

# Lung cancer in a defined geographical area: history and histological types

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**ABSTRACT** Lung cancer was diagnosed in 446 patients during four years in a population living in a defined geographical area in northern Finland. The series comprised 420 men and 26 women, with a male/female ratio of 16.6:1. The diagnosis was confirmed histologically or cytologically in 431 cases (97%). Epidermoid carcinoma was the most common histological type of tumour in the men, followed by small cell anaplastic and adenocarcinoma, whereas in the women all these types were of equal frequency. Almost all the men, but only about half of the women, were smokers or ex-smokers. The amount smoked daily had no correlation with the histological type of cancer, whereas those patients who had started smoking early had relatively more Kreyberg group I tumours (epidermoid, small cell, and large cell carcinoma) than those who had started smoking late. Cancer was usually detected on the basis of symptoms, but 17% emerged from mass radiography or some health examination, and 12% from examinations for another disease. Fifteen per cent of the patients had no symptoms at the time of diagnosis, this being more common among the patients with epidermoid or adenocarcinoma than among those with anaplastic forms.

A hospital series of patients gives a distorted or defective picture of a disease. Even in the case of a serious disease such as cancer, the patients may be treated in different wards or departments according to the apparent stage of the disease and this is reflected in the series compiled from the respective wards. Some patients at an advanced stage of cancer may not be admitted to hospital at all, and if no special attention is paid to a disease, some cases of it almost certainly remain undiagnosed. This may happen among old people in particular, if the exact diagnosis appears to be of little consequence for the patient's outcome.

In 1968 we began a survey for the purpose of studying prospectively all cases of lung cancer diagnosed during four years in the population living in a limited geographical area. We wanted especially to examine the distribution of various histological types of bronchial carcinoma, the clinical picture, and the prognosis. The project was carried through as planned, giving a total of 446 cases of lung cancer diagnosed in this unselected population over the four years. We

describe here the history and distribution of the histological types in these 446 patients.

## Location and time of survey

The survey area consisted of the tuberculosis hospital district of Northern Ostrobothnia in northern Finland, with a population of 297 339 people at the end of 1970. The district is sparsely populated but includes two towns, Oulu (population 85 000) and Kajaani (population 20 000). The largest industrial undertakings are two large pulp mills and one chemical factory in Oulu, and one pulp mill in Kajaani. These industrial areas and their vicinity are often contaminated with foul-smelling mercaptans (pulp mills), or transiently with very low concentrations of ammonia, hydrogen sulphide, and sulphur dioxide (chemical factory) but in the residential areas the air is clean without any general air pollution worth mentioning.

All subjects within this district who had lung cancer diagnosed between 1 January 1968 and 31 December 1971 were included. The date of diagnosis was taken as the day when a doctor first suspected lung cancer or, indeed, any lung disease and sent the patient to hospital. For this

purpose, every doctor practising in the area was informed of the survey by a letter twice a year and was asked to send every patient with diagnosed or suspected lung cancer to Päivärinne Hospital or the University Central Hospital in Oulu for definitive examination and treatment. Other hospitals in the area and their physicians were similarly informed.

## Methods

The necessary clinical examinations were carried out at the hospital in order to verify the diagnosis, and two of the present investigators personally interviewed more than 90% of the patients. Checks against the Finnish Cancer Register and various other sources after the end of the study period, revealed 24 cases of lung cancer diagnosed during the same period which had not been reported to the investigators. The data concerning these patients had to be gathered retrospectively from the records, and were usually defective. All data were transferred to precoded sheets and then to punch cards for computer analysis. The data were recorded at the initial examination, and refer to the time of diagnosis unless otherwise specified. The smoking habits of the patient, however, were recorded as of one year before the diagnosis, according to the patient's own account. In the case of an ex-smoker, the typical amount smoked each day was accepted.

The diagnosis and classification of lung cancer were usually based on a biopsy obtained at bronchoscopy, mediastinoscopy, or thoracotomy, or a tissue specimen obtained at necropsy. The number of lung resections was 72 (16%), and that of necropsies 138 (31%). In a few cases the biopsy was obtained from the pleura or cervical lymph nodes, and in one case from the axillary lymph nodes. A histological diagnosis was possible in 376 cases (84%). In 338 cases the tissue specimen was from primary tumour, including all biopsies taken at bronchoscopy, and 38 cases from a metastasis. If no tissue was obtained for histological examination, the diagnosis was made cytologically from sputum, bronchial washings, pleural fluid, or a sample obtained through needle aspiration of the lesion using a disposable lumbar puncture needle with an outer diameter of 1 mm.

The histological specimens were processed and stained as suggested by the working group of the World Health Organisation.<sup>1</sup> Additional sections were also stained with haematoxylin—van Gieson, haematoxylin—eosin, and according to Ladewig<sup>2</sup>

in all cases where sufficient material was available. The cytological samples were fixed in 50% ethyl alcohol and stained according to Papanicolaou. Pleural fluids and samples obtained by needle aspiration of the lesion were usually processed by the millipore filter technique before staining. Two pathologists examined all the slides independently. If they disagreed on the diagnosis, the problem was resolved by consultation. The lung cancers were classified into five groups according to their histological or cytological picture<sup>1</sup>: (1) epidermoid carcinoma, (2) small cell anaplastic carcinoma, (3) adenocarcinoma, (4) large cell anaplastic carcinoma, and (5) other or unclassified forms. The last group included mainly cases where the diagnosis of a malignant tumour could be made but the sample was inadequate for further classification, but there were also a few cases of sarcomas and rarer carcinomas that were not included in groups (1) to (4), and one case of malignant histiocytosis. Although in principle all primary malignant tumours of the lung were included in the series, we decided to exclude patients with bronchial carcinoids (only one case of which was diagnosed during the period concerned).

## Results

The 446 cases of lung cancer included 15 men in whom the diagnosis was based only on clinical findings without histological or cytological confirmation (table 1). The series included 420 men (94%) and 26 women (6%), giving a male/female ratio of 16.6:1. The age distribution of the patients is shown in the figure. No notable difference of ages was found between the men and the women, the mean for the men at diagnosis being 61.8 years (SD 9.0 years), and that for the women 62.3 years (SD 10.3 years). Only two patients, both men, were under 40 years.

### HISTOLOGICAL TYPES

The distribution of the cases by histological type is shown in tables 2 and 3; only the patients with a confirmed diagnosis are included. Among the

Table 1 Confirmation of diagnosis in 446 patients with lung cancer

	Men		Women		Total	
	Number	%	Number	%	Number	%
Histological	350	83	26	100	376	84
Cytological	55	13	—	—	55	12
No confirmation	15	4	—	—	15	3
Total	420	100	26	100	446	100

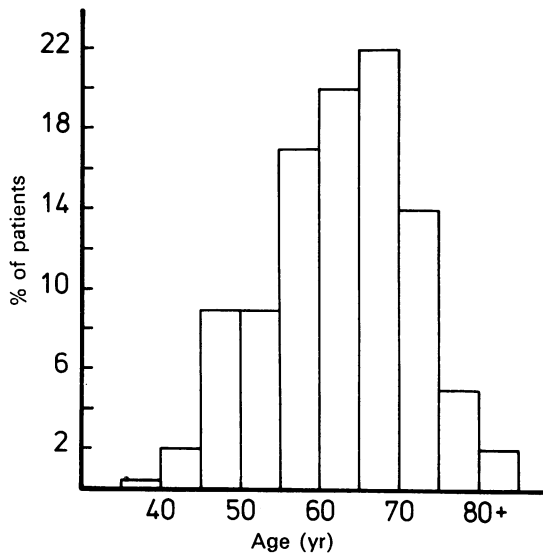


Figure Age distribution of patients.

men, 47% of the cases consisted of epidermoid carcinoma (53% excluding the other/unclassified forms) and 27% of small cell carcinoma (30% excluding other/unclassified forms). Adenocarcinoma and large cell carcinoma showed a lower prevalence. The proportion of unclassified forms was high among the men with only cytological confirmation of the diagnosis.

Epidermoid, small cell, and adenocarcinoma were of similar frequency in the women, and the distribution into the four main histological types differed significantly between the men and women ( $\chi^2=9.93$ ; 3 df;  $p<0.02$ ). The male/female ratios for epidermoid, small cell, adenocarcinoma, and large cell carcinomas were 27, 15, 6, and 6 respectively.

The patients with anaplastic forms of carcinoma were younger than the others (table 4), the differences being significant, even though small

Table 2 Histological type of bronchial carcinoma in 405 men with a histological or cytological confirmation of malignancy

	Histological confirmation		Cytological confirmation		Total	
	Number	%	Number	%	Number	%
Epidermoid	159	45	32	58	191	47
Small cell anaplastic	105	30	3	5	108	27
Adenocarcinoma	37	11	6	11	43	11
Large cell anaplastic	18	5	—	—	18	4
Other/unclassified	31	9	14	25	45	11
Total	350	100	55	100	405	100

Table 3 Histological type of bronchial carcinoma in 26 women. All cases histologically confirmed

	Number	%
Epidermoid	7	27
Small cell anaplastic	7	27
Adenocarcinoma	7	27
Large cell anaplastic	3	12
Other/unclassified	2	8
Total	26	100

Table 4 Age at diagnosis in the various groups of lung cancer cases

	Number of patients	Mean age (yr)	SD
Epidermoid	198	62.6	8.5
Small cell anaplastic	115	60.8	8.7
Adenocarcinoma	50	61.8	10.2
Large cell anaplastic	21	58.2	9.0
Other/unclassified	47	62.0	11.2
Not confirmed	15	66.2	7.5
Total	446	61.9	9.1

Not confirmed = diagnosis not histologically/cytologically confirmed.

( $F=5.47$ ,  $p<0.01$  for the four classified groups). The patients without confirmation of diagnosis were older than the others.

#### SMOKING HABITS

The smoking habits were known for 400 men and 24 women. Only two men and 13 women were lifelong non-smokers, the others all being ex-smokers or smokers. Of the smokers and ex-smokers, only 12 men and four women had been smoking for less than 25 years, hence smoking was of long duration among these patients. When the smokers and ex-smokers were divided into three groups according to the amount smoked daily (1–14 g, 15–24 g, and 25+g; one cigarette was assumed to contain one gram of tobacco), no significant difference in the distribution of histological types was seen between these groups.

There were 338 patients who were either smokers or ex-smokers and who had epidermoid, small cell, or large cell carcinoma (Kreyberg group I) or adenocarcinoma (Kreyberg group II), 206 of whom had started smoking under the age of 20 years, and 132 at 20 years of age or older. The former group included 189 patients (92%) with a Kreyberg group I tumour and 14 (8%) with adenocarcinoma, and the latter 111 (84%) and 21 (16%) respectively.

#### MODE OF DETECTION

The cause for the initial examination was known in the case of 445 patients (table 5). Most had experienced symptoms of lung cancer, but in 77

Table 5 Initial cause for examination in the various groups of lung cancer cases

Number of patients	Histological group												Total Number	%
	Epidermoid		Small cell		Adeno- carcinoma		Large cell		Unclassified		Not confirmed			
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Mass radiography or other health examination	40	20	12	10	11	22	2	10	10	21	2	13	77	17
Other illness	22	11	16	14	5	10	3	14	6	13	1	7	53	12
Own initiative because of symptoms	135	69	87	76	34	68	16	76	31	66	12	80	315	71

n one case the cause for examination was not known.  
Not confirmed = diagnosis not histologically/cytologically confirmed.

Table 6 Prevalence of symptoms (%) in patients with various types of lung cancer

Number of patients	Epidermoid	Small cell	Adenocarcinoma	Large cell	Other/ unclassified	Not confirmed	Total
	194	113	50	21	47	14	439
Cough	46	50	42	52	43	36	46
Sputum	31	40	24	38	23	29	32
Loss of weight	32	37	28	33	23	14	32
Breathlessness	27	38	34	29	28	7	30
Chest pain	21	40	48	33	19	36	30
Haemoptysis	32	26	12	38	26	14	27
Fever	31	27	20	33	30	21	28
Fatigue	10	12	10	14	9	7	10
Other symptoms	7	8	4	5	11	21	8
No symptoms	16	8	18	14	21	14	15

In seven patients the occurrence of symptoms could not be ascertained.  
Not confirmed = diagnosis not histologically/cytologically confirmed.

cases (17%) it was first suspected on the basis of a chest radiograph taken at a mass radiography or other health examination, and in 53 (12%) it was detected at an examination for another disease. There were no significant differences in the mode of detection between the men and the women. In the combined group of epidermoid and adenocarcinomas, 21% of the cases were detected on the basis of mass radiography or other health examination, whereas in the combined group of small cell and large cell anaplastic carcinomas the figure was only 10% ( $\chi^2=5.96$ ; 1 df;  $p<0.02$ ).

**SYMPTOMS**

The symptoms complained of at the time of diagnosis were known in the case of 439 patients. We have tried to include only those symptoms that were probably caused by lung cancer, and have hence arbitrarily excluded those that had been present for more than five years before diagnosis and had not changed in severity during this time. This limitation proved to be of importance only in a few patients with long-standing cough and sputum, obviously caused by chronic bronchitis. All other symptoms could be included.

The prevalence of symptoms is shown in table 6. The most common symptom was cough, occurring in about a half of the patients. Sputum production, loss of weight, breathlessness, chest pain, haemoptysis, and fever were of equal frequency, and only 10% of the patients complained of fatigue. Other symptoms—hoarseness, vertigo and so on—were not common and 15% of the patients had no symptoms at all.

The prevalence of symptoms varied in the various histological groups (table 6). On the whole, they tended to be more common in the patients with small cell or large cell anaplastic carcinoma than in the other groups.

The only notable difference between the men and the women was in sputum production: 136 men (33%) but only four women (15%) had

Table 7 Duration of symptoms before diagnosis in 430 patients with lung cancer

	Men		Women		Total	
	Number	%	Number	%	Number	%
< 6 months	329	81	15	60	344	80
6 months -	48	12	6	24	54	13
1 year -	28	7	4	16	32	7
Total	405	100	25	100	430	100

In 16 patients the duration of symptoms was not known.

sputum. All the other differences were smaller and none was significant.

A total of 344 patients (80% of those for whom information was available) had had symptoms for less than six months before diagnosis (table 7). Long-standing symptoms were more common in the women than in the men ( $\chi^2=6.70$ ; 2 df;  $p<0.05$ ), but no notable or significant differences in the duration of symptoms were found between the various histological groups.

## Discussion

An important feature of the present series of patients is that all cases of lung cancer occurring during a period of four years in a defined yet unselected population are included and studied prospectively. Most previous series have been selected in some way which makes comparison with the present one difficult or unjustified. The cancer register for a country or a limited geographical area should in principle contain all cases of cancer from the population concerned, but the data in cancer registers are often incomplete, and it is difficult or impossible to obtain the required information from the case records afterwards. This was realised in the 24 cases which came to light only after the end of the study period. It is also obvious that even in a well-functioning register the number of cases recorded is lower than the real incidence of cancer. Chiazzo<sup>3</sup> has shown that the incidence of lung cancer in Allegheny County, Pennsylvania, as detected in the morbidity survey, was underestimated by 12.3% from the data in the cancer register. Case registers may be incomplete because of under-reporting, but it is also obvious that more cases will be found where special attention is paid to a certain disease. Even though the number of cases reported to the register may approach the real incidence, the detailed information may be imperfect or erroneous—for example, regarding the histological types of lung cancer.<sup>4</sup>

The male/female ratio was high, but even higher ratios have been found in previous Finnish series.<sup>5-8</sup> Among those lung cancer patients reported to the Finnish Cancer Register from 1968 to 1971,<sup>9-12</sup> the male/female ratio was 11.1, which is clearly less than in the present series, and lower ratios still have frequently been found in other countries.<sup>13</sup> The higher male/female ratios in the Finnish series may be attributable to the fact that smoking among women was not as common in the past as it was elsewhere.

The men and women were of similar age, and the largest number of patients came from the age group of 65 to 69 years. The age distribution in different series of cancer patients is modified by many factors, but on the whole it seems that in recent years an increasing proportion of lung cancer has originated in the older age groups and the mean age of the patients is rising.<sup>14-18</sup>

The diagnosis was confirmed histologically or cytologically in 97% of the cases, and only in 15 men was it based on a chest radiograph and other "clinical" findings. In four of these obvious cancer tissue was seen at bronchoscopy, but no biopsy was obtained, or else the tissue sample was necrotic and did not allow histological diagnosis. All bronchoscopies were carried out using a rigid bronchoscope. If a fiberoptic bronchoscope had been available, a histological diagnosis might have been achieved more often. Histological confirmation of the diagnosis was possible in 371 of the patients (84%). A bronchial biopsy is not always representative of the tumour as a whole, and another histological type may be found in larger tissue sections obtained at operation or necropsy. On the whole, however, bronchial biopsy or even biopsy from a lymph node metastasis seems to be a good indicator of the type of primary tumour,<sup>19-22</sup> and the cell type can usually be determined from a cytological sample if the proper technique<sup>23-24</sup> is used. However, the typing of adenocarcinoma may be difficult on the basis of cytological samples alone,<sup>23, 25</sup> and even a histological biopsy may not allow the differentiation between primary and secondary adenocarcinoma. Hence, necropsies were often performed when adenocarcinoma was suspected, the necropsy rate in these cases being 56% (28/50) whereas it was only 31% (138/446) in the total series. Similarly, the diagnosis of a large cell carcinoma was based on findings at necropsy in 11 cases (52%). We did not attempt classification if the cytological or histological findings were not definite, hence the number of unclassified cancers is relatively large.

The typing of tumours was as suggested by the World Health Organisation Committee,<sup>1</sup> and the same two pathologists examined all the slides. The proportion of the various histological types of lung cancer varies considerably in published series.<sup>13</sup> This may be partly explained by the selection of the patients, and by the inter-observer variation in typing noted in many previous studies,<sup>26-28</sup> but the distribution of histological types may also be genuinely different in different populations or geographical areas. Epidermoid carcinoma was more common in the

men than in the women, and adenocarcinoma less so, but the number of women was small, and hence the results should be treated with caution. Adenocarcinoma has usually proved the most common type in women,<sup>13</sup> but it has been suggested that its incidence may be increasing among men.<sup>29</sup> In a survey of all patients with lung carcinoma diagnosed in a defined area in Sweden during a period of five years (from 1971 to 1976), comprising 273 patients,<sup>30</sup> the diagnosis was histologically or cytologically confirmed in all cases and 95% of those who died had necropsies. The distribution of the patients into WHO groups I, II, III, and IV<sup>1</sup> was 53%, 20%, 19%, and 8% in the men, and 12%, 12%, 62%, and 15% in the women respectively. Hence, the proportion of patients with adenocarcinoma in this recent series was higher than among our patients. It is not clear why adenocarcinoma was not more common in our series. We tried carefully to exclude all patients with primary tumours elsewhere and only secondaries in the lungs, but so did Nöu<sup>30</sup> Smoking was relatively common among our female patients, about 50% of them being smokers or ex-smokers, whereas in Nöu's series only 35% of the women were smokers.

Kreyberg<sup>31</sup> divides lung carcinomas into two groups: group I, comprising epidermoid, small cell, and large cell carcinomas, and group II composed mainly of adenocarcinomas, and suggests<sup>32</sup> that smoking increases the incidence of group I tumours in particular. The present series contained too few male and female non-smokers to enable conclusions to be drawn on the distribution of the histological types among them, and we found no association between the amount smoked daily and any particular histological type, although the patients who started smoking early had more Kreyberg group I tumours and less adenocarcinomas than those who started smoking later. Conflicting reports are given in the literature on the effect of smoking on the cell type in lung cancer. Doll *et al*<sup>33</sup> found a dose-response relationship for smoking with squamous and small cell carcinomas, but not with adenocarcinomas, and Herrold<sup>20</sup> noted more squamous and oat cell tumours in current smokers than in non-smokers, but no correlation between the histological type and the amount smoked or the age of starting smoking. In the investigation of Weiss *et al*<sup>34</sup> well-differentiated squamous cell carcinoma, small cell carcinoma, and adenocarcinoma showed a dose-response relationship with cigarette smoking, but poorly differentiated squamous cell carcinoma did not. Yesner *et al*<sup>27</sup> reported that adenocarcinoma was the most com-

mon cell type among patients who did not smoke cigarettes, while among cigarette smokers the amount of smoking seemed to be related to the prevalence of small cell carcinoma but not to that of epidermoid or other cell types. Auerbach *et al*<sup>35</sup> found a greater percentage of small cell tumours in heavy than in light smokers, but only in men below 70 years of age. The question of the relation between the amount smoked or the age of starting smoking and the cell type of lung cancer remains unsettled at present. The variable results may be partly caused by difficulties in determining the amount of smoking at earlier ages. Moreover it is obvious that large cell carcinoma forms a heterogenous group, and Kreyberg<sup>36</sup> has later excluded it from his group I tumours. The chromosomal distribution of large cell carcinoma may mimic that of pulmonary adenocarcinoma,<sup>37</sup> and intracytoplasmic mucin can be demonstrated in one of its subgroups.<sup>1</sup> The present series shows similar male/female ratios for the patients with adenocarcinoma and large cell carcinoma, and it is probable that at least some of the latter should more properly be classified as adenocarcinomas.

The patients with small cell or large cell carcinoma were younger on average than those with epidermoid or adenocarcinoma. Theoretically, younger patients should have more anaplastic, fast growing cancers than older patients,<sup>38</sup> and small cell and large cell carcinomas have indeed been found more often in younger age groups in many series, or else the patients with these types have been younger than those with more slowly growing cancers, but the differences have been slight and not always significant.<sup>30 39-41</sup> It is understandable that the patients without histological or cytological confirmation of their diagnosis should have been the oldest group, since complicated diagnostic procedures were avoided in old patients if confirmation seemed to be of little importance to the fate of the patient.

Seventeen per cent of all cases were first found at mass radiography or some other health examination. This proportion is similar to the 19% reported by Nöu,<sup>30</sup> also in a series comprising all patients from a limited geographical area. Regular surveys of all people above 15 years of age by miniature chest radiography were performed every three years in both populations. Approximately one-fifth of the epidermoid and adenocarcinomas, but only one-tenth of the small cell and large cell carcinomas, were found in this way (table 5). This evidently derives from the fact that the patients with the former types

of cancer remain symptomless more often or longer than those with the latter types (table 6), for symptomless cases were about twice as frequent among the patients with epidermoid or adenocarcinoma as among those with anaplastic carcinomas. On the whole, the proportion of the patients without symptoms was rather larger compared with previous series.<sup>6 7 39 42 43</sup> The prevalence of various symptoms is highly variable,<sup>44</sup> but selective factors probably explain the differences between the series.

The finding that the women had longstanding symptoms more often than the men (table 7) should be interpreted cautiously because of the small number of women, but the series included every case of lung cancer in a defined population, and it is possible that women pay less attention to their symptoms than men. Half of the women were non-smokers, and so far the likelihood of lung cancer has been emphasised among smokers in particular. The men may thus have consulted a doctor more readily than the women when respiratory symptoms appeared.

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