26% 2- and 5-year survival rates, respectively (Noordijk et al. 1988). Patients with tumors too extensive for surgery but no distant metastases are likely to benefit from radiotherapy. Preoperative radiotherapy does not improve postoperative survival (Shields et al. 1970). A meta-analysis of post-operative radiotherapy data indicated a 7% reduction in survival at 2 years (Stewart et al. 1998).

Chemotherapy. Around 70% of NSCLC tumors are unresectable at the time of diagnosis (Chute et al. 1985, Feigal et al. 1993). It has been estimated that at least half of the remaining patients, whose disease is localized, will eventually develop metastatic involvement despite treatment. More than 80% of patients with NSCLC would therefore need effective systemic therapy (Belani 1992). Despite the numerous efforts to produce effective treatments, the outcome of patients with advanced NSCLC remains poor. Meta-analyses of randomized trials in advanced NSCLC employing a cisplatin-based regimen
compared to the best supportive care have documented statistically improved survival; a benefit that is clearly modest, with only a 2-3 month increase in median survival (Grilli et al. 1993, Souquet et al. 1993, Marino et al. 1994, Stewart et al. 1995). The are new promising drugs: taxanes (paclitaxel and docetaxel), camptothecins (topotecan and irinotecan), new antimetabolites (such as gemcitabine and difluorodeoxycytidine), and antitubulin agents (vinorelbine), which have produced good response rates in NSCLC (Halme et al. 1997, Mattson et al. 1997, Giaccone et al. 1998).

Combined modality therapy. Clinical trials and meta-analyses demonstrated that combined chemotherapy and radiotherapy improve the therapeutic outcome in patients with locally advanced, unresectable stage III NSCLC (Schaake-Koning et al. 1992, Sause et al. 1995, Stewart et al. 1995, Pritchard & Anthony 1996). Combined modality therapy given to these patients increased median survival to 13 to 14 months and 5-years survival to 15% to 20%, nearly three times that reported with radiation therapy alone (Sause et al. 1995, Dillman et al. 1996). Based on these results, the American Society of Clinical Oncology (ASCO) recommends combined modality therapy for patients with unresectable stage IIIA and IIIB NSCLC (American Society of Clinical Oncology 1997). The study results have not yet demonstrated a benefit for one combined modality strategy over the others in terms of survival, toxicity, or time to progression.

**2.1.6.2. Small-cell lung cancer**

Modern chemotherapy has yielded multifold increases in median survival, but only minimal improvements have occurred over the last decade. Combination chemotherapy with etoposide/cisplatin prolongs survival, especially in patients with limited disease. Combined-modality treatment employing chemotherapy and chest irradiation appears to produce cytotoxic effects and is relatively well tolerated by patients with limited disease. A meta-analysis of 13 randomized trials showed a modest but significant 14% reduction in the relative mortality rate of patients with SCLC receiving chemotherapy/chest irradiation versus those receiving chemotherapy alone (Pignon et al. 1992). The absolute survival difference was about 5.5% at 3 years in favor of the combined-modality treatment. In SCLC, surgery is rarely possible, since most patients have either locally advanced disease or distant metastases. An analysis of long-term survivors with small-cell lung cancer indicated that resection may prolong survival in patients with limited disease (Shah et al. 1992), especially when employed as an adjuvant to chemotherapy (Karret et al. 1989) or radiotherapy (Shepherd et al. 1991, Mentzer et al. 1993, Skarin 1993). Surgery may also reduce the rate of local recurrence.

**2.1.7. Survival**

Lung cancer is the major determinant of overall cancer mortality in the developed countries, and a similar trend is emerging in the developing countries. In Finland, as in the USA, lung cancer is the number one cause of cancer deaths, being responsible for 19% of all cancer deaths and 4% of all deaths in Finland (Statistics Finland 1999) and for 28%
and 6% respectively, in the USA (Beckett 1993). Compared with many other malignancies, little progress in survival has taken place: the five-year survival rate for all cases of lung cancer was 6% in 1950-1954 and 13% in 1981-1987 (Beckett 1993).

The histologic type of cancer is a fairly consistent determinant of survival. A retrospective study from North America showed that patients with $T_1N_0M_0$ squamous cell carcinoma had a mean 5-year survival rate of 83%, whereas patients with $T_1N_0M_0$ adenocarcinoma had a mean 5-year survival rate of 69% ($p=0.02$) (Gail et al. 1984, Mountain et al. 1987). Other studies have also corroborated consistently longer survival for patients with squamous tumors than for those with nonsquamous tumors (Nagasaki et al. 1982, Feld et al. 1984, Read et al. 1990, Kadri & Dussek 1991). The Mayo Clinic showed that patients with solitary bronchoalveolar cell carcinoma have a favorable outcome (5-year survival rate 81%) similar to that seen with squamous cell carcinoma (Williams et al. 1981). On the other hand, Naruke and co-workers (1988) reported no significant difference in survival rates according to histological type for stage I disease, and Shimizu and colleagues (1993) identified a survival difference favoring adenocarcinoma in their series. The degree of cellular differentiation, determined by histological analysis, also appears to influence survival. Patients with poorly differentiated or undifferentiated tumors seem to survive for a shorter time overall than those with well-differentiated tumors (Kadri & Dussek 1991, Watanabe et al. 1991).

Mountain has published survival curves for the different stage of the international staging system (1986) based on a study of over 1000 lung cancer patients. He gives the following estimated 5-year survival rates for the different clinical stages of NSCLC: 35-62% for stage I, 25% for stage II, 10-15% for stage IIIA, <10% for stage IIB and <5% for stage IV (Mountain 1988). The significant differences are clearest for squamous cell carcinoma. There was a small difference in survival between the tumor cell types in patients with stage I disease. At stages II and IIIA, the outcome for patients with squamous cell carcinoma was better than for those with adenocarcinoma or large cell carcinoma. The prognosis was equally bad for all tumor cell types at stages IIB and IV (Mountain 1988).

The T status alone consistently influences survival. Patients with T1 tumors have an overall 5-year survival advantage of 15% to 20% over those with T2 tumors (Williams et al. 1981, Mountain et al. 1987, Watanabe et al. 1991). Tumor size, irrespective of the other factors that determine T status, also appears to affect survival. Several authors have reported longer survival for patients with small tumors than for those with larger tumors (Treasure & Belcher 1981, Ishida et al. 1990, Read et al. 1990).

Women may survive somewhat longer than men. The reviews by Williams (1981), Mountain (1987), and Shimizu (1993) and co-workers showed higher rates of 5-year survival in women, independent of other factors.

### 2.2. Benign intrathoracic tumors

Benign intrathoracic tumors are rare. Several classifications of benign intrathoracic tumors are presented in the literature (Miller 1968, Spencer 1977, WHO 1981, Steele 1983). The one used here (Table 4) is based on the origin of the tumor. It has been estimated that only 1% of all bronchial tumors are benign and the higher percentage usually

Chondromatous hamartoma is the most common benign solitary lung lesion, accounting for 5-8% of all solitary lung lesions and up to 75% of benign pulmonary diseases (Hayward & Carabasi 1967, Madewell & Feigin 1977, van den Bosch et al. 1987). Hamartomas are endobronchial only in 1-14% of cases (Bateson 1973, Fudge 1980, Hurt 1984, van den Bosch et al. 1987). In a series of 8000 postmortem examinations, 20 hamartomas were found with a prevalence of 0.25% (McDonald et al. 1945, Rubin & Berkman 1952). Chondromatous hamartoma may appear at any age, but is rare in childhood and adolescence (Hartman & Shochat 1983, van den Bosch et al. 1987). Hamartomas are more common in men than women at a the ratio of 1.7-3/1 and the peak incidence occurs in the sixth decade of life (Bateson 1973, Hurt 1984, van den Bosch et al. 1987).

Mesenchymal tumors, such as chondromas, lipomas, fibromas and myomas, may be situated within the tracheobronchial tree or in the lung parenchyma. When solitary, they are more often seen endobronchially (Corona & Okeson 1974, Politis et al. 1979, Archambeaud-Mouveroux et al. 1988). Lipomas constitute 0.1% of all and 13% of benign pulmonary tumors (Schraufnagel et al. 1979, Iannicello et al. 1987). Pulmonary fibroma may be situated within the bronchi or in lung tissue (Spencer 1977). Leiomyomas account for 1.5% of all benign lung tumors (Yellin et al. 1984). They are more common in females than males, the female/male ratio being 1.6/1 with a mean age of about 36 years (Yellin et al. 1984). Women are also more prone to develop sclerosing hemangiomas (Katzenstein et al. 1980). The patients are usually middle-aged (average 42 years), with an age range 15-69 years (Katzenstein et al. 1980, Chan et al. 1982). Bronchial adenomas account for 1-3% of all pulmonary tumors and 3-10% of surgically excised bronchial neoplasms (Spencer 1977, de Lima 1980). They comprise a group of tumors with malignant features, called “mixed tumors”, and the benign mucous gland adenomas (Cooper & Belcher 1976, Attar et al. 1985, Halevy et al. 1985, Ferguson & Cleeland 1988).

Benign intrathoracic tumors cause bronchial obstruction with non-specific symptoms, similar to those associated with malignant disease: cough, dyspnea, chest pain, recurrent lung infections, hemoptysis, wheezing and weight loss (van den Bosch et al. 1987, Salminen 1990). Although intraparenchymal tumors are mostly asymptomatic, they may provoke such symptoms as cough, hemoptysis and chest infections (Spencer 1977, Katzenstein et al. 1980).
Table 4. Benign tumours of the lung and the tracheobronchial tree according to Greenfield and Oldham.

<table>
<thead>
<tr>
<th>Tumors</th>
<th>Variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelial tumours</td>
<td>1. papilloma</td>
</tr>
<tr>
<td></td>
<td>2. polyps</td>
</tr>
<tr>
<td>Mesodermal tumors</td>
<td>1. vascular</td>
</tr>
<tr>
<td></td>
<td>a. angiomas</td>
</tr>
<tr>
<td></td>
<td>b. lymphangioma</td>
</tr>
<tr>
<td></td>
<td>c. hemangioendothelioma</td>
</tr>
<tr>
<td></td>
<td>d. lymphangiomyomatosis</td>
</tr>
<tr>
<td></td>
<td>2. bronchial</td>
</tr>
<tr>
<td></td>
<td>a. fibroma</td>
</tr>
<tr>
<td></td>
<td>b. chondroma, osteochondroma</td>
</tr>
<tr>
<td></td>
<td>c. lipoma</td>
</tr>
<tr>
<td></td>
<td>d. granular cell myoplastoma</td>
</tr>
<tr>
<td></td>
<td>e. leiomyoma</td>
</tr>
<tr>
<td></td>
<td>f. neurogenic tumours</td>
</tr>
<tr>
<td>Developmental or unknown origin</td>
<td>1. hamartoma</td>
</tr>
<tr>
<td>tumours</td>
<td>a. chondromatous</td>
</tr>
<tr>
<td></td>
<td>b. adenomatous malformation</td>
</tr>
<tr>
<td></td>
<td>2. teratoma</td>
</tr>
<tr>
<td></td>
<td>3. chemoectoma</td>
</tr>
<tr>
<td></td>
<td>4. clear cell tumour</td>
</tr>
<tr>
<td></td>
<td>5. thymoma</td>
</tr>
<tr>
<td>Inflammatory and other</td>
<td>1. plasma cell granuloma</td>
</tr>
<tr>
<td>pseudotumours</td>
<td>2. pseudolymphoma</td>
</tr>
<tr>
<td></td>
<td>3. xanthoma</td>
</tr>
<tr>
<td></td>
<td>4. amyloid</td>
</tr>
<tr>
<td></td>
<td>5. tracheobronchopathia osteoplastica</td>
</tr>
<tr>
<td>Polypoid lesions (bronchial</td>
<td>1. carcinoid</td>
</tr>
<tr>
<td>adenomas)</td>
<td>2. salivary gland types</td>
</tr>
<tr>
<td></td>
<td>a. cylindroma</td>
</tr>
<tr>
<td></td>
<td>b. mucoepidermoid tumor</td>
</tr>
<tr>
<td></td>
<td>c. mixed tumour</td>
</tr>
</tbody>
</table>

As to endobronchial tumors, signs and symptoms typical of an obstructive process often require further investigations. The radiographic examination usually reveals most intrathoracic tumors, and they are mostly visualized on the x-ray as coin lesions (Corona & Okeson 1974, Attar et al. 1985). Computed tomography has a limited value for differentiating between benign and malignant lesions (Zwirewich et al. 1991). Bronchoscopy offers an opportunity to see intrabronchial tumors, but cytological specimens with bronchial brush are of little help, since endoluminal tumors are usually covered by bronchial mucosa (Burchaart & Axellson 1972). Most cases of intrathoracic tumors require thoracotomy for histologic confirmation (Oldham 1980).
3. Purpose of the study

The purpose of this study was to evaluate lung cancer and benign intrathoracic tumors from various perspectives in a prospective and unselected series of patients. The specific aims were:

1. to investigate the presentation, incidence and histology of lung cancer,
2. to investigate the treatment and survival of lung cancer patients,
3. to find out what changes, if any, had taken place during 20 years in the incidence and histological picture of lung cancer and in the survival of lung cancer patients,
4. to investigate the association of exposure to asbestos fibers with histological findings and p53 accumulation in lung cancer, and
5. to investigate the occurrence of benign intrathoracic tumors.
4. Subjects and methods

4.1. Subjects

A total of 602 patients with lung cancer and 36 patients with benign intrathoracic tumors were investigated for this study. The patient whose lung cancer was diagnosed between January 1, 1990 and December 31, 1992. The study was conducted in the province of Oulu in northern Finland (56 000 km²), with a population of 442,900, at the end of 1991 were collected. All the five hospitals in the province (Päivärinne Hospital, Kainuu Central Hospital, Oulaskangas District Hospital, Raahed District Hospital and Oulu University Hospital) were informed of the survey and requested to refer all patients with suspected lung tumors to the Päivärinne Hospital or the Oulu University Hospital, the latter being the only hospital performing thoracic surgery in this area. If a patient was not referred, the authors requested to be informed of the case.

Patients with a suspicion of lung cancer and all patients with benign intrathoracic tumors were personally interviewed by two of the investigators. A detailed history of smoking, other diseases, working history with or without asbestos exposure, symptoms related to lung cancer, their duration, close relatives having lung cancer and clinical status were recorded. Most of the adult patients with lung cancer (72%) were interviewed like this. Otherwise, data were derived from the national cancer register and the patients records of primary health care centers and hospitals, and analyzed retrospectively. Permission for the use of the registry data was obtained from the Finnish Ministry of Social Affairs and Health.

A summary of patient characteristics in the studies I-IV is presented in Table 5. Six hundred and two patients with lung cancer constituted the study population for the studies I-II. Seventy consecutive patients operated on for primary lung carcinoma in the Oulu University Hospital between January 1990 and April 1992 were included in study III. Study IV included 36 patients with benign intrathoracic tumors, twenty men and sixteen women. A reference series of lung cancer patients had been collected with similar methods 20 years earlier from the largely same geographical area.
Table 5. Summary of patients characteristics in studies I-IV.

<table>
<thead>
<tr>
<th>Study</th>
<th>I, II</th>
<th>III</th>
<th>IV</th>
<th>Comparison series*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>602</td>
<td>70</td>
<td>36</td>
<td>446</td>
</tr>
<tr>
<td>Male/female</td>
<td>510 / 92</td>
<td>61 / 9</td>
<td>20 / 16</td>
<td>420 / 26</td>
</tr>
<tr>
<td>Mean age, SD</td>
<td>67.7 ± 9.9</td>
<td>64.6 ± 7.7</td>
<td>54 ± 12.3</td>
<td>61.9 ± 9.1</td>
</tr>
<tr>
<td>Ex or current smokers</td>
<td>564 (94 %)</td>
<td>67 (96 %)</td>
<td>24 (67 %)</td>
<td>409 (92 %)</td>
</tr>
<tr>
<td>Packyears</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48 ± 25 SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>31 ± 20 SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histological/cytological confirmation</td>
<td>516 (86 %)</td>
<td>70 (100 %)</td>
<td>24 (67 %)</td>
<td>431 (97 %)</td>
</tr>
</tbody>
</table>

* Reference series of lung cancer patients from the years 1968-71 from the same geographical area (Huhti et al. 1981)

4.2. Methods

4.2.1. Evaluation of smoking habits

A detailed smoking history, including the year of starting and stopping smoking, the number of cigarettes smoked per day and abstinence periods longer than one month were obtained in the interview. The pack-years of cigarette smoking were calculated by multiplying the number of years of smoking with the average number of packs smoked per day. Ex-smokers were defined as people who had quit smoking at least 6 months before the diagnosis of lung cancer. Passive smoking was not recorded for this study.

4.2.2. Evaluation of asbestos exposure

The patients were interviewed about their occupational history. A detailed history of their asbestos exposure was taken, and the exposure periods in months were recorded and summarized. The patients were classified into four groups according to their asbestos exposure, as modified from a classification by Karjalainen et al. (1993) as follows:

1. Definite exposure. Persons with more than 10 years exposure in construction work before the year 1975, or more than one year’s exposure in insulation work or the manufacturing of asbestos products.
2. Probable exposure. Persons with exposure in a garage or engineering works, or less than 10 years’ exposure in construction work.
3. Possible exposure. Persons employed in various occupations with possible exposure to asbestos, e.g. maintenance work.
4. Unlikely exposure. Persons employed in occupations with no known exposure to asbestos, e.g. farming.

In 1975, stricter safety regulations against asbestos exposure were enforced in Finland. Therefore, a minimum of 10 years’ exposure before 1975 was considered definite exposure. Patients with less exposure, e.g. mechanics, iron-plate workers and part-time construction workers, were considered either possibly or probably exposed, depending on the time and duration of exposure. The patients with fibrosis or pleural plaques in chest x-ray were included in group 2.

4.2.3. Clinical evaluation

Fiberoptic bronchoscopy was performed on 452 lung cancer patients (75%) and all the 36 patients with benign intrathoracic tumors. Computed tomography was done on 358 patients (60%) with lung cancer and all the patients with benign tumors. Mediastinoscopy was done on seventeen patients (2.8%). Other investigations, such as bone scans, were made as indicated. The TNM classification and staging of the cancer (Mountain 1986) could be carried out in 519 (86%) patients.

4.2.4. Symptomatic stages according to Feinstein

The lung cancer patients were classified into the four symptomatic stages described by Feinstein (1990): stage I asymptomatic; stage II primary symptoms only; stage III systemic symptoms with or without primary symptoms, but no metastatic symptoms; stage IV metastatic symptoms with or without primary symptoms and with or without systemic symptoms. Primary symptoms were associated with the primary tumor (e.g. hemoptysis, a new type of cough, wheezing, fever associated with pneumonia, breathlessness). Systemic symptoms were ones arising at a site remote from the primary tumor, but not indicating tumor dissemination (e.g. anorexia, weight loss, fatigue). Metastatic symptoms also increased at a site remote from the primary tumor, but indicated metastasis (e.g. superior vena cava syndrome, dysphagia, hoarseness). The symptomatic stage was determined at the first interview. Of the patients whose files were reviewed retrospectively, only those with evident systemic or metastatic symptoms or those who were definitely asymptomatic according the patient records were included in this part of the study.

4.2.5. Histological determination of exposure to asbestos

In study III, to histologically evaluate the exposure to asbestos, 5-µm-thick sections of one or two peripheral lung blocks in each case were stained with Perls’ method for iron. From the same blocks, 30-µm unstained sections were also cut. All the sections were screened with 200x magnification, and the asbestos bodies were counted by two pathologists blinded to the results of the p53 stainings (Roggli & Pratt 1983). The number of
asbestos bodies per square centimeter was calculated by dividing the total count of asbestos bodies with the surface area of given section. The surface areas of the sections were measured with an image analyzer. 512x512 pixel 8-bit gray-level images were digitized with a CCD camera Dage 72-E (Dage-MTI, Michigan City, IN). The morphometry was done by using MCID-M1 (version 4.12) software (Imaging Research, St. Catharines, Canada). An imaging system based on an Intel 386/25 MHz microcomputer (Santa Clara, Ca) equipped with an image processor FG-100 AT (Imaging Technology, Woburn, Massachusetts) was used. The slides were placed on a desktop illuminator (Northern Light precision illuminator model B90, Imaging Research, St. Catharines, Canada) and a Micro-Nikkor 55 mm (1:2.8) objective was used.

For histologically significant asbestos exposure, 1 asbestos body (AB)/cm² or more in a 30-μm section was required, for which the reasons are given below. The presence of 2 ABs in 4 cm² 5-μm sections, which correspond to 200 ABs per gram of wet, fixed lung tissue, is conventionally regarded as evidence of significant asbestos exposure (Craighead et al. 1982, Roggli & Pratt 1983). Counted with the mathematical model of Vollmer & Roggli (1985) and assuming that the mean length of the ABs is 51.6 μm, the significant number in a 30-μm section would be 0.9 AB/cm². For practical reasons, the limit was set at 1AB/cm². In addition, lung tissue sections were evaluated and fibrosis peribronchially or elsewhere was recorded, to diagnose histologic asbestosis (Craighead et al. 1982).

### 4.2.6. Immunohistochemical staining for p53

5-μm-thick sections were cut from the specimens and placed on slides coated with poly-L-lysine solutin (Sigma Chemicals, St.Louis, MO). The specimens were then dewaxed in xylene and rehydrated in graded alcohol. Endogenous peroxidases were blocked by immersing the sections in hydrogen peroxide 0.1% in absolute methanol for 20 min. Non-specific binding was blocked by incubating the slides in 20% fetal calf serum in phosphate-buffered saline (PBS) for 20 min.

For immunostaining, the avidin-biotin-complex method was used as described by Soini et al. (1992). The sections were first incubated overnight at 4°C with primary polyclonal rabbit antihuman p53 antibody CM-1 at a dilution of 1:1000 (Soini et al. 1992), followed by secondary biotinylated anti-rabbit antibody (dilution 1:400) (Dakopatts, Copenhagen, Denmark) and avidin-biotin complex (Dakopatts). Rinses were done with several changes of PBS between each stage of procedure. The color was developed with diaminobenzidine, whereafter the sections were lightly counterstained with hematoxylin and mounted with Eukitt (Kindler, Freiburg, Germany).

Negative controls for immunostaining were obtained by substituting PBS for primary antibody. As a positive control, lung carcinoma sections previously known to be strongly p53-positive were used (Soini et al. 1992).

The results were evaluated semiquantitatively and divided into four groups (- = negative, + = 1 to 5% of cells positive, ++ = 6 to 10% of cells positive, +++ = 11 to 40% of cells positive, ++++ = more than 40% of cells positive) according to the estimated num-
4.2.7. Histologic specimens

The histologic specimens were processed and stained as suggested by the World Health Organisation (WHO 1981). All histologic and cytologic slides were re-examined by lung pathologist (P Pääkkö). The lung cancers were classified into five groups according to their histological or cytological picture: 1) squamous cell carcinoma 2) adenocarcinoma 3) small-cell carcinoma 4) large cell carcinoma 5) other or unclassified forms. The last group included mainly cases where the sample was inadequate for classification, but allowed the diagnosis of a malignant tumor. Cases regarded as metastases of primary cancers outside the lung were not included in the series. In 86 patients (14%), the diagnosis of lung cancer could not be confirmed histologically or cytologically.

4.2.8. Treatment

If there were no contraindications (other diseases, nonoperability) and the patients consented, all the patients with non-small-cell lung cancer were operated on. The other treatment modalities included radiotherapy, chemotherapy (the most common agents being vincristine, doxorubicin and cyclophosphamide) or a combination of radio- and chemotherapy, or supportive treatment.

4.2.9. Survival of lung cancer patients

Every patient with lung cancer was followed up for 5 years or until death. The follow-up period started on the day when the diagnosis was first made; the histological or cytological confirmation, if it was possible, usually came later.

4.2.10. Reference series of lung cancer patients from the years 1968-71

Over twenty years earlier, during 1968-71, in almost the same geographical area (the tuberculosis hospital district of Northern Ostrobotnia), a prospective, population-based survey of lung cancer was carried out with largely similar patient recognition methods (Huhti et al. 1980, Huhti et al. 1981) (Table 6 and 7). 446 patients were diagnosed during 4 years in a population of approximately 300,000 individuals. The mean age was 61.9 (SD 9.1) years. Histologic and/or cytologic confirmation of the diagnosis was achieved in 431 cases (97%). All of the histologic and cytologic slides were similarly reviewed by
experienced lung pathologists then, which makes comparison of these two surveys possible. There was no second reading of the earlier material together with the newer material. Squamous cell carcinoma was the most common histologic type (47%), followed by small-cell carcinoma (27%), adenocarcinoma (11%) and large cell carcinoma (4%). 71 patients (16%) were operated on. All patients were followed up until death or for five years. Additional unpublished data (survival of patients who were operated on) were also reviewed from the old material for comparison. The survival of these patients was compared with the patients of this study.

Table 6. Lung cancer by histological type in 405 males in the years 1968-71 (Huhti et al. 1980) and 440 males in the years 1990-92 with histologic or cytologic confirmation of malignancy.

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell</td>
<td>159 (45)</td>
<td>137 (33)</td>
<td>32 (57)</td>
<td>52 (43)</td>
<td>191 (47)</td>
<td>189 (43)</td>
</tr>
<tr>
<td>Small cell</td>
<td>105 (30)</td>
<td>76 (24)</td>
<td>3 (5)</td>
<td>26 (22)</td>
<td>108 (27)</td>
<td>102 (23)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>37 (11)</td>
<td>67 (21)</td>
<td>6 (11)</td>
<td>33 (27)</td>
<td>43 (11)</td>
<td>100 (23)</td>
</tr>
<tr>
<td>Large cell</td>
<td>18 (5)</td>
<td>20 (6)</td>
<td>0 (0)</td>
<td>3 (2)</td>
<td>19 (5)</td>
<td>23 (5)</td>
</tr>
<tr>
<td>Other/unclassified</td>
<td>31 (9)</td>
<td>19 (6)</td>
<td>14 (25)</td>
<td>7 (6)</td>
<td>45 (11)</td>
<td>26 (6)</td>
</tr>
<tr>
<td>Total</td>
<td>350 (100)</td>
<td>319 (100)</td>
<td>55 (100)</td>
<td>121 (100)</td>
<td>405 (100)</td>
<td>440 (100)</td>
</tr>
</tbody>
</table>

The data are shown as n (%). A significant difference in histological distribution by the chi-square test between the two series, p<0.001

Table 7. Lung cancers by histological type in 26 females in the years 1968-71 (Huhti et al 1980) and in 76 females in the years 1990-92.

<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell</td>
<td>7 (27)</td>
<td>11 (47)</td>
<td>4 (29)</td>
<td>15 (20)</td>
<td>23 (20)</td>
<td>30 (25)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>7 (27)</td>
<td>30 (48)</td>
<td>5 (35)</td>
<td>35 (46)</td>
<td>40 (46)</td>
<td>46 (46)</td>
</tr>
<tr>
<td>Large cell</td>
<td>3 (12)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (12)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other/unclassified</td>
<td>2 (8)</td>
<td>6 (10)</td>
<td>1 (7)</td>
<td>7 (9)</td>
<td>9 (9)</td>
<td>16 (9)</td>
</tr>
<tr>
<td>Total</td>
<td>26 (100)</td>
<td>62 (100)</td>
<td>14 (100)</td>
<td>76 (100)</td>
<td>90 (100)</td>
<td>92 (100)</td>
</tr>
</tbody>
</table>

All cases in the older series were confirmed histologically and those in the newer series either histologically or cytologically. The data is shown as n (%). A significant difference in histological distribution by the chi-square test between the two series, p= 0.026.
4.2.11. Statistical methods

SPSS for Windows (Statistical Package for Social Sciences, Inc., Chicago, IL) and Stata (Texas) were used for the statistical analyses. 95% confidence intervals (CI) were calculated for differences of proportions (I, III). An analysis of survival data was undertaken using the survival curves and applying the Kaplan-Meier method (II). The means of smoked pack-years in the p53-negative or slightly positive and the strongly p53-positive groups were compared using Student’s t-test (III). The effect of asbestos exposure on p53 protein accumulation, with cigarette smoking controlled for, was assessed in a multivariate logistic regression analysis (III). P-values under 0.05 were regarded as statistically significant.
5. Results

5.1. Lung cancer

5.1.1. Lung cancer incidence (I)

The number of new lung cancer cases was 602 (510 males (84.7%), 92 females (15.3%)). The annual age-standardized incidence per 100,000 was 63 for males and 9.5 for females, whereas the incidence in the earlier series of patients collected 20 years previously had been 87 for males and 4.1 for females (94 and 6%, respectively) (Huhti et al. 1980). The mean ±SD age, 67.7±9.9 years, did not differ significantly between the males (67.7±9.8) and the females (68.1±12.7), but was higher than 20 years ago (61.8 for males and 62.3 for females) (95% CI for the age difference with all patients 4.6-7.0). The majority of patients (93%) had been suffering from the typical symptoms of lung cancer, such as cough, dyspnoea, haemoptysis and fatigue. In 123 cases (21%) the cancer was found in an examination for another disease, and in 22 cases (4%) the cancer was initially suspected on the basis of a chest radiograph taken for a health examination. The cancer was diagnosed at autopsy without any previous suspicion of the disease in eight cases (1%), the mean age of these patients being 64.1 years. Information from the Finnish Cancer Register revealed that three patients had not been reported (0.5%) and four additional cases had been misclassified by the cancer registry as other types of cancer due to inadequate information.

5.1.2. Lung cancer histology (I)

A histologic diagnosis was obtained in 381 cases (63%). In 343 cases the tissue specimen was from the primary tumor and in 38 cases from metastases. In 20 cases a biopsy was obtained from the pleura or cervical, mediastinal or axillary lymph nodes. Altogether 79 autopsies were performed (13%). A cytologic diagnosis without histology was available in 135 cases (23%). For 70 males (14%) and 16 females (17%), the diagnosis was based on clinical findings without histologic or cytologic confirmation. The diagnosis of lung
cancer in these cases was based on a new, growing tumor on the chest x-rays and by excluding other possible causes. The patients without confirmation of the diagnosis were older than the others: their mean±SD age was 73.5±9.1 years and the age difference was statistically significant (95% CI for age difference 5.6-9.9, p<0.001).

The earlier series collected 20 years earlier had comprised 446 patients, and 84% of their diagnosis had been confirmed histologically and 125 cytologically. The number of autopsies had been 138 (31%). (Huhti et al. 1980).

### 5.1.3. Histologic types (I)

The distribution of histologic types is shown in the tables 6 and 7. The most common type was squamous cell carcinoma (40%), which accounted for 43% of all cases among the males and 20% among the females. The overall proportion of adenocarcinoma was 26%, with 23% among the males and 46% among females. The percentages of small-cell carcinoma among males and females were similar, being 23% and 25%, respectively. The histologic distribution differed between males and females (x²=46.7, 4df, p<0.001). A bronchoalveolar subtype of adenocarcinoma was found in six out of the 100 male patients (6%) with adenocarcinoma and in six out of the 34 (18%) female patients. Large cell carcinoma was found in 4% of the cases. In addition, six adenosquamous carcinomas, one low-grade sarcoma, one carcinosarcoma, two lymphomas, two adenoid cystic carcinomas, three carcinoid tumors and 18 unclassified malignant tumors were detected. The mean age did not differ significantly between the histologic types.

The percentage of adenocarcinoma among the females had increased from 27 to 46% and that among the males from 11 to 23% compared with the situation 20 years earlier (Huhti et al. 1980). The annual age-adjusted incidence of adenocarcinoma per 100,000 had increased from 4.5 to 7.5, i.e. from 9 to 13 for males and 1.2 to 3 for females.

### 5.1.4. Smoking history (I,III)

The smoking habits of 558 patients were known. Eleven (2%) of the males and 27 (29%) of the females were life-long non-smokers, while all the others were ex-smokers or smokers. The percentage of adenocarcinoma was significantly higher in the non-smokers (50%) than in the smokers and ex-smokers (21%), with an odds ratio of 3.8 (95% confidence interval 2.0-7.4, p<0.001). The percentage of adenocarcinoma among non-smokers was similar to that recorded 20 years earlier (50%) (Huhti et al. 1980). A majority of the smokers smoked cigarettes, while thirty were pipe smokers and nobody smoked cigars. All the patients in study III were cigarette smokers.
5.1.5. Exposure to asbestos fibers (I,III)

Occupational asbestos exposure was reported by 145 of the patients (24%). The most common occupations with asbestos exposure were jobs in construction, including carpenters, plumbers, painters and masons (82 persons). There were two men who had been working with insulation. None of the patients had been working with asbestos manufacturing. In study III, according to the occupational history, 13 patients had definite, 10 probable, and seven possible exposure to asbestos. Forty patients had no indication of asbestos exposure. Peripheral lung tissue for AB counting was available from 63 patients. The surface areas of the sections varied from 0.6 to 5.9 cm², mean 2.8±1.1 cm². At least 1 AB was found in 30μm unstained sections of 37 patients, and in 5μm Pi stained sections of 14 patients. Only in one instance was one AB found in a 5-μm Pi section and none in a 30-μm unstained section. Among the patients with more than one AB/cm², there were more patients with a history of asbestos exposure (groups 1-3; 43%) than with unlikely exposure (group 4; 11%). The difference was significant (p=0.005; with 95% CI for difference of proportions 10 to 53%) (Table 8). The proportions of patients with more than 1 AB/cm² increased with the certainty of clinical exposure.

Table 8. Relation between clinical exposure to asbestos and the histological presence of asbestos bodies in lung tissue sections.

<table>
<thead>
<tr>
<th>Clinical asbestos exposure group</th>
<th>Histological presence of asbestos bodies (no. cases)</th>
<th>&gt; 1 AB/cm²</th>
<th>&lt; 1 AB/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) definite</td>
<td></td>
<td>6 (50%)</td>
<td>6 (50%)</td>
</tr>
<tr>
<td>(2) probable</td>
<td></td>
<td>4 (44%)</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>(3) possible</td>
<td></td>
<td>2 (29%)</td>
<td>5 (71%)</td>
</tr>
<tr>
<td>(4) unlikely</td>
<td></td>
<td>4 (11%)</td>
<td>31 (89%)</td>
</tr>
</tbody>
</table>

Group 1 versus 2-4: p = 0.04. Group 1 and 2 versus 3 and 4: p = 0.006. Groups 1-3 versus 4: p = 0.005

5.1.6. p53 accumulation associated with clinical and histological asbestos exposure and smoking (III)

Clinicopathological findings of the patients are presented in Table 9. Twenty of the 30 (67%) patients exposed to asbestos were p53-positive compared with 16 of 40 (40%) patients with unlikely exposure. The difference was statistically significant (p = 0.027; 95% CI for difference of proportions 4 to 50%) (Table 10).
Among the patients with p53-positive lung tumors, 12 out of 34 (35%) had > 1 AB/cm² compared with only four of the 29 (14%) patients with p53-negative tumors. The difference was statistically significant (p= 0.047; 95% CI for difference of proportions 1 to 41%).

There was no difference in the frequency of p53 accumulation in the tumors of the patients with mild histologic asbestosis (78%, 7/9) compared with the tumors of the patients with a significant number of ABs in their lung tissue but no asbestosis /71%, 5/ 7).

No difference was seen in the number of cigarettes smoked between the patients with p53-positive and p53-negative lung carcinomas (44.2±27.6 and 40.4±22.2 pack years, respectively). However, the patients with strongly p53-positive lung tumors (>10% of positive nuclei) were significantly heavier smokers (57.2±38.2 pack years) than the patients with p53-negative or slightly positive tumors (38.9±19.9 pack years) (p=0.017; a 95% CI for the difference of proportions 3.4% to 33%).
Multivariate analysis by logistic regression with cigarette smoking controlled for showed that an asbestos body count above 1 AB/cm² gave a 3.9-fold probability for p53 protein accumulation compared with the lung tumors of patients with lower asbestos body concentrations (p=0.04). In the same analysis, patients with clinical asbestos exposure turned out to have a 3-fold probability for p53 positive lung tumors compared to unexposed patients (p=0.03).

5.1.7. Other risk factors (I)

None of the patients had been exposed to uranium or heavy metals. According to the Finnish Centre for Radiation and Nuclear Safety, the radon content of ambient air in this northern part of Finland is low. Twenty-two patients (4%) had a family history of lung cancer (parents).

5.1.8. Clinical TNM classification and survival (III)

Clinical TNM classification and staging were available in 519 cases (86%). Stage I included 97 (19%), stage II 21 (4%), stage IIIA 57 (11%), stage IIIB 128 (25%) and stage IV 216 (41%) patients. The survival patterns in stage I and II were similar. As expected, the patients with stage IV (metastatic) disease had the worst prognosis (Fig. 1). The difference in survival between the stages was significant ($\chi^2_{\text{logrank}}=199.6$, p<0.0001).
Fig. 1. Survival (Kaplan-Meier) of lung cancer patients with staging according to the TNM classification. (stage I ---, stage II ——, stage IIIa ----, stage IIIb ———, stage IV ————).

5.1.9. Symptomatic stages and survival (III)

Feinstein’s symptomatic stages could be defined in 517 patients. Only 47 (8%) patients were asymptomatic, while 141 patients (27%) had primary symptoms, 217 patients (42%) had systemic symptoms and 112 (22%) had metastatic symptoms. Survival differed between the four symptomatic stages, being best among the asymptomatic patients and worst among those with metastatic symptoms, none of whom lived for 3 years (Fig. 2). The difference in survival between the symptomatic stages was significant ($X^2_{logrank} = 120, p < 0.0001$).
5.1.10. Treatment (III)

The 123 (20%) patients operated on included 57 (46%) with squamous cell carcinoma, 41 (33%) with adenocarcinoma, 11 (9%) with large cell carcinoma and five (4%) with small-cell carcinoma. Nine additional cases of operated patients included adenosquamous cell carcinoma, carcinoid tumors, adenomatoid cystic carcinoma and sarcoma. Seven additional explorative thoracotomies were performed. Resections were significantly more frequent in the younger age group (18-59 yrs) than in the older group (≥60), i.e. 36% versus 17% (difference between the proportion of resection rates: 19%, 95% CI 9-29%, p<0.001). Radiotherapy was given to 189 patients and twenty patients had chemotherapy, the most common agents being vincristine, doxorubicin and cyclophosphamide. A combination of radiation and chemotherapy was given to 54 patients (48 patients with small-cell carcinoma and six patients with non-small-cell carcinoma).
Seventy-two of the 602 patients (12%) were alive after 5 years. The survival of men and women was similar, thirteen women (14%) and 59 men (12%) being alive after 5 years. The 5-year survival of the patients with squamous cell carcinoma was 16%, with adenocarcinoma 19%, with small cell carcinoma 3%, with large cell carcinoma 9% and with unclassified or other types of lung cancer 18%. Of the patients with no histologic or cytologic confirmation, only two survived for 5 years. Since especially the prognosis of small-cell carcinoma is poor, with very few being alive after 5 years, the 2-year survival was also assessed. The 2-year survival rates were 27%, 23%, 7%, 17% and 27%, respectively. The difference in survival between the histological types was statistically significant ($\chi^2_{\text{logrank}}=59.2$, $p<0.001$) (Fig. 3).
5.1.12. Survival according to treatment (III)

The survival of the patients who were operated on was best, their 5-year survival being 48%. The patients with radiotherapy had a 5-year survival of 4%. Of the twenty patients given chemotherapy only one survived for 5 years. Of the patients given combination treatment, only 4%, i.e. two out of 52 patients survived for 5 years. The 2-year survival of the patients with small-cell carcinoma who received combination therapy was 12.5% (six out of 48 patients). None of the small-cell carcinoma patients treated with chemotherapy, radiation or supportive care alone survived for two years. The difference in survival according to treatment modalities other than surgery was significant ($x^2_{\text{logrank}} = 66.4$, $p<0.0001$). These treatment groups are not identical, which is why the survival difference is likely due to selection bias. The patients with no active treatment had the shortest survival. The overall difference in survival according treatment was significant ($x^2_{\text{logrank}} = 277$, $p<0.001$) (Fig. 4).

Fig. 4. Survival (Kaplan-Meier) of lung cancer patients by treatment. (----- surgery, —— combination, —— radiation, ---- chemotherapy, - - - no treatment).
The overall 5-year survival was better in the newer series (12%) than in the earlier series (4%) (Huhti et al. 1981) (p<0.001). In contrast, the 2-year survival did not differ significantly between these series of patients (19% and 15%, respectively, p=0.079) (Fig. 5).

![Survival graph](image)

Fig. 5. Survival of lung cancer patients in the years 1968-71 (Huhti et al. 1981) and 1990-92.

### 5.2. Benign intrathoracic tumors (IV)

Thirty-six patients had benign intrathoracic tumors, 20 men and 16 women. These tumors were classified as pulmonary (n=25), mediastinal (4) or pleural (5) and neoplastic or non-neoplastic. Histological confirmation was obtained in 24 cases. The mean age of the 36 patients was 54 years, and two were younger than 30. Twenty-four (67%) were smokers. In 23 of the 36 patients the lesions were detected as an intrathoracic nodule at a health examination or investigations for other disease. Of the 25 patients with an intrapulmonary nodule, 17 (68%) had no symptoms, while six had cough, one (with aspergilloma) reported haemoptysis and fatigue, and two had chest pain. Three of the five patients with
mediastinal lesions had symptoms – cough, chest pain or (in the case of mediastinal thymoma) weakness and dysphagia. Three of the six patients with pleural lesions complained of cough, dyspnoea or chest pain. Bronchoscopy did not confirm the diagnosis in any case. Thoracotomy was considered necessary in 24 cases, and histologic diagnosis was therefore obtained in 67% of the series.

The seven pulmonary tumors histologically identified as benign neoplasms are tumourlet, two fibromas and four hamartomas. An intrabronchial hamartoma was also observed, but not confirmed, at bronchoscopy. The nine non-neoplastic pulmonary lesions with histologic diagnosis included two inflammatory pseudotumors, two aspergillomas, an adenomatoid cystic malformation, a bronchogenic cyst, a silicotic nodule, a rheumatoid nodule and a lymph node. In eight of the nine patients found to have an intrapulmonary lesion without histologic verification, thoracotomy was considered unnecessary, as the lesions could be identified on radiographs taken 5-15 years previously. In one patient, who had never smoked and who had primary subcutaneous amyloidosis, chest radiographs showed two lung nodules, which were regarded as amyloid and remained stable during 5 years of follow-up.

All the five benign mediastinal lesions were histologically confirmed. Four proved to be neoplastic: two thymomas, one schwannoma and one teratoma. One consisted of ectopic lung tissue.

Histologic diagnosis was obtained in three of the six pleural lesions. The only neoplastic lesion was fibrous mesothelioma. Four non-neoplastic lesions were classified as Blesovsky’s syndrome (folding lung, rounded atelectasis). In two of these four cases the diagnosis was based exclusively on typical CT without histologic verification. Another lesion was not histologically verified because of its stability in 5-year observation.

Bilobectomy was performed in one case and lobectomy in three cases, and 20 lesions were extirpated by sleeve resection or local excision.
6. Discussion

6.1. Lung cancer

The series of lung cancer patients are usually based on cancer registries or selected hospital populations. In this prospective epidemiological study, the current cancer incidence and histology were compared with the situation that prevailed 20 years ago. It was found that the incidence decreased in males, but increased in females, mainly owing to an increase in adenocarcinomas.

Lung cancer is one of the most common malignancies in the world. Cancer registers show that lung cancer accounts for 21% of all cases among males and 4% among females in the European Community (Jensen et al. 1990). In Finland, and in many other countries as well, prostate cancer is the most common cancer among males and breast cancer among females. Lung cancer causes 29% of all cancer deaths among males and 8% among females in the EC, and the corresponding figures gathered from Statistics Finland (1999), are identical 29% and 8%. According to the present results, the incidence of lung cancer in northern Finland was 31.4 per 100,000, whereas it had been 53 per 100,000 in this area 20 years earlier (Huhti et al. 1980).

The increase in lung cancer among females follows the trend in cigarette smoking. Likewise, the percentage of female lung cancer patients has increased from 6 to 15% in northern Finland during the last 20 years (Huhti et al. 1980). The present results suggest that in particular, adenocarcinoma among females has increased during the past 20 years, its proportion being 27% (seven patients) and 46% (35 patients), respectively. This result is in agreement with the reports from cancer registries in other countries (Wu et al. 1986, Rennert et al. 1991). The three largest population studies published in the USA (Dodds et al. 1986, Wu et al. 1986, Travis et al. 1995) all suggest that the age-adjusted incidence of adenocarcinoma is increasing. All of these studies were retrospective and register-based without any pathological review of slides. Only one longitudinal study has been conducted in Europe, in the Netherlands, and this similarly showed an increase in the incidence of adenocarcinoma (Janssen-Heijnen et al. 1995). However, some surveys have failed to show this change: a study from the Tumor Register of New Mexico showed an increasing proportion of small-cell carcinomas rather than adenocarcinomas among the female population, but a histological diagnosis was only available in half of the cases.
(Butler et al. 1987). A study from Minnesota, USA, showed an equal increase in all histologic cell types of bronchogenic carcinoma; 96% of the cases had histologic confirmation and all the slides had been re-evaluated (Beard et al. 1988). A trend towards an increase of adenocarcinomas among females and non-smokers has also been reported by Dodds et al. (1986), Ko et al. (1997) and Hirayama (1981).

The frequency of autopsies is lower now than 20 years ago (13 versus 31%), which is partly associated with the altered legislation in Finland. If no histological or cytological diagnosis was available, only radiologically typical cases of lung cancer were included in this study.

Given that adenocarcinomas are less closely related to smoking, the increase of adenocarcinomas suggests additional risk factors that may play an important role in the etiology of lung cancer. Passive smoking was not recorded in this series of patients. Most of the patients started with non-filtered cigarettes, but probably smoked filtered cigarettes most of their smoking time. The use of filtered cigarettes was more common in the new series of patients than in the older one, and this change has been suggested to contribute to the increase of adenocarcinomas (Charloux et al. 1997). The advanced needle biopsy technique and flexible bronchofiberscopy have facilitated access to the lung periphery, which may also increase the proportion of more peripheral tumors, such as adenocarcinomas. It is theoretically possible that some of the adenocarcinomas of this study represent gynecological metastatic tumors. However, these tumors are diagnosed more accurately now than earlier, since both mammography and CT are widely available. The study was conducted in northern Finland, where the environmental factors have not changed over the years. No exposure to radon or uranium was detectable.

The WHO standards for histologic processing have been designed for surgical and autopsy samples, for which they are suitable and work well. Smaller samples, such as those taken by bronchofiberscopy, are more problematic in the WHO classification, but the squamous cell, adenomatoid and small-cell differentiations are still recognizable. Large cell differentiation is difficult to identify in small biopsy samples, and this may be a potential source of error. In this survey, cytological samples were used together with small biopsies to determine the histologic type, and this was especially helpful in the squamous and small cell differentiation. Since the latest WHO standard does not include the diagnosis of undifferentiated carcinoma, this term was only used in cases where the bronchoscopy sample was inadequate for classification but allowed the diagnosis of a malignant tumor.

Hopefully, the increased awareness of the risks of smoking, the antismoking propaganda, and the increased restrictions on smoking will significantly reduce tobacco use and eventually the incidence of lung cancer.

6.2. Survival

Most studies on the prognosis of lung cancer are retrospective and based on cancer registers or selected hospital series, whereas few studies are available on the management or outcome of unselected groups of patients with lung cancer. We collected a prospective series of all new lung cancer patients in a defined geographical area. The patients with a
low performance status who had been treated in primary centers without further referral were also included. All the patients were followed up for five years or until death. The present study therefore gives information about the survival of lung cancer patients in general. The earlier series of lung cancer patients followed up some 20 years ago (Huhti et al. 1980) in this same geographical area was collected with the same prospective method and thus allows a comparison of the survival rates over the years. The results indicate that the overall survival of patients with lung cancer has increased. The 2-year and 5-year survival increased during the past 20 years from 15% to 19% and from 4% to 12%, respectively. Since the mean age of the patients increased from 62 years to 68 years, the increase in survival is even more significant.

A few corresponding studies have been conducted. A retrospective study from Scotland reported the 2-year survival of lung cancer patients to be 14% (Fergusson et al. 1996), which is slightly lower than the 2-year survival in our study (19%). The Scottish study included only patients who had been referred to a specialist for respiratory or thoracic surgical consultation. According to the cancer register, they accounted for 63% of all lung cancer patients in the area and included histologic confirmation in 58% of the cases. A retrospective and register-based study from the Yorkshire region in England showed modest improvements in the prognosis of patients with lung carcinoma as a result of the application of new methods of diagnosis (fiberoptic bronchoscopy) and treatment (chemotherapy for small-cell carcinoma) (Connolly et al. 1990). These patients had been followed up for 2 years.

The present study indicated that the 5-year survival of the patients with adenocarcinoma was better (19%) than the survival of patients with other histological types. This result is in agreement with the study of Watkin and co-workers (1990), who used the largest register data set on lung cancer with over 90% completeness of the register. This register-based study showed that the histologic type of lung cancer is an important prognostic factor, and that the patients with adenocarcinoma have the best survival, their 5-year survival being 22% (Watkin et al. 1990).

The prognosis of small-cell carcinoma continues to be poor. The 5-year survival of these patients did not change significantly in 20 years, the respective 5-year survival rates being 2% and 3%. The 2-year survival improved from 4% to 7%. The 5-year survival in our study is very similar to the result obtained in the register-based study by Watkin and co-workers (3.5%), which also showed improvement in the 2-year survival of small-cell lung cancer from 2.5% to 7.5% and improvement in the median survival from 13 to 30 months (Watkin et al. 1990). Another register-based study showed an increase in the 9-month survival of patients with small-cell lung cancer, but no change in the median survival of lung cancer patients during the years 1976–1983 (Connolly et al. 1990). According to their study, the survival of patients treated with chemotherapy improved significantly. Furthermore, at the time of that particular study the effects of combined multimodality-based chemotherapies had not yet been introduced. Their histological confirmation rate was 58.4% and the proportion of small-cell carcinomas 9.8%, the corresponding numbers in our study being 85% and 25%, respectively. It should be noted that the purpose of our study was to evaluate the prevailing treatment of lung cancer in general and its effects on survival, not to compare the survival rates of patients with different radiation and/or chemotherapy protocols. In conclusion, the long-term survival of the patients with small-cell carcinoma has remained unchanged over the years.
Staging is an important procedure in the application of various treatment modalities (Mountain 1986). In our earlier series, mediastinal lymph nodes (N) were assessed by mediastinoscopy, whereas CT of the thorax was used in the clinical staging of the present series of patients. About 60% of the patients underwent CT in our series, which percentage is remarkably higher than the corresponding figure (18%) in a recent study from Scotland (Fergusson et al. 1996). CT evaluates the whole mediastinum, including the lymph nodes which are not reached by mediastinoscopy, such as the aorto-pulmonary and inferior subcarinal nodes. On the other hand, CT has low specificity and sensitivity in the staging of lung cancer; when the size of the lymph node is used to determine malignancy, sensitivity and specificity remain below 70% (Lähde et al. 1990, McLoud et al. 1992). The relatively good survival of the patients who were operated on in the present series probably reflects better preoperative staging. The more extensively a patient is investigated, the more probably there will be stage migration, with more patients being categorized as having an advanced stage and fewer patients being classified as having less advanced disease. This may also be the reason for the relatively low numbers of surgically treated patients in the present series.

Surgery is regarded as the most effective treatment for lung cancer, which has improved the prognosis of this disease (Watkin et al. 1990, Hircsh et al. 1993, Damhuis & Schutte 1996). Since the recent studies have shown a better prognosis among patients with stage IIIa disease (Mountain 1990, Roth et al. 1994), one might expect that the number of resected cases is increasing. However, only a small portion of all patients with lung cancer are operated on: about 10% in Scotland (Fergusson et al. 1996), 20% in the Netherlands (Damhuis & Schutte 1996), 25% in Spain (Mane et al. 1994) and 10% in the USA (Zagonel et al. 1994). Most of these studies have been made on hospital series, and hence overestimate the percentage of operated patients. The modern surgical techniques allow the resection of fairly large tumors invading the neighboring organs. However, more patients suffer a relapse than are cured by surgery. In our present series, 20% were operated on and 48% of the operated patients were alive after 5 years, the corresponding numbers in the earlier series being 16% and 23%, respectively (Huhti et al. 1981– unpublished data). These series comprised all known patients, including those with low performance status who were treated in primary centers without further referral. Our result is in line with the study by Watkin and co-workers (between 1974 and 1986)(1990), where the outcome of surgery continuously improved. The reason for the unchanged frequency of surgery over the past 20 years may be associated with the persistent difficulty of diagnosing limited disease, the relative increase in lung cancer among old people and/or the unchanged attitude towards the treatment of these patients. The proportion of older patients (> 60 yrs) operated on had increased from 6% to 17% during the last 20 years and it is generally accepted that the operative risk for elderly patients is not markedly higher than that for younger patients (Roxburg et al. 1991). On the whole, the prognosis of patients with non-small-cell lung cancer who are operated on has clearly improved over years.

In the present series, 14% of the patients had only a clinical diagnosis, and their survival was the worst. It is possible that some of these patients may not have had lung cancer at all, despite the clinical diagnosis. There are always patients with a low perfor-
mance status who do not tolerate invasive investigations. Their exclusion, which is usu-
ally done, causes a bias and gives an excessively optimistic view of the survival of lung
cancer patients.

It appears that screening for lung cancer does not prolong the survival of the patients
although there is a re-evaluation of the trials with a more favorable attitude towards risk
group screening (Strauss et al. 1997, Salomaa et al. 1998). Mass radiography surveys of
the older population were still performed in Finland during the 1960s and 1970s, but this
practice had been discontinued before the present survey; hence the proportion of asymp-
tomatic patients was higher in the earlier (16%) than in the present series (8%). However,
survival was now better, suggesting that radiographic screening is ineffective. Asbestos-
induced diseases were screened for in some groups working in construction, shipyards
and the manufacturing of asbestos products in Finland during the years 1990–92 (Koski-
nen et al. 1996). However, only six out of 602 lung cancer patients in this series were rec-
ognized through this screening.

6.3. Asbestos exposure

The methods used to assess the asbestos exposure of the patients were the working history
of each patient taken in an interview and the counting of asbestos bodies by light micros-
copy from histological slides of peripheral lung tissue. The main source of error in the
former method is that its reliability depends on the patient’s ability to memorize his/her
whole working history. Even working periods of a few months duration may be critical, if
the person has been heavily exposed to asbestos during this period. The patients were
interviewed at the time of the lung cancer diagnosis, at which particular time they some-
times had difficulties to concentrate on their previous working history decades ago. The
histologic assessment of asbestos bodies involves many sources of error. The most impor-
tant of them is the uneven distribution of ABs in the lung – a fact that also affects the
electron-microscopic assessment, which is the most reliable method (Roggli & Pratt
1983). The accuracy of the histologic estimation of the asbestos burden is also impaired
by variations in the lengths of ABs, the thickness of the tissue sections, tissue shrinkage
during the processing, and the degree of distension of lung tissue (Roggli & Pratt 1983).
A good correlation between the light-microscopic and electron-microscopic evaluations
of the asbestos burden in lung tissue has been obtained (Roggli & Pratt 1983). In our
study, the association between p53 accumulation in the tumors and the increased number
of ABs in lung tissue was detected both when a clinical (historical) and a histologic eval-
uation of asbestos exposure was made. The number of ABs increased progressively with
the likelihood of asbestos exposure, as suggested by the working history, when clinical
and histologic exposures were compared.
Our study shows an association between p53 protein accumulation and asbestos exposure. This suggests that p53 inactivation has a role in asbestos-induced lung carcinogenesis. The most common genetic alterations in the p53 gene are point mutations. On the other hand, it is not clear that asbestos fibers characteristically cause point mutations, though they are able to induce chromosome loss and deletions (Barrett et al. 1989). Another possibility for the mechanism of asbestos-induced gene defects is oxidative damage through an induced inflammatory response. Macrophages exposed to crocidolite and chrysotile fibers in vitro release reactive oxygen metabolites (Goodglick & Kane 1986, Mossman et al. 1986). The release of these metabolites has been found to be mutagenic and tumor-promoting (Goodglick & Kane 1986). The tumorigenicity or reactive oxygen metabolites could possibly be mediated through inactivation of the p53 gene.

One explanation for the low number of asbestos bodies in lung tissue in some of our patients with clinical asbestos exposure could be the clearance of ABs from lung tissue, especially with chrysotile asbestos (Rom et al. 1991). This could lead to an underestimation of exposure as evaluated by AB counting at the time of the tumor presentation. Another possibility is a large interindividual variation in AB formation (Dodson et al. 1985). Some of our patients who were clinically exposed but did not show histologic signs of exposure could have a reduced ability to form ABs.

Our result also showed an association between strong p53 positivity in carcinomas and heavy smoking. This differs from the results of other studies (Westra et al. 1993). However, their information about smoking habits was obtained from medical records, which is generally not regarded as a reliable method. Patients were also classified as ex-smokers if they had stopped smoking only two weeks before the lung cancer operation. We regarded as ex-smokers only those who had quit smoking at least six months before the operation. Despite these differences, our results are consistent with the results of Westra and co-workers (1993) in that we were unable to demonstrate an effect of smoking abstinence on p53 accumulation. Interestingly, of our 70 patients, the three who had never smoked all had a p53-negative tumor. This is in line with the 12 non-smokers in the study of Westra and co-workers (1993).

6.5. Benign intrathoracic tumors

Benign intrathoracic tumors are difficult to detect, being often symptomless for years. The 36 cases found in our hospital’s catchment area over a 3-year period is in agreement with the approximately 5% reported from previous surgical series (Bateson 1965, Toomes et al. 1983, Mitsudomi et al. 1990).

As expected, bronchoscopy did not confirm the diagnosis in any case. CT, which permits a detailed analysis of intrathoracic nodules, was performed in all cases. Given the limited value of CT for differentiating between benign and malignant lesions (Zwirewich et al. 1991), 67% of our patients underwent thoracotomy. Because of a clinical suspicion of malignancy, preoperative transthoracic needle aspiration biopsy was not employed.
According to some earlier authors (Salazar & Westcott 1993) about 20–30% of patients in whom such biopsy is negative (non-diagnostic) may have malignant disease, and only a specific benign diagnosis can exclude malignancy.

The male/female ratio of 1.25 differed from that in malignant tumors (Nou et al. 1979, Huhti et al. 1980, Dodds et al. 1986), a finding consistent with the previous reports showing that benign intrathoracic tumors are equally common in both genders and tend to occur at younger ages than malignant lesions (Bateson 1965, Salminen et al. 1990).

In contrast to the previous surgical series (Mitsudomi et al. 1990, Salminen et al. 1990), there were no cases of sclerosing haemangioma, leiomyoma or lipoma, presumably because of the rarity of these tumors (Schraufnagel et al. 1979, Katzenstein et al. 1980, Toomes et al. 1983). Hamartoma, as previously found in surgical cases, was the most common benign intrathoracic neoplasm (Bateson & Abbott 1960, Toomes et al. 1983, van den Bosch et al. 1987, Salminen et al. 1990). In the only available study of pulmonary hamartoma from Finland (Salminen et al. 1990), it accounted for 2.6% of all surgically treated intrathoracic tumors. Since benign intrathoracic tumors need not be notified to national cancer registries, and since the general autopsy rate is only about 30% in Finland (Statistics Finland 1999), our figures are not comparable with the previous studies (McDonald et al. 1945, Rubin & Berkman 1952) comprising more than 8,000 autopsies, in which the incidence of hamartoma was 0.25–0.33%.

In conclusion, our prospective study indicated that about 5% of all intrathoracic tumors are benign. Although bronchoscopy and CT were always performed, thoracotomy could not be avoided in two-thirds of the patients.
7. Conclusions

1. The incidence of lung cancer has decreased significantly among males but increased among females, the increase being mainly due to adenocarcinoma.

2. The overall 5-year survival of patients with lung cancer has increased significantly during the past twenty years, and especially the prognosis of patients with non-small-cell lung cancer is better now than 20 years ago. The improved prognosis is mainly associated with the surgical treatment of these patients. The five-year survival of patients with small-cell lung cancer has remained the same.

3. The lung cancers of patients exposed to asbestos fibers are more often p53-positive than those without exposure to asbestos fibers. This suggests that the carcinogenetic effect of asbestos fibers is mediated through p53 gene mutation.

4. About five percent of all suspected intrathoracic tumors are benign, hamartoma being the most common benign tumor. Despite the modern investigation methods, CT and fiberbronchoscopy, thoracotomy can not be avoided in most of these cases.
8. References


