Lung cancer in males
An epidemiological study in northern Sweden
with special regard to smoking and occupation

by
LENA DAMBER

Umeå 1986
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av
LENA DAMBER

Umeå 1986
ABSTRACT

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Lena Damber, Department of Oncology, University of Umeå, S-901 87 Umeå, Sweden.

In a case-control study comprising 589 cases of male lung cancer in northern Sweden longitudinal data concerning occupations, employments and smoking habits were collected by questionnaires.

Pipe smoking was as common as cigarette smoking and gave very similar relative risk. The pipe smoking cases, however, had significantly higher mean age and mean smoking years at the time of diagnosis than the cigarette smoking cases. In ex-smokers, the relative risk gradually decreased from 5 years after smoking cessation but this decrease was much less pronounced in ex-pipe smokers than in ex-cigarette smokers. High relative risks were obtained for small cell and squamous cell carcinomas. For adenocarcinoma the relative risk was considerably lower but still significantly increased. The population etiologic fraction attributable to smoking was about 80% in this series.

Some occupational groups (underground miners, copper smelter workers, electricians and plumbers) exposed to previously known lung carcinogenic agents had considerably increased odds ratios, which persisted after adjustment for smoking. A slightly elevated odds ratio was observed in a group of blue collar workers potentially exposed to lung carcinogenic agents but this elevation generally disappeared after adjustment for smoking. For two specific subgroups, asphalt and concrete workers and pulp workers, the overrisk persisted after adjustment for smoking. Farmers and foresters had strikingly low odds ratios, which could only partly be explained by their more moderate smoking habits. The population etiologic fraction attributable to occupation was in the reported material assessed to 9 per cent.

Professional drivers had higher average tobacco consumption than non-drivers, which explained the slightly increased crude odds ratio found for the occupational group as a whole. Smoking drivers in an upper age group (70 and over), however, had a high relative risk of lung cancer, while in a lower age group (under 70) no significant increase was found. The results in the older age group suggested a multiplicative effect between smoking and the occupational exposure.

The study clearly verified the increased lung cancer risk in underground miners. An obvious dose-response relation was found with high risk after long time exposure. All analyses concerning underground miners suggested an interaction of a multiplicative type between underground mining and smoking in the causation of lung cancer. The cases of small cell carcinoma among the underground miners had shorter average latency time and in contrast to the other part of the material, shorter average age than the cases with epidermoid cancer.

Key-words: case-control study, epidemiology, lung cancer, occupational risk factors, smoking, radon, cell types, validity.
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To
Janne
Helena, Sara and Erik
This thesis is based on the following papers:


V. Damber L, Larsson L-G: Lung cancer in males and type of dwelling. An epidemiological pilot study. Accepted for publication in Acta Radiol Oncol.


In the text these papers will be referred to by their Roman numerals.
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INTRODUCTION

In many countries the lung cancer incidence rate has increased rapidly during recent decades. Large differences in incidence or mortality rates exist between different parts of the world and have also been observed within several countries (1, 2, 3, 4); generally higher rates have been found in large metropolitan regions than in urban areas. Remarkably low rates have been observed in special religious groups as Mormons and Seventh-Day Adventists in the USA (5, 6). As for most types of malignant tumours such differences are at present regarded mainly as expressions of differences in life-style and/or other environmental factors.

Tobacco smoking is recognized today as the dominating cause of lung cancer. This is supported by many epidemiological investigations (cf 7). In several Western countries, such as the US, the UK and Sweden, it has been estimated that smoking is responsible for about 80-90 percent (population etiologic factor) of all lung cancer cases in males (8, 9, 10). A dose-response relationship between cigarette smoking and the risk of lung cancer has been well established in several studies (cf 7).

Several chemical and physical agents are identified as lung carcinogenic and can be of considerable importance for specific occupational groups. These agents include radon, asbestos, chromium, arsenic, nickel, mustard gas, bischloromethyl ether and polycyclic hydrocarbons in soot, tar and oil (8). Some of these agents appear to interact synergistically with tobacco smoking (11, 12, 13, 14, 15).

General air pollution (in the form of polycyclic hydrocarbons) has been much discussed concerning lung cancer risk. For several reasons, the size of the risk has been difficult to assess by epidemiological methods. However, for the individually exposed persons, it seems, to be low compared to smoking and some occupational exposures (8). Another risk factor much discussed in recent years is passive smoking (environmental tobacco smoke). From a theoretical point of view, exposure to passive smoking ought to increase the lung cancer risk, and this is also suggested by some epidemiological studies (16, 17).

Ionising radiation is an epidemiologically fairly well verified cause of lung cancer (18) both as regards photon radiation (x-rays, γ-rays) and α-radiation (radon daughters). Experience from underground miners exposed to high concentration of radon daughters gives convincing evidence about the lung carcinogenic effect of this type of exposure (19). During recent years increased concentrations of indoor
radon (due to building material or leakage from the ground) have caused concern about the lung cancer risk. Some epidemiological studies suggest a risk of increased indoor radon concentrations but, so far there is no firm epidemiological evidence concerning the size of this risk.

Other suspected risk factors for lung cancer that can be mentioned are hereditary differences in the enzymatic modification of some carcinogenic substances (20) and a dietary lack of protective substances as vitamin A (21).

The relationship between risk factors and a specific disease such as lung cancer, can be elucidated by several types of epidemiological investigation. Hypotheses can be generated by descriptive epidemiologic studies showing geographical incidence variations, differences between ethnic groups or time-related trends. Correlation studies (for instance between lung cancer incidence and smoking habits) can give support to a causal interrelation. However, the most convincing evidence for an association between specific risk factors and lung cancer has been obtained using cohort studies and case-control studies. Both types of studies have been extensively used in order to verify or elucidate different risk factors for lung cancer.

The present report is exclusively based on case-control studies in which data were obtained by questionnaires. The incentive for the studies was the finding that the male lung cancer incidence rate within the northern region of Sweden showed large geographic variations, with very low rates in most municipalities in the inner part of the region and considerably higher rates in most coastal municipalities and in the 2 municipalities Kiruna and Gällivare with extensive iron ore mining (22, 23). It was felt that a large case-control study might yield information of interest concerning etiologic factors, particularly smoking and occupational exposures.

The principle aims of the study were:

- to analyse the effects of smoking
- to analyse occupational risk factors and the interaction between such factors and smoking
- to study the possible effects of building material in dwellings (with regard to risks from radon)
MATERIALS AND METHODS

Selection of cases and controls. Data collection.

Paper I - V.
The study comprised male patients with lung cancer diagnosed in the three most northern counties in Sweden. A survey of the Swedish Cancer Registry revealed 660 cases reported from these counties from 1972 to 1977. For ethical reasons, however, only the 620 cases who had died at least one year before the start of the study (May 1979) were included in the investigation. Sixteen cases for whom no close relatives could be found were also excluded before the start of the study. To each of the remaining 604 cases, one deceased control was drawn from the National Registry for Causes of Death, matched according to sex, year of death, age and municipality. Lung cancer cases and suicides were not accepted as controls. The following causes of death were registered among the controls: malignant tumours 20%, cardiovascular diseases 45%, cerebrovascular diseases 9% and other causes 26%. This death cause pattern did not essentially deviate from the general pattern. A living control was also included for each case, and this control did not exceed an age of 80 years. The living controls (467 controls) were drawn from the National Population Registry and matched against the cases according to sex, year of birth and municipality.

Individual information concerning several factors was collected through postal questionnaires for all cases and controls. The questionnaires were answered by close relatives of the cases and of the deceased controls and by the living controls themselves. Both among cases and deceased controls the surrogate respondent was for 50% the wife, 35% an adult child, and 15% other relatives. The respondents were by an introductory letter asked for participation and informed that the study concerned relation between environment and health.

The questionnaire was constructed to yield longitudinal data (time periods) concerning:
1. municipality and type of dwelling (building material and construction year).
2. occupation and employment held for at least 1 year with name of company.
3. smoking habits including year of start, daily number of cigarettes, other types of smoking and year of possible cessation.

The questionnaires answers were scrutinized by a interviewer not physically associated with the department and not knowing whether the answers concerned cases or controls. According to defined control criterias the answers were
supplemented by telephone interviews. All questionnaires with incomplete smoking data were supplemented by telephone interviews, which were required in the same proportion (about 30%) among both cases and controls. Furthermore, all questionnaires with lack of data on municipality, type of dwelling, occupation or employment for any period between age 20 and the time of diagnosis (or corresponding time for the controls) were supplemented. The occupational history required supplementation in about 40% of the cases and the deceased controls, and in about 30% of the living controls.

Answers were obtained in 589 of 604 cases (98%), in 582 of 604 deceased controls (96%) and in 453 of 467 living controls (97%).

The information obtained in the questionnaires was coded. For the occupations a 5-digit code was used (24). Special codes were used for the specific companies.

**Paper VI**

Lung cancer cases reported from the municipalities of Kiruna and Gällivare during the period 1972-1982 were included in this study. Five cases without relatives were excluded before the start of the study. The study material then consisted of 69 cases, each with one deceased control. Sixty of these cases also had one living control. The selection and matching procedures for the controls were the same as described for paper I-V.

The same type of questionnaires and procedures of data collection were used in this study as in the previously described studies. Answers were obtained for all persons with the exception of two deceased controls.

**Statistical methods**

The estimation of odds ratios was performed with dissolved matching in all studies. Several essential results were, however, controlled by parallel analyses with individual matching (25). The effect of the matching was also evaluated by examining the correlation of exposure between cases and their matched controls (26). According to Miettinen (27) the matching can be ignored in the analyses if this correlation coefficient is low. On the whole, low correlation coefficients were obtained in the present study, and the size of the two risk estimates were very similar (Table 1). According to Seigel and Greenhouse (28) the expected odds ratio resulting from an analysis incorporating the matching is always more extreme than the expected odds ratio obtained ignoring the matching. Actually, a tendency
towards somewhat higher estimates was obtained with individual matching in the present study.

Table 1. Comparison between relative risks calculated with and without dissolved matching

<table>
<thead>
<tr>
<th>Absolute value of the correlation coefficient</th>
<th>Paper</th>
<th>Factor</th>
<th>Odds ratios estimated with individual matching</th>
<th>Odds ratios estimated with dissolved matching</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>Paper I</td>
<td>smoking in general</td>
<td>8.1</td>
<td>7.3</td>
</tr>
<tr>
<td>0.10</td>
<td>Paper II</td>
<td>plumbers and electricians</td>
<td>1.7</td>
<td>1.9</td>
</tr>
<tr>
<td>0.08</td>
<td>Paper II</td>
<td>pulp workers</td>
<td>1.8</td>
<td>1.7</td>
</tr>
<tr>
<td>0.04</td>
<td>Paper III</td>
<td>professional driving</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>0.17</td>
<td>Paper IV</td>
<td>underground mining</td>
<td>3.1</td>
<td>2.5</td>
</tr>
<tr>
<td>0.05</td>
<td>Paper V</td>
<td>non-wooden houses</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>0.02</td>
<td>Paper VI</td>
<td>underground mining</td>
<td>5.2</td>
<td>4.6</td>
</tr>
</tbody>
</table>

Test-based confidence intervals were estimated in paper III and IV according to Miettinen (29). A method for calculation of exact confidence limits (30) was consistently used in papers I, II, V and VI and for small subgroups in paper III. Miettinen's method produces a valid confidence interval for odds ratios only rather close to unity (31, 32). The exact confidence limits are therefore used in most analyses.

The homogeneity of the odds ratio across age strata was tested with an asymptotic likelihood test (27). If a heterogeneity of the odds ratio was found, the analyses were performed with separate age groups. Otherwise, the age adjusted relative risks were computed by the Mantel and Haenzel method (33).
The estimate of the population etiologic fraction (EF_{pop}) in all studies was calculated according to the formula: EF_{pop} = CF_{E_x} \times (RR - 1)/RR, where CF_{E_x} is the case fraction (proportion of exposed cases and RR relative risk) (34).

To study occupational exposure with adjustment for smoking, a logistic model was used in paper II, with three discrete levels of occupational exposure and four levels of life-time tobacco consumption used in the analyses. In paper VI the logistic model was used to elucidate the joint effects of underground mining and smoking. Maximum likelihood estimates were performed for the logistic regression coefficients (35). An index of synergy was estimated on the basis of principles described by Rothman (36, 37) and was used in papers III and VI to assess deviation from additivity.
METHODOLOGICAL CONSIDERATIONS

Representativity of the cases
At the start of this study in 1979, the Swedish Cancer Registry suffered from several years of delay in data entry. The lung cancer cases for the years 1975-1977 were therefore collected manually among the notifications from the counties studied. Due to incomplete sorting at the registry, 90 cases were lost in this collection. Including cases without close relatives and cases collected from the register but alive in May 1978 (and therefore excluded from the study), the total deficit was 146 cases (19%) of the 750 cases registered in all. There were no obvious differences in distribution of age and microscopic types between the total registry material and the study material (Table 2).

Table 2. Distribution of microscopic types for the total registry material and the study material.

<table>
<thead>
<tr>
<th>Microscopic type</th>
<th>The 604 cases</th>
<th>The 750 cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>bronchiolar and alveolar ca</td>
<td>076 1</td>
<td>2</td>
</tr>
<tr>
<td>Adenoca</td>
<td>096 13</td>
<td>13</td>
</tr>
<tr>
<td>Squamous cell ca</td>
<td>146 46</td>
<td>49</td>
</tr>
<tr>
<td>Unspecified ca incl small cell ca</td>
<td>196 40</td>
<td>36</td>
</tr>
<tr>
<td>Mean age</td>
<td>68 year</td>
<td>67 year</td>
</tr>
</tbody>
</table>

Microscopic types of cancer
Copies of all cytology and histopathology reports were collected. The reports were read by one oncologist (L.-G. L.). In cases with questionable lung cancer diagnosis copies of the hospital records were also collected. From this material, the cases were classified in the following groups:
Groups 7 and 8 were very small in relation to the total material and were included in papers II-V. However, in papers III and V none of the cases with the specifically studied occupational exposures (professional drivers and underground miners, respectively) belonged to groups 7 and 8. In paper I, these groups were excluded from the analyses.

Completeness and validity of the data

Smoking habits

In order to elucidate the reliability of smoking data collected by questionnaires to close relatives, these data, for a sample of the cases, were compared to data in hospital records deriving from the patients themselves. This sample (86 cases) consisted of all cases admitted to the department for respiratory diseases at the University Hospital in Umeå. It was the routine in this department to register fairly detailed smoking histories. The result of this comparison is illustrated in Fig. 1. Among the 86 patients, 3 had no smoking data registered in the records. For the remaining 83 cases, the two sources showed good agreement (99%) as regards discrimination between smokers and non-smokers. In 53 records, information about the total number of smoking years was available. The average number of smoking years given in the questionnaires was 47.9 and in the records 47.7. The individual difference was < 5 years in 39 of the 53 smokers.
It was possible to distinguish between cigarette, pipe or cigar smokers in 61 records, and the agreement between the two sources was good in 48 of these. In 37 of these records, the daily tobacco consumption was registered. This could be used for stratification into low, moderate and heavy tobacco consumers. According to this stratification, the information in 31 of these records agreed with the questionnaires. In 5 of the 6 records, with disagreement between the two sources, the relatives had reported a higher tobacco consumption than the subjects themselves.

**Figure 1. Comparison between smoking data from questionnaires answered by close relatives and from hospital records.**

**Occupation**

The years between age 20 and the time of diagnosis or retirement were well-surveyed concerning the occupational history both for cases and controls. Including education periods, time of sick-leave, pension and unemployment, this period could be mapped out in an average of 44.3 years for the cases, 44.9 years for the deceased controls and 41.7 years for the living controls. If only the real occupation time was included the corresponding figures were 38.9 y, 38.4 y and 38.1 y respectively.
The answers deriving from two specific occupation groups, the non-iron miners and the copper smelter workers, were controlled against employment registers in order to validate the information obtained from the questionnaires. The first of these groups consisted of 10 cases and 11 controls which had been employed by one company (Boliden). Only 2 of the 21 questionnaires were misleading concerning underground work (+ 8 years and - 6 years). In none of the remaining 19 questionnaires did the data about underground work deviate more than one year from the register.

The second occupational group consisted of employees at a copper smelter (Rönnskärsvverken). The lung cancer risk among these employees had previously been analysed in a cohort study including all male workers, employed at least 3 months any time between 1928 and 1966 (38). Of the total number of 76 lung cancer cases found in the cohort, 26 were included in the present study. In 25 of these cases, the employment at the smelter was obvious in the questionnaires. Three of these 25 cases were employed less than 1 year and were therefore not classified as copper smelter workers in the present study. In 21 cases data in the questionnaires concerning length of employment could be compared with corresponding data in the cohort, which derived from the employment register at the factory. In only one of the 21 cases did the declared length of employment time deviate more than 2 years from the registry data.

Municipality
As regards municipality, the time period between age 20 and time of diagnosis for the cases (corresponding time for the controls) was well covered in the answers. Only a mean of 1 year per case and 1/3 year per control was missing. To study the validity of these data, a sample of cases and controls were selected. This sample consisted of all cases who lived in one specific municipality (Sundsvall) at the time of diagnosis and their controls. Information about all municipalities where these cases and controls had lived during their life-time was obtained from the parish authorities. This information was compared with data in the questionnaires from the age of 20 years and forwards. By accepting a difference of 4 years between the two sources, agreement was obtained in 79% of the cases, 86% of the deceased controls and 85% of the living controls. (Table 3). In only 2% of the cases, 5% of the deceased controls and 3% of the living controls the questionnaires gave data that deviated with more than 20 years from the truth. The data between the birth and the age of 20 years was, however, more often omitted or inadequate in the questionnaires. Information about municipalities covering the whole period from
birth to diagnosis (corresponding time for controls) was thus obtained in only 65% of the cases, 69% of the deceased controls and 74% of the living controls. A tendency to more complete and sufficient data was obtained by self-respondents (living controls), especially regards the early lifetime. However, the difference in data quality between surrogate- and self-respondents was less pronounced than expected.

Table 3. Data about municipalities obtained by the questionnaires compared to data from the parish authorities. Concerns only data after age 20.

<table>
<thead>
<tr>
<th>Difference in years</th>
<th>Cases No.</th>
<th>Deceased controls No.</th>
<th>Living controls No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4</td>
<td>72</td>
<td>78</td>
<td>53</td>
</tr>
<tr>
<td>5-10</td>
<td>10</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>11-20</td>
<td>7</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>&gt;20</td>
<td>2</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>91</td>
<td>91</td>
<td>62</td>
</tr>
</tbody>
</table>

Building material
A special study of the validity of the information in the questionnaires concerning building materials was performed at the National Institute of Environmental Medicine (39). For a sample of 30 cases and 30 deceased controls, the data given by the surrogate responders were compared to information obtained from the local public health boards. The analysis concerned 54 of these 60 persons, for whom data were obtained from both sources and only dwelling periods longer than 2 years were included. As regards 2 broad categories of building material, wood/not wood, the information was identical for 117 of 121 dwellings in the two sources (Table 4).
Table 4. Comparison of data on building material of dwellings for deceased subjects obtained from a next-of-kin and from local public health boards.

<table>
<thead>
<tr>
<th></th>
<th>Wood</th>
<th>Not wood</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public health</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>wood</td>
<td>90</td>
<td>3</td>
<td>93</td>
</tr>
<tr>
<td>Not wood</td>
<td>1</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>Total</td>
<td>91</td>
<td>30</td>
<td>121</td>
</tr>
</tbody>
</table>

Concerning specific type of non-wood building material (such as lightweight concrete) the questionnaires did not give useful information. No question about the basement construction was included, as leakage of radon from the ground not was recognized as a source of indoor radon when the present study started.

Comparison between cases and controls
The material included the following groups of cases and controls:

(a) all cases
(b) cases born after 1900
(c) all deceased controls
(d) deceased controls born after 1900
(e) all living controls (born after 1900)

In papers I and II cases (a) were compared to controls (c) (study model A) and cases (b) compared to controls (e) (study model B).

In papers III, IV and V cases (a) were compared to controls (c) (study model I) and cases (b) compared to controls (d) + (e) (study model II).

In the different papers and in the thesis, estimates based on study model B or II are presented in parentheses after the estimates based on study model A or I.

The philosophy behind the different comparisons is discussed under Comments and conclusions.
RESULTS

Smoking and lung cancer (Paper I)
In this study the material was used for analyses concerning the lung cancer risk of smoking with special emphasis on dose-response relations, type of smoking, type of cancer and effects of smoking cessation.

The information from the questionnaires concerning smoking habits included approximate year of start of smoking, daily number of cigarettes, other types of smoking and year of possible cessation of smoking:

Smokers □ Yes □ No
If the answer is yes:
Age at which smoking began .......... Smoking break more than 1 year ..........

Cigarettes
□ occasionally
□ 1-7 cig/day
□ 8-15 cig/day
□ 16-25 cig/day
□ more than 25 cig/day

Pipe
□ occasionally
□ less than 1 packet (100 gr)/week
□ more than 1 packet (100 gr)/week

Cigarillos
□ occasionally
□ 1-4 cigarillos/day
□ 5-10 cigarillos/day
□ more than 10 cigarillos/day

Cigars
□ occasionally
□ 1-2 cigars/day
□ more than 2 cigars/day

Stopped smoking □ Yes □ No
If yes, at which age? ...........

Individuals who had smoked at least one cigarette daily or equivalent amount of tobacco for one year or more at any time were classified as smokers. With this definition 93% of the cases, 64% of the deceased controls and 62% of the living controls were smokers. The odds ratios obtained for all smokers were 7.3 in study model A and 9.0 in study model B. The population etiologic fraction attributable to smoking was 80% (83%).
The material in this study included different types of smokers. Pipe smoking was quite as common as cigarette smoking, and also a combination of pipe and cigarettes was frequent, while cigar and cigarillo smokers were rare. The relative risks obtained for pure cigarette smokers was 7.0 (9.2), for pure pipe smokers 6.9 (8.1) and for combination smokers 8.9 (11.8). The pipe smoking cases, however, had significantly higher mean age and mean smoking years at the time of diagnosis than the cigarette smoking cases. With measures such as smoking time, smoking intensity and life-time tobacco consumption obvious dose-response relations were observed both in cigarette and pipe smokers.

The relative risk gradually declined with increasing years of smoking cessation. However, this reduction was dependent upon the previous smoking time and the decrease was less pronounced for smokers with long smoking histories. Furthermore, the decrease of the relative risk in ex-smokers was dependent on the type of smoking and was more pronounced in ex-cigarette smokers than for ex-pipe smokers.

The relative risk for smoking was related to the microscopic subtypes. A strong association between lung cancer and smoking was observed for small cell carcinoma (RR=13.8 (44.6)), squamous cell carcinoma (RR=11.8 (9.8)), and a group of poorly differentiated carcinoma (large cell ca or poorly diff. ca not further classified) (RR=7.3 (7.4)). The association between adenocarcinoma and smoking was much weaker (RR=2.4 (3.1)) but still statistically significant. Some differences between different types of cancer were observed concerning the distribution of cigarette and pipe smokers. Cigarette smokers were more common among the smokers with small cell carcinoma than among the smokers with squamous cell carcinoma (41% versus 34%), while the reverse was true for pure pipe smokers (30% versus 41%).

Occupation and lung cancer (Paper II)

In this paper, odds ratios for different occupations are presented concerning lung cancer, with and without adjustment for smoking.

In the questionnaire, one overview question concerned general data on occupations, employments, branches of business, company names, specific tasks and time periods. Fourteen additional questions concerned specific occupations or groups of occupations such as miners, professional drivers, smelter workers, mechanics, machinists, welders, plumbers, electricians, carpenters, painters etc. Most of these questions contained several subquestions aimed at a closer identification of the
type of work. One question also concerned occupational exposure to asbestos (regardless of the specific occupation.)

A person who had been active at least one year in a specific occupation was assigned to this occupation in the analyses. One person could therefore be counted for more than one profession.

The lung cancer risk was calculated for different occupations; some occupations, however, were pooled into groups and not separately presented. The odds ratio for a specific occupation was estimated relative to all remaining persons and performed both with and without adjustment for smoking. Farmers, foresters, carpenters and navvis had low odds ratios (OR=0.4-0.8) while underground miners, copper smelter workers and electricians and plumbers had high odds ratios (OR=1.6-2.8). The corresponding estimates after adjustment for smoking were very similar OR=0.5-0.9 and OR=1.5-2.8, respectively. Professional drivers, pulp workers, one group including teachers, clerks, salesmen etc ("white collar workers") and one group including employees in mechanical industry, work shops, metal industry, garages and machineries ("mechanics") had all a tendency towards slightly increased odds ratios. This increase for mechanics and professional drivers did not, however, persist after adjustment for smoking. The odds ratios obtained for some occupations or groups of occupations are shown in Fig. 2.

With the use of a linear logistic regression model, smoking adjusted relative risks for two different groups of "risk occupations" were estimated. One group included workers with more than 5 years employment in occupations known or definitely suspected from previous studies to increase the lung cancer risk. The other group consisted of workers with occupations somewhat suspected of increasing the lung cancer risk. A third group (all the remaining persons) were used as a reference in relation to which the relative risks were estimated. After adjustment for smoking only the first group showed an increased relative lung cancer risk. With some assumptions, the population etiologic fraction attributable to occupation was estimated to 9 per cent.
Figure 2. Odds ratios for different occupations (or groups of occupations) concerning lung cancer. Vertical solid lines: without adjustment for smoking. Vertical dashed lines: with adjustment for smoking.

Professional driving, smoking and lung cancer (Paper III)

Through the exhaust of diesel and gasoline engines, professional drivers are exposed to benzo(a)pyrene and other carcinogenic polycyclic aromatic hydrocarbons. Some previous studies had suggested an increased lung cancer risk in this occupational group, e.g., a study based on the Swedish Cancer-Environment Register (40). In the present case-control study, professional driving was a rather common and geographically well distributed occupation which, in combination with the longitudinal smoking data and occupational data, made the material suited for analyses of this specific group.
In paper III, mainly analyses performed with the 456 cases (all born in 1900 or later), which had one deceased and one living control, are presented. Analyses based on all 589 cases with one deceased control were also performed. They gave very similar results and are not presented in this overview.

The questionnaire included a specific question concerning the type of professional driving (truck, van, bus or taxi) and time periods for the different types of driving. All persons who had been active in the profession for at least one year were classified as professional drivers. Occupation-years was the only measure of exposure used.

Sixty-three cases and 95 controls were classified as professional drivers. Bus, taxi and van drivers were few and truck drivers constituted the only subgroup large enough for separate analyses.

The unadjusted odds ratio for professional driving for more than 1 year was 1.4 and for more than 20 years 1.6. A heterogeneity of the odds ratio across the age strata (age at diagnosis and corresponding time for controls) was found and separate analyses were therefore performed for two age classes; <70 y and >70 y.

For both professional drivers as a whole and truck drivers, a significantly increased relative lung cancer risk was found in the higher age group, 3.2 and 5.7 respectively, while the relative risk in the younger age group did not exceed 1.0. Both among cases and controls, the smoking habits were different in drivers and non-drivers. The drivers included relatively more smokers than the non-drivers and they were more often high tobacco consumers. Without consideration of the age distribution, the smoking drivers showed an odds ratio of the same size as smoking non-drivers. The stratification according to age, however, gave a much higher relative risk for smoking drivers in the group aged 70 or over (RR=23.0) than for smoking non-drivers in the same age group (RR=6.7). Further stratification according to daily tobacco consumption showed a very high relative risk for professional drivers with heavy consumption (>20 cig/day) aged 70 or over compared to a corresponding group of non-drivers. A slightly (but not significantly) increased odds ratio was obtained for non-smoking drivers. However no estimate could be obtained for this category in the older age group due to lack of non-smoking cases.
Radon, smoking and lung cancer (Papers IV, V, VI)

Underground iron ore miners in several Swedish studies have been shown to run an increased risk for lung cancer, in all probability due to increased radon daughter concentration in poorly ventilated mines (41, 42, 43). Within the region for this study large iron ore mines existed in the municipalities Kiruna and Gällivare. The case-control material was therefore utilized for a special study concerning the lung cancer risk in these miners and analyses of interaction between smoking and underground mining.

Information on the specific miners, employments and employment times was obtained by an overview question. One specific question concerned type of mining (surface mining, underground mining and other tasks) with corresponding time periods.

In this paper, only underground mining in iron ore mines was regarded as exposure. However, the results were in principle similar if other types of underground mining (sulphide mines) were also included as exposure (44).

A number of 23 (22) cases and 10 (16) were classified as underground miners (> 1 year) and the average time of employment for the cases was much longer than for the controls. The estimated relative risk of lung cancer for underground miners was 2.5 (2.8). In the lung cancer cases exposed to underground mining the average time from the start of this work to diagnosis ("latency time") was 34.8 year. An overrepresentation of small cell carcinoma was also found among the cases exposed to underground mining compared to the total material. The latency time was considerably shorter for small cell carcinoma (28.7 years) than for epidermoid carcinoma (40.8 years). Among cases exposed to underground mining those with small cell carcinoma were an average younger (58.4 years) than those with epidermoid cell carcinoma (67.0 years). This observation was in sharp contrast to the material as a whole, in which no age difference was found between small cell carcinoma and epidermoid carcinoma cases. (Paper II).

The relative risk for smoking underground miners compared with non-smokers without underground mining was 18.2 (16.1). Very high relative risks were estimated for underground miners with high tobacco consumption. The estimates suggested a synergistic interaction between smoking and the occupational exposure.
The above report (Paper IV) was based on the total case-control material which included many cases and controls without exposure to underground mining in iron ore mines. A supplementary study was designed, limited to the municipalities of Kiruna and Gällivare, where the iron ore mines are located, and a larger proportion of exposed cases and controls could therefore be expected. This study included cases reported to the Cancer registry during the extended period 1972-1982 (Paper VI).

The material consisted of 69 cases, 67 deceased controls and 60 living controls. The analyses in this report were performed according to two study models in a similar way as in Paper IV. Of the 69 cases included in this study, 42 were classified as underground miners. The cases in underground miners diagnosed 1978-1982 were mainly squamous cell carcinomas and the over-representation of small cell carcinoma found in Paper IV could not be observed in this material. However, in this material the median age and latency time were also significantly lower for small cell than for squamous cell carcinoma.

The age-adjusted relative risk for underground mining was 4.5 (3.3) in this study. An obvious dose-response relationship between employment time (underground work) and lung cancer risk was found; ≥ 20 years of employment gave a relative risk of 7.7 (5.1). Estimates obtained after stratification for smoking and underground mining (Paper VI, Table 5) strongly suggested a multiplicative effect of smoking and underground mining. This type of interaction was supported by a linear logistic, regression analysis. The results did not change in principle if ex-smokers of more than 10 years were reclassified as non-smokers.

The calculated population etiologic fraction was 48 (40) % for underground mining and 78 (79) % for smoking in this material.

The questionnaires contained one question about the type of building material in the dwellings and time periods for living in these dwelling. From the answers, only wooden and non-wooden houses could be separated. The data was used for a case-control study meant as a pilot investigation (Paper V). Living in wooden houses strongly predominated in this population. No overrisk for lung cancer due to living in non-wooden houses could be found after adjustment for smoking. The strong predominance of wooden houses suggested that increased indoor radon concentrations due to building material played a negligible role in this region. The study could, of course, not exclude that other sources of increased radon concentrations (leakage from a ground) could have played a role.
Can the findings explain the geographical incidence differences?

Large geographical variations in the age-standardized incidence rates of male lung cancer was found within the studied region (Fig 3) and was actually one incentive for the case-control study. The principle aim of this study was, however, not to find explanations of these differences but rather to elucidate effects of smoking and occupational exposures. Against the background of the large incidence variations there was reason to suspect great variations concerning these exposures, which could be a good basis for a case-control study. The controls were matched against the cases according to municipality in order to reduce confounding from factors other than smoking and occupation (for instance, general air pollution). The design of the study was thus not aimed at measuring the effects of geographical domicile.

<table>
<thead>
<tr>
<th>County/Municipality</th>
<th>Age standardized incidence rate 1969-78</th>
<th>Mean population 1969-78</th>
</tr>
</thead>
<tbody>
<tr>
<td>VÄSTERNORRLAND</td>
<td>26.7, 36.2, 31.4</td>
<td>134513</td>
</tr>
<tr>
<td>Ånge</td>
<td>27.1, 33.0, 29.1</td>
<td>7339</td>
</tr>
<tr>
<td>Tierp</td>
<td>22.4, 33.7, 29.1</td>
<td>9299</td>
</tr>
<tr>
<td>Hornsund</td>
<td>25.4, 59.0, 31.2</td>
<td>13277</td>
</tr>
<tr>
<td>Sundsvall</td>
<td>37.1, 43.9, 40.5</td>
<td>44648</td>
</tr>
<tr>
<td>Krånsfors</td>
<td>20.8, 34.3, 31.6</td>
<td>14169</td>
</tr>
<tr>
<td>Sollefteå</td>
<td>17.8, 28.2, 23.0</td>
<td>13881</td>
</tr>
<tr>
<td>Ornsköldsvik</td>
<td>19.1, 24.3, 21.7</td>
<td>30469</td>
</tr>
<tr>
<td>VÄSTERBOTTEN</td>
<td>16.7, 31.2, 24.0</td>
<td>119433</td>
</tr>
<tr>
<td>Normling</td>
<td>11.6, 31.0, 21.3</td>
<td>4006</td>
</tr>
<tr>
<td>Vendeln</td>
<td>18.8, 43.2, 31.1</td>
<td>3705</td>
</tr>
<tr>
<td>Robertsfors</td>
<td>9.9, 23.5, 16.7</td>
<td>3917</td>
</tr>
<tr>
<td>Norsjö</td>
<td>8.7, 23.2, 15.9</td>
<td>5419</td>
</tr>
<tr>
<td>Storneman</td>
<td>9.5, 16.4, 12.9</td>
<td>4479</td>
</tr>
<tr>
<td>Sorsele</td>
<td>3.9, 3.7, 3.8</td>
<td>2192</td>
</tr>
<tr>
<td>Vännäs</td>
<td>6.6, 26.6, 16.6</td>
<td>6627</td>
</tr>
<tr>
<td>Väneholm</td>
<td>3.9, 7.2, 5.6</td>
<td>4627</td>
</tr>
<tr>
<td>Åselö</td>
<td>2.9, 14.6, 8.7</td>
<td>4856</td>
</tr>
<tr>
<td>Umeå</td>
<td>24.2, 40.0, 32.1</td>
<td>36386</td>
</tr>
<tr>
<td>Lycksele</td>
<td>8.9, 12.0, 10.5</td>
<td>7500</td>
</tr>
<tr>
<td>Skellefteå</td>
<td>25.1, 41.4, 33.2</td>
<td>36293</td>
</tr>
<tr>
<td>NORDBOTTEN</td>
<td>23.9, 34.3, 29.1</td>
<td>133433</td>
</tr>
<tr>
<td>Arvidsjaur</td>
<td>6.0, 19.4, 12.7</td>
<td>4276</td>
</tr>
<tr>
<td>Arjeplog</td>
<td>7.9, 7.5, 6.3</td>
<td>2272</td>
</tr>
<tr>
<td>Jokkmokk</td>
<td>11.4, 26.5, 19.0</td>
<td>4084</td>
</tr>
<tr>
<td>Överkalix</td>
<td>9.0, 6.6, 3.3</td>
<td>2968</td>
</tr>
<tr>
<td>Kelle</td>
<td>21.8, 26.3, 24.0</td>
<td>9398</td>
</tr>
<tr>
<td>Överlomåd</td>
<td>12.2, 18.6, 15.4</td>
<td>3577</td>
</tr>
<tr>
<td>Pajala</td>
<td>12.0, 20.3, 16.2</td>
<td>5376</td>
</tr>
<tr>
<td>Gällivare</td>
<td>26.1, 54.7, 40.4</td>
<td>13237</td>
</tr>
<tr>
<td>Altviken</td>
<td>12.5, 41.4, 37.0</td>
<td>4585</td>
</tr>
<tr>
<td>Luleå</td>
<td>32.4, 42.7, 37.6</td>
<td>31694</td>
</tr>
<tr>
<td>Piteå</td>
<td>20.2, 35.1, 31.7</td>
<td>17428</td>
</tr>
<tr>
<td>Boden</td>
<td>25.6, 30.0, 31.8</td>
<td>12315</td>
</tr>
<tr>
<td>Haparanda</td>
<td>20.3, 46.6, 37.5</td>
<td>4538</td>
</tr>
<tr>
<td>Kiruna</td>
<td>45.2, 35.1, 40.2</td>
<td>16097</td>
</tr>
<tr>
<td>WHOLE REGION</td>
<td>22.8, 34.0, 28.4</td>
<td>367439</td>
</tr>
</tbody>
</table>

Figure 3. Age standardized incidence rates (per 100,000 and year) of male lung cancer in the municipalities 1969-1978 (45). The right map illustrates the deviations from the average for the whole region during the period 1969-1978. The Swedish population 1970 served as standard population.
Nevertheless, some differences observed between the municipalities were of interest in relation to the observed incidence variations. The controls from the different municipalities could thus serve as samples of the male populations in these domiciles with an age distribution defined by the samples.

In order to compare smoking habits and occupational profiles in different parts of the region the municipalities were grouped with guidance of the age-standardized incidence rates during the period 1969-1978:

<table>
<thead>
<tr>
<th>Area</th>
<th>Per cent of average in whole region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area 1</td>
<td>&lt;90 per cent of the average in the whole region</td>
</tr>
<tr>
<td>Area 2</td>
<td>90 - 130 per cent</td>
</tr>
<tr>
<td>Area 3</td>
<td>&gt; 130 per cent</td>
</tr>
</tbody>
</table>

The persons were referred to the municipality where they were registered at the time of the report to the Cancer Registry. Moving from one area to another had only marginal importance in this material and was therefore neglected.

Table 5 shows smoking habits among the controls from these 3 areas. The highest rate of non-smokers and the lowest average life-time tobacco consumption was observed in area 1 for both deceased and living controls.

Table 5. Smoking habits among the controls from the geographically defined areas.

<table>
<thead>
<tr>
<th>Geographical area</th>
<th>Non-smokers per cent</th>
<th>Average life-time tobacco consumption, $10^3$ cig</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deceased controls</td>
<td>Living controls</td>
</tr>
<tr>
<td>1</td>
<td>41</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>37</td>
</tr>
</tbody>
</table>
Occupations known, definitely suspected or somewhat suspected of giving increased lung cancer risk either based on epidemiologic observations or on the character of the work were classified as "risk occupations". The definitions were identical with those used in paper II for the logistic regression analysis. Table 6 shows the distribution of controls in these "risk occupations". "Risk occupations" occurred more frequently in area 2 and 3 than in area 1.

Table 6. "Risk occupations" among the controls.

<table>
<thead>
<tr>
<th>Geographical area</th>
<th>&quot;Risk occupation&quot; (Known or definitely suspected)</th>
<th>Deceased controls</th>
<th>Living controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Per cent</td>
<td>Per cent</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>41</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>50</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>53</td>
<td>56</td>
</tr>
</tbody>
</table>

It was of interest to estimate the relative lung cancer risk due to smoking in different geographical areas. If the cases and controls within a specific area were analysed as a separate case-control study, a high relative risk for smoking was obtained in area 3 compared to areas 2 and 1 giving the impression that smoking could be less dangerous in area 1 and 2 than in area 3 (Table 7). This conclusion can, however, not be drawn. In the low and median incidence areas the proportion of lung cancer cases not associated with smoking was larger than in the high incidence area, which can be seen in Table 7. This proportion strongly influences the size of the relative risk estimates.

The comparison between the controls in the 3 geographical groups suggested that the incidence differences were at least partly due to different smoking habits and different occupational profiles. However, it can not be excluded that also other factors may have played a role.
Table 7. Relative risks for smoking with the cases and controls within each area regarded as a separate case-control study.

<table>
<thead>
<tr>
<th>Area</th>
<th>Cases</th>
<th>Non-smokers</th>
<th>Smokers</th>
<th>Controls</th>
<th>Non-smokers</th>
<th>Smokers</th>
<th>RR (1.0)</th>
<th>RR (1.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cases</td>
<td>9</td>
<td>36</td>
<td>18</td>
<td>20</td>
<td>16</td>
<td>2.8</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>1</td>
<td>2.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Cases</td>
<td>32</td>
<td>350</td>
<td>144</td>
<td>23</td>
<td>270</td>
<td>6.8</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>350</td>
<td>6.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Cases</td>
<td>5</td>
<td>157</td>
<td>51</td>
<td>4</td>
<td>122</td>
<td>14.3</td>
<td>18.2</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>112</td>
<td></td>
<td></td>
<td>79</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
COMMENTS AND CONCLUSIONS

Selection of controls
In the present case-control studies, two types of controls were used, living and deceased. For deceased controls and for the cases, the data were collected through surrogate respondents and were from this point of view comparable. The studied exposures might, however, have caused an increased mortality for other reasons than lung cancer. A comparison with only deceased controls may therefore underestimate the risk. In a recently reported study (46), dead controls reported heavier consumption of cigarettes, spirits and certain drugs and more adult diseases than living controls, which caused an underestimation of the risk. Living controls in the present study were matched with the cases according to year of birth and had thus outlived the cases by some years. They may thus have represented a positively selected group concerning health and caused overestimation of the risk. These mechanisms have been recently discussed by another author (47).

Comparison with living controls in the present study gave as a rule higher risk estimates for smoking than the comparison with deceased controls. These estimates can probably be regarded as upper and lower limits, with the true value somewhere between. The risk estimates obtained for different occupations with deceased and living controls showed on the whole fairly good agreement. This result could also be expected as occupations per se seldom cause pronounced overmortality. Some observed differences may, however, be mentioned.

Occupational exposure to asbestos according to the questionnaires (irrespective of specific occupation) gave a high odds ratio with use of deceased controls, but not with use of living controls. The explanation was that 15% of the self-respondent controls and only 8% of the surrogate-respondents for controls reported this exposure. It is easy to understand that asbestos exposure not connected with a specific occupation can be underestimated by surrogate respondents. A similar finding concerning reporting of asbestos exposure has previously been published (48). Underground miners and asphalt and concrete workers were more frequent among the living controls than among the deceased controls. This may have been a "healthy worker effect", i.e. persons suitable for heavy work might have been overrepresented among the living controls. No difference in reporting rate of underground mining between living and deceased controls was found in a small sample, in which the data could be controlled (11).

In papers I and II it was of interest to separate estimates obtained with deceased
and living controls. In the other papers (III-VI) both estimates with only deceased controls and estimates based on pooled deceased and living controls were presented. By pooling deceased and living controls, a larger control group was obtained and the tendencies of underestimation and overestimation of the risk caused by these control groups might have been counterbalanced.

Reliability of data
Most data used in the present case-control study were obtained by questionnaires answered by close relatives to cases and deceased controls and by the living controls themselves. Of importance was therefore to investigate the reliability of the collected data. The answers from the surrogate respondents were of special interest as these could be suspected to be less reliable. Small samples of the total material were studied concerning the validity. For the studied questions, which included smoking habits, municipality, type of dwelling and two specific occupations, it was found that the surrogate respondents provided fairly adequate data. To assess the validity of surrogate respondents, interviews of spouse pairs have been performed in several investigations (49, 50, 51). As in the present study, a good agreement between the two respondents was found concerning the classification of smokers and non-smokers (49, 50). Detailed information about the smoking habits was, as expected, more difficult to obtain through surrogate respondents (51, 52). In the present investigation, however, a rather good agreement was found between the two sources concerning the type of smoking (80 per cent) and daily tobacco consumption (84 per cent). In the present study, the validity of surrogate data was possible to elucidate for two specific occupational groups, underground miners and smelter workers. For both occupations the length of employment time given in the questionnaires agreed well with data in the employment registers (93% agreement if a difference of ± 2 y. was accepted). The same type of comparison has been performed by Pershagen and Axelson (53). A correct classification regarding ever-employment at a copper smelter was found in 158 of 160 subjects. Concerning life-time occupational histories it has been showed, however, that surrogate information included fewer jobs and covered fewer years (51).
Results

The presented large case-control study could be regarded as a screening procedure with a search for possible occupational risk factors and analysis of interaction between such factors and smoking.

As smoking is a dominating etiologic factor for lung cancer, the study gave information of interest concerning the association between smoking and lung cancer (Paper I). The relative overall risk of smoking agreed strikingly well with results in a large Swedish cohort study (54). Both investigations gave also approximately the same relative risk for cigarette and pipe smoking which differs from most international reports (7). The pipe smokers among the cases in the present study, however, had on average a significantly higher age at diagnosis and more smoking years than the cigarette smoking cases. As in several reported studies the relative risk decreased rapidly in ex-cigarette smokers after about 5 years (cf. 55). This effect was much less pronounced in ex-pipe smokers, who after 10 years of smoking cessation still ran a rather high relative risk. A possible explanation could be the long smoking histories in the pipe smokers, which might have caused more irreversible changes. The relative risk of smoking was high for small cell and squamous cell carcinoma and much lower, but still significantly increased, for adenocarcinoma. Previously published data concerning adenocarcinoma are somewhat conflicting; some studies have shown no or only slight association between smoking and adenocarcinoma (56, 57), while other reports have strongly suggested that smoking also increases the risk of this type of lung cancer (58, 59, 60).

In the screening for possible occupational risks (Paper II), some occupations previously shown or highly suspected of involving such risks gave high odds ratios (underground miners, copper smelter workers, electricians and plumbers). It is reasonable to assume (but of course not specifically verified by the present studies) that these overrisks were due to radon daughters, arsenic and asbestos, respectively.

When the whole group of somewhat suspected risk occupations ("blue collar jobs") was analysed with use of a logistic, multivariate regression model including more detailed smoking data, the overrisk disappeared after adjustment for smoking. However, this group was strongly dominated by professional drivers and "mechanics". It can not be excluded that some small specific subgroups represented real risk occupations. Some support in this direction was obtained for asphalt and concrete workers and for pulp workers, which may indicate further studies. An
increased lung cancer risk among asphalt workers has been indicated by previous studies (61). Among pulp workers an increased prevalence of respiratory disease (chronic bronchitis) has been reported (62).

Farmers and foresters had significantly low odds ratios, which also have been reported from several other studies (63, 64). This group was compared to another group also without suspected occupational risk exposures ("white collar workers") concerning smoking habits (Paper II). There were quantitative and qualitative differences in smoking habits between the two groups, but detailed adjustment for smoking only slightly reduced the difference between the odds ratios. The smoking habits could thus not completely explain the different lung cancer risk in these two groups in the present study. It is possible though that even a detailed adjustment for smoking was inadequate. Other explanations can also be discussed such as environmental tobacco smoke, indoor radon, general air pollution, diet etc but these could not be elucidated in the present study.

The present case-control material was used to elucidate risks of lung cancer in two specific occupations, professional driving and underground mining. The analysis of professional drivers yielded some observations of interest (Paper III). Professional drivers had considerably higher average tobacco consumption than non-drivers which indicated that a careful examination of smoking habits is necessary when occupational lung cancer risks are studied. Furthermore, an increased relative risk was found only in an older age group (70 y and over). A possible explanation might have been changes in occupational exposure over time due to different car constructions or fuel composition. The results in the older age group suggested a multiplicative effect between smoking and the occupational exposure.

The second occupation specifically studied was underground mining. An increased risk for underground miners to develop lung cancer was found (Papers IV and VI) in close agreement with several other reports (41, 42, 43). The main purpose of the present investigations was, however, to study the interaction between underground mining and smoking. The data strongly suggested a multiplicative effect of smoking and underground mining. This finding is in agreement with those of Whittemore and McMillan (13) in US uranium miners. Some other epidemiologic studies have, however, suggested a merely additive effect of smoking and radon daughter exposure. (65, 66). There can be several reasons for the divergent results concerning this interaction. One explanation may be the quality of the smoking data. In some studies, the smoking data was crude, without details concerning type of smoking and tobacco consumption, and in other studies largely extrapolated (especially in cohort studies). Furthermore, the classification of ex-smokers as
nonsmokers may be questionable when interaction between smoking and radon exposure is studied. A long previous smoking history may have changed the bronchial epithelium and thereby the relevant radiation dose in the dividing cells (due to the short range of the α-particles). According to some observations, radon-induced lung cancer appears after longer latency times in non-smokers than in smokers (cf. 67). In such cases the relation between the relative risks in non-smokers and smokers changes with length of observation time. In the present study (Paper VI), however, the latency times in the exposed cases (and the corresponding times for the controls) were very long, on average 39.3 and 35.7 years respectively. Only 3 of 42 exposed cases and 5 of 38 exposed controls had shorter latency time (corresponding time for controls) than 20 years (68). Therefore it does not seem likely that too short latency times would explain the observed multiplicative type of interaction.
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