J. W. Wolter

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A case-referent study of lung cancer, occupational exposures and smoking

I Comparison of title-based and exposure-based occupational information

by Helge Kjuus, MD,[1] Rolv Skjærven, MSc,[2] Sverre Langård, MD, MSc,[1] Jan T Lien, MD,[3] Terje Aamodt, MD[4]

KJUUS H, SKJÆRVEN R, LANGÅRD S, LIEN JT, AAMODT T. A case-referent study of lung cancer, occupational exposures and smoking: I Comparison of title-based and exposure-based occupational information. *Scand J Work Environ Health* 12 (1986) 193—202. The role of occupational exposures and smoking in the development of lung cancer has been studied among 176 male incident lung cancer cases and 176 referents admitted to two county hospitals in southeast Norway during 1979—1983. After the allocation of all occupational titles in the Nordic Classification of Occupations into three exposure groups according to potential exposure to respiratory carcinogens and other contaminants, each subject was classified according to exposure status of main occupation and number of years in each exposure category. An excess risk of lung cancer was observed both among those in possibly exposed occupations and among those definitely exposed. A more than threefold excess risk was observed among subjects with more than 30 years in exposed occupations. Exposure to 22 agents/processes was further assessed by a separate questionnaire and estimated simultaneously in a logistic regression model. Elevated risks were associated with exposure to asbestos and several other agents/processes, which largely correlated to each other. Smoking was strongly associated with all histological subtypes of lung cancer, while for occupational exposures the risk ratio was highest for small cell carcinoma and lowest for adenocarcinoma. Very high risk ratios for lung cancer were observed among heavy smokers in exposed occupations.

Key terms: chemicals, logistic regression, occupational titles, respiratory carcinogens, tobacco lifetime dose.

A major challenge in studies of the role of occupational exposures in relation to lung cancer is to form an appropriate operational scale for the determinant in question. This challenge refers in particular to case-referent studies of limited size, in which the pooling of different occupational exposures into broad groups of the determinant is often a prerequisite for the analysis.

Traditionally some kind of occupational title-based information has been applied to such studies, although an exposure-based approach would conceptually be more relevant (11, 13, 30). By combining these approaches, the present study aimed to examine the role of occupational exposures in the development of lung cancer among men in two counties in southeast Norway.

In a previous study, a crude dichotomous determinant scale related to length of stay in a polluted workplace was applied to 103 cases of cancer and 103 referents (18). Among 32 lung cancer cases [International Classification of Diseases (ICD) 162, 163], a threefold increase in relative risk was observed for exposed subjects (≥ 10 years in a polluted workplace) in comparison to unexposed subjects (< 10 years in a polluted workplace). The lung cancer part of that study has been continued, and in the present report we give the results from 176 male lung cancer cases and 176 referents, selected during a five-year period from the Telemark and Vestfold County Hospitals.

The study has been divided into three parts. This paper describes the design and the main results of the study, while the role of asbestos exposure and the quantitative importance of all occupational exposures in the development of lung cancer are subjects of separate presentations (17, 19).

Subjects and methods

The neighboring counties Telemark and Vestfold are located in the southern part of Norway and have 162 000 and 190 000 inhabitants, respectively. The industrial areas are mainly located near the towns along the coast, with a predominance of chemical industry in Telemark and shipbuilding and, previously, whaling in Vestfold. The remaining parts of the counties are dominated by farming and forestry. During the period

[1] Department of Occupational Medicine, Telemark County Hospital, Porsgrunn, Norway.
[2] Section for Medical Informatics and Statistics, University of Bergen, Bergen, Norway.
[3] Lung Division, Telemark County Hospital, Skien, Norway.
[4] Lung Division, Vestfold County Hospital, Tønsberg, Norway.

Reprint requests to: Dr H Kjuus, Department of Occupational Medicine, Telemark County Hospital, N-3900 Porsgrunn, Norway.

1979—1983, 136 male incident lung cancer cases and 136 referents were identified in the medical ward of Telemark County Hospital. In the last two years of the period, all 40 incident lung cancer cases admitted to the medical ward of Vestfold County Hospital in Tønsberg were also included in the study. Besides the Vestfold County Hospital in Tønsberg, which covers both county and local hospital functions, there are three smaller hospitals in this county. The proportion of urban and rural parts of the referral area for each of the four hospitals is fairly similar.

Subject identification

Male patients who were under 80 years of age and admitted to the medical ward with a recent diagnosis of lung cancer (ICD 162—163) were selected as cases. For each case, one age-matched reference patient (± 5 years) was randomly selected from the admissions list or from the inpatient list of the same department. Patients with conditions implying physical or mental handicaps which would have precluded employment in heavy industry were not accepted, neither were patients with poor general health or those who were obviously mentally diminished. Patients admitted because of chronic obstructive lung disease were excluded from the reference series. The diagnoses among the referents accepted for the study were ischemic heart disease (N = 64), other cardiovascular disease (N = 37), other malignant neoplasms (N = 6), other lung disease (N = 12), gastrointestinal disease (N = 9), hepatobiliar disease (N = 6), urological disease (N = 3), musculoskeletal disease (N = 5), diabetes mellitus (N = 6), and miscellaneous (N = 28). The distribution of the histological subtypes of lung cancer (WHO, 1980) is shown in table 1.

Table 1. Histological type of respiratory cancer among the cases.

Histological type	Number	Percentage
Squamous cell carcinoma	94	53.4
Small cell carcinoma	38	21.5
Adenocarcinoma	21	11.9
Large cell carcinoma	4	2.3
Alveolar cell carcinoma	1	0.6
Mesothelioma	4	2.3
Uncertain histology	6	3.4
Not histologically verified	8	4.5

Subject interviews

All the subjects were interviewed at the bedside by one of us (HK). They were not informed of the purpose of the study, which was presented as a "survey of occupational exposures among patients in a medical ward." The subjects were instructed not to give any information about their disease to the interviewer. In most cases, the interview took place either before the diagnosis had been confirmed or before the patient had been informed of his diagnosis. Thus 14 subjects interviewed as potential cases were found not to have

Table 2. Exposure classification of 99 occupational groups. (The Nordic Classification of Occupations, 1965, two-digit code precedes the occupational group.)

Definite exposure (OT+)	Possible exposure (OT?)	No exposure (OT−)
50 Mining and quarrying	01 Chemical and physical work	00 Technical work
52 Mineral treating work	51 Well drilling and related work	02 Biological work
59 Other mining and quarrying work	60 Ship officers and pilots	03 Medical work
73 Smelting, metallurgical and foundry work	61 Deck and engine-room crew work	04 Nursing care
75 Iron and metalware	63 Railroad locomotive engineers and firemen	05 Other professional health and medical work
78 Painting and paperhanging work	70 Textile work	06—29 Administrative and clerical work
83 Chemical and related process work	72 Shoe and leather work	30—33 Sales work
	74 Precision mechanical work	40—44 Agriculture, forestry, fishing
	76 Electrical work	62 Air transport work
	77 Wood work	64 Road transport work
	79 Construction work	65 Conductors, dispatchers and freight assistant work
	80 Graphic work	66 Traffic supervising
	81 Glass, ceramic and clay work	67 Postal and telecommunication work
	84 Tobacco work	68 Postal and other messenger work
	85 Other production-process work	69 Other transport and communication work
	86 Packing and wrapping	82 Food and beverage work
	87 Stationary engine and motor-power work	90 Public safety and protection work
	88 Longshoremen	91 Hotel, restaurant and domestic work
	89 Miscellaneous laboring work	92 Table waiting
	93 Building caretaking and cleaning work	97 Photographic work
	94 Hygienic and beauty treatment work	98 Funeral service
	95 Laundering, dry-cleaning and pressing work	99 Other service work
		X1 Military work

lung cancer and were initially excluded. Four of these were accepted as referents, however. The interview was, as far as possible, performed "blind" as to the subject's status as case or referent. Information on smoking habits was collected at the end of the interview, and referents with ischemic heart disease were not interviewed as long as they were in the coronary care unit. For approximately 10 % of the participants the case-referent status was unintentionally revealed, and for another 10 % their status was suspected. If potential study subjects were discharged from the hospital before the interview had taken place, they were not recalled. Some cases were interviewed however during a subsequent hospital stay. The average length of an interview was 30 min. One potential case and two potential referents refused to participate in the study.

Assessment of exposure

For each subject the interviewer obtained a complete work history of all jobs held since the age of 14 years. For each job, the occupational title (OT), the duties usually performed, and detailed information on relevant exposure factors were ascertained. Characterization of exposure has partly been based upon an approach based on occupational titles and partly on an approach based on exposure.

Occupational title-based approach

Initially in this study, the 99 occupational groups (two-digit level) and all of the over 4 000 occupational titles (five-digit level) in the Nordic Classification of Occupations (1965) were allocated into the following three exposure groups according to possible exposure to respiratory carcinogens or other contaminants experienced in a typical job in that particular occupation: definite exposure (OT+), possible exposure (OT?), and no exposure (OT−). To cover the possibility that pollutants not known as specific carcinogens might act as cocarcinogens, eg, in combination with smoking, we classified occupations with definite exposure to most kinds of dust, gases, and fumes as exposed occupations. Obviously, several jobs were classified into different exposure groups at the two levels, as the most comprehensive classification corresponded more closely to the actual job performed. For example, furniture makers, who were allocated to the OT? category at the two-digit level (wood workers according to code 77), were classified in the OT+ category at the five-digit level, due to the possible carcinogenic effect of hardwood exposure. The classification of the 99 occupational groups (two-digits) into the three exposure groups is shown in table 2. Exposure status of the occupational title of the longest job held (two-digit level), together with the number of years in exposed occupations (five-digit level) up to 1970, was then recorded, omitting the last 9 to 13 years of possible exposure.

Exposure-based approach

From 1 January 1982 on, a standardized questionnaire concerning past exposure to 17 types of chemical agents and five specific work processes was used. For the 68 cases and 68 referents ascertained before this date, the questionnaire was filled out retrospectively on the basis of the exposures and occupational tasks stated in the detailed occupational history. A dichotomous scale of exposure was used in which regular exposure for more than three years was classified as "exposed."

Smoking habits were classified according to status (never a smoker, present smoker and exsmoker (> 1 year since cessation of smoking)], type (cigarettes, pipe and cigar), and amount, measured as lifetime consumption of tobacco (in grams). The categories for this lifetime dose were chosen so that they corresponded to traditional categories for the average number of cigarettes smoked daily, assuming a 45-year smoking period, which was the average smoking period among the present and former smokers in the study. One cigarette was estimated to be equal to 1 g of tobacco. As a crude indicator of possible domestic radon exposure, the subjects were also asked if they had lived in a dwelling of wood or brick/stone for most of their lives. The distribution of cases and referents according to age, hospital, urban/rural place of residence, and smoking habits is shown in table 3.

Statistical methods

Multivariate analyses were performed with logistic regression models with the rate of cases within the sample of cases and referents as the dependent variable (4, 6). The program for unconditional logistic regression as in the BMDP statistical program package was used (8). Following the proposals of Holford et al (15), conditional analyses of the matched pairs were also performed. The results were, however, similar to those obtained with the unconditional analyses, and, as the number of concordant pairs reduced

Table 3. Number of cases and referents according to age, hospital, urban/rural place of residence, and smoking habits.

Indicator	Cases		Referents	
	N	%	N	%
Age (years)				
40—59	32	18.2	36	20.5
60—69	87	49.4	86	48.9
70—79	57	32.4	54	30.7
Hospital				
Telemark County Hospital	136	77.3	136	77.3
Vestfold County Hospital	40	22.7	40	22.7
Urban/rural status				
Urban	125	71.0	101	57.4
Rural	51	29.0	75	42.6
Smoking habit status				
Present smoker	135	76.7	77	43.8
Former smoker	39	22.2	75	42.6
Never a smoker	2	1.1	24	13.6
Type of tobacco used				
Cigarettes	151	86.8	127	83.6
Pipe, other	23	13.2	25	16.4

the material and therefore gave wider confidence intervals, we chose to report the results of the unconditional estimation procedure, which is known to give conservatively biased estimates (4). Since age was the most important matching criterion in the material, selected age-specific results have also been presented.

Odds ratios were used as estimators of the risk ratio (RR) (14). The significance of the models was tested for goodness of fit, using likelihood ratio tests (8, 29), and the models were compared from the differences of the likelihood ratios (G), which were assumed to be chi-square distributed. Factors were introduced as additive terms within the logistic scale. Departure from additivity was evaluated through first-order interaction effects in a backward stepping procedure with a removal level set at 15 %. Ninety-five percent confidence intervals (95 % CI) were calculated with the use of the estimated coefficients and standard errors from the regression models. For a few analyses (table 7 in the Results section, exposure group OT −), a test-based method was used (25).

Table 4. Risk ratio (RR) for lung cancer according to exposure status (OT − = no exposure, OT? = possible exposure, OT + = definite exposure) based upon title for main lifetime occupation (two digits), adjusted for smoking and urban/rural status.

	OT −	OT?	OT +	Total
Cases (N)	44	63	69	176
Referents (N)	79	52	45	176
Risk ratio[a]				
Unadjusted	1.0	2.2	2.8	
Adjusted 1	1.0	1.8	2.5	
Adjusted 2	1.0	1.7	2.3	
Adjusted 3	1.0	1.8	2.4	
Adjusted 4	1.0	1.7	2.2	
Adjusted 5	1.0	1.9	2.6	
95 % confidence interval for RR, adjusted 2		0.9—3.0	1.3—4.2	

[a] Adjusted 1 = smoking, three levels (0—9, 10—19, ≥ 20 cigarettes/d).
Adjusted 2 = smoking, three levels (0—9, 10—19, ≥ 20 cigarettes/d) and urban/rural status.
Adjusted 3 = smoking, five levels (0—4, 5—9, 10—19, 20—29, ≥ 30 cigarettes/d).
Adjusted 4 = smoking, five levels (0—4, 5—9, 10—19, 20—29, ≥ 30 cigarettes/d) and urban/rural status.
Adjusted 5 = smoking, linear adjustment.

Results

The risk ratio for lung cancer according to exposure status (OT −, OT?, OT +) of main lifetime occupation is shown in table 4. After adjustment for smoking (three levels) and urban/rural status, there was a risk ratio for lung cancer of 2.3 among persons in definitely exposed occupations (OT +) when they were compared to those in unexposed occupations (OT −). After the same type of adjustment, the main age group (60—69 years) gave the estimates 2.0 and 3.5 for the OT? and OT + category, respectively. There were only small changes in the risk ratio with further adjustment for smoking. Although it was not possible to assess the significance between the different models in terms of the likelihood ratio tests, it seemed that the risk ratio estimates increased somewhat when the control for smoking was more elaborate (10 levels or linear adjustment) in that it gave more weight to the tails in the smoking distribution. Table 5 shows the risk ratio for

Table 5. Risk ratio for lung cancer, according to number of years in definitely exposed occupations (OT +) for the total material and the main age group (60—69 years).

Years exposed (OT +)	Number of subjects		Risk ratio			95 % confidence interval[d]
	Cases	Referents	Unadjusted	Adjusted[a] Cat[b]	Adjusted[a] Lin[c]	
Age group 60—69 years						
—	22	43	1.0	1.0	1.0	
1— 9	13	18	1.4	1.2	1.6	0.4— 3.2
10—19	20	13	3.0	2.7	2.6	1.0— 7.1
20—29	21	7	5.9	4.5	4.1	1.5—13.6
≥ 30	11	5	4.3	5.5	6.6	1.5—19.9
Total material						
—	47	83	1.0	1.0	1.0	
1— 9	29	33	1.6	1.3	1.4	0.7— 2.7
10—19	38	25	2.7	2.2	1.9	1.1— 4.3
20—29	35	24	2.6	2.2	2.5	1.1— 4.4
≥ 30	27	11	4.3	3.8	3.4	1.6— 8.9

[a] Smoking, three levels (0—9, 10—19, ≥ 20 cigarettes/d) and urban/rural status.
[b] Cat = effect of OT + estimated in five separate categories
[c] Lin = effect of OT + estimated assuming a linear relation.
[d] Confidence interval based on categorical estimates

Test for trend:
60—69 years: G = 13.5, 4 df, p = 0.009
Total: G = 12.8, 4 df, p = 0.012

Test for departure from linearity:
60—69 years: ΔG = 0.63, 3 df, p = 0.89
Total: ΔG = 0.66, 3 df, p = 0.88

lung cancer according to the number of years in exposed occupations. There was a statistically significant effect with length of exposure [G = 12.8, 4 degrees of freedom (df), p = 0.012], with a risk ratio of 3.8 for those with more than 30 years in OT + occupations. The effect was nearly linear in the log scale (ΔG = 0.66, 3 df, p = 0.88). The association between occupational exposure and lung cancer was the most pronounced in the 60- to 69-year age group, followed by the age group 70—79 years.

When half the years in possibly exposed occupations (½ OT?) was added to the number of years in OT + occupations, the risk ratios became even higher, with a more than fivefold risk of lung cancer among those with more than 30 years of exposure (table 6). The test for trend was significant (G = 16.9, 4 df, p = 0.002), and, again, the age group 60—69 years showed the strongest effects. The trend in this age group, however, seemed to depart from exponentiality, although not significantly (ΔG = 5.73, 3 df, p = 0.13).

The results for some selected occupational groups are shown in table 7. The unexposed group (OT −) was used as the reference category for exposed occupations (OT + and OT?), while for the unexposed occupations (OT −) the remaining occupations in the same group were used as reference. Elevated risk ratios were observed for several occupational groups, being highest among miners and quarriers (RR = 10.2). Many of these results were, however, based upon small numbers and were consequently subject to large sampling errors.

The risk ratios for lung cancer according to smoking habits were estimated for lifetime consumption of tobacco, transformed into the equivalent number of cigarettes smoked per day and assuming a 45-year smoking period. Only two of the lung cancer cases had been "nonsmokers," and even one of these was a sporadic smoker for a few years in his youth. The associations observed between smoking and lung cancer were strong, with risk ratios of 3, 6, 16, 40, and 100 for the smoking levels 1—4, 5—9, 10—19, 20—29, and 30 cigarettes or more per day, respectively. The data fit closely a model of exponential dose-response relationship (ΔG = 2.48, 4 df, p = 0.65). There were no obvious differences between the histological subtypes of lung cancer, with risk ratios for adenocarcinomas at the same level as for the other subtypes.

Among subjects in definitely exposed occupations (OT +), however, the highest risk ratio was observed for small cell carcinoma (RR = 4.2), followed by squamous cell carcinoma (RR = 2.3), and adenocarcinoma (RR = 1.5). These relationships were also reflected when the lung cancers were divided into type-I tumors (squamous cell carcinoma and small cell carcinoma) and type-II tumors (here: adenocarcinoma), according to Kreyberg (20). The group I:group II ratio was highest among those definitely exposed, being 7.4, 6.9, and 4.6 for exposure status OT + , OT?, and OT − , respectively. No difference in the group I:group II ratio was found between the highest and the lowest smoking level, being 6.8 for both groups.

When exposure-based information from the questionnaire was considered, statistically significant increases in the risk ratios were found for persons exposed to asbestos, rock drilling, quartz/stone dust, cement dust, "other gases," and for fertilizer produc-

Table 6. Risk ratio for lung cancer, according to number of years with combined exposure (number of years in definitely exposed (OT +) occupations plus half the years in possibly exposed occupations (½ OT?)) for the total material and the main age group (60—69 years).

Years exposed (OT + and ½ OT?)	Number of subjects		Risk ratio			95 % confidence interval[d]
	Cases	Referents	Unadjusted	Adjusted[a] Cat[b]	Adjusted[a] Lin[c]	
Age group 60—69 years						
—	12	30	1.0	1.0	1.0	
1— 9	15	16	2.3	2.9	1.5	1.0— 8.9
10—19	24	23	2.6	2.6	2.3	0.9— 7.1
20—29	21	11	4.8	3.4	3.6	1.1—10.8
≥30	15	6	6.3	7.8	5.4	2.1—28.5
Total material						
—	25	57	1.0	1.0	1.0	
1— 9	30	33	2.1	2.5	1.4	1.2— 5.5
10—19	46	36	2.9	2.8	1.9	1.3— 5.7
20—29	41	37	2.5	2.2	2.6	1.1— 4.6
≥30	34	13	6.0	5.6	3.5	2.3—13.6

[a] Smoking, three levels (0—9, 10—19, ≥20 cigarettes/d) and urban/rural status
[b] Cat = estimated in five separate categories.
[c] Lin = estimated assuming a linear relation.
[d] Confidence interval based on categorical estimates.

Test for trend:
60—69 years: G = 11.5, 4 df, p = 0.022
Total: G = 16.9, 4 df, p = 0.002

Test for departure from linearity:
60—69 years: ΔG = 1.91, 3 df, p = 0.59
Total: ΔG = 5.73, 3 df, p = 0.13

Table 7. Risk ratios for lung cancer in selected occupational groups according to exposure status based upon title for main lifetime occupation (two-digit code) (Reference category: no exposure group)

Occupational group (two-digit code)	Number of subjects		Risk ratio		95 % confidence interval
	Cases	Referents	Unadjusted	Adjusted[a]	
No exposure (OT−)[b]					
Academic, artistic, administrative and clerical work (00, 02—29)	6	20	0.5	0.5	0.2—1.2
Salesmen, commercial travelers (31—33)	7	7	1.9	1.7	0.7—4.1
Farming, forestry (40—42, 44)	12	31	0.6	0.7	0.4—1.2
Road transport work (64)	8	9	1.7	1.4	0.7—2.6
Food, hotel, public safety, other specified work (82, 90—92, 96—99)	8	6	2.7	2.0	0.9—4.3
Possible exposure (OT?)					
Ship offices, deck and engine-room crew work (60—61)	18	9	3.6	1.5	0.6—4.2
Electrical work (76)	6	1	10.9	9.8	1.0—100.9
Wood work (77)	7	16	0.8	0.7	0.2—2.3
Construction work (79)	9	6	2.7	3.0	0.9—10.2
Longshoremen, freight handlers (88)	11	4	5.0	5.7*	1.5—21.2
Packing and wrapping, stationary engine and motor power work, various production process work, building caretaking (81, 84—87, 93—95)	11	10	2.0	1.7	0.6—4.8
Definite exposure (OT+)					
Mining and quarrying work (50—52, 59)	14	2	12.7	10.2*	2.0—52.1
Smelting, metallurgical, foundry work (73)	4	—			
Iron and metalware work (75)	22	20	2.0	1.7	0.8—3.8
Painting and paperhanging work (78)	5	5	1.8	1.7	0.4—7.3
Chemical and related process work (83)	24	18	2.4	2.6*	1.2—5.7

[a] Adjusted for smoking, three levels (0—9, 10—19, ≥20 cigarettes/d)
[b] Reference category: remaining occupational groups in the no exposure category.
* $p<0.05$.

tion and the welding of stainless steel (table 8). The risk ratio for wood dust exposure was significantly reduced (RR = 0.4). Several of the exposures were highly correlated, however. For instance, half of the cases exposed to either stainless steel welding fumes or fertilizers also reported moderate to heavy asbestos exposure. A stepwise logistic regression procedure was therefore applied to the material; it included the different variables into the model according to significance level. Risk ratios for asbestos, wood dust, rock drilling, and fertilizer production remained significant after this procedure (table 9).

With regard to the combined effect of smoking and occupational exposures, the logistic regression model used in this study yielded an independent, additive estimation of ln RR, which implies multiplicative effects at the risk ratio level. Table 10 shows that the risk of lung cancer was considerably increased among heavy smokers who had also been occupationally exposed. Only three cases and three referents had lived the longest part of their life in a dwelling mainly made out of brick or stone.

Discussion

When either title-based or exposure-based occupational information was used, this study showed a statistically significant increased risk of lung cancer among persons judged to have experienced exposure to respiratory carcinogens and other industrial pollutants at their workplace. This finding is in accordance with the results of a nationwide cohort study of 12 000 Norwegians which will soon be published by Kvåle and co-workers (G Kvåle, personal communication). They used the same exposure categorization for main occupation as in the present study and found a risk ratio of 1.6 among subjects in the OT? category and one of 2.6 among those in the OT + category when adjust-

Table 8. Risk ratios for lung cancer according to occupational exposures, based upon questionnaire information (Exposed >3 years of relevant exposure)

Exposure factor	Number of exposed subjects		Risk ratio		95 % confidence interval
	Cases	Referents	Unadjusted	Adjusted*	
Asbestos	55	24	2.9	2.7*	1.5—4.8
Rock drilling	33	17	2.2	2.0*	1.0—3.9
Tunnel/mining	19	10	2.0	1.9	0.8—4.6
Quartz/stone dust	59	35	2.0	1.9*	1.1—3.2
Cement dust	29	13	2.5	2.6*	1.2—5.7
Rockwool/glassfiber	13	11	1.2	1.0	0.4—2.5
Wood dust	20	39	0.5	0.4*	0.2—0.8
Hardwood dust	—	9			
Cellulose/paper	13	10	1.3	1.0	0.4—2.6
Fertilizer production	16	5	3.4	4.2*	1.4—12.7
Plastic/rubber dust	7	7	1.0	0.9	0.3—2.8
Metal dust	56	43	1.4	1.6	1.0—2.7
Tar/asphalt	11	8	1.4	1.1	0.4—3.2
Coke/coal	23	12	2.1	1.5	0.7—3.2
Fuel oils/gasoline	42	35	1.3	1.0	0.6—1.8
Paints, glues, lacquer	17	17	1.0	1.2	0.6—2.6
Solvents or degreasing liquids	47	35	1.5	1.5	0.9—2.6
Welding, all types	28	19	1.6	1.9	0.9—3.7
Welding, stainless, acid proof	16	6	2.8	3.3*	1.2—9.3
Nickel/chromium (excluding welding)	7	6	1.2	1.4	0.4—4.4
Other gases (ammonia, nitrogen oxides, chlorine and sulfur dioxide)	50	32	1.8	1.9*	1.1—3.3

* Smoking, three levels (0—9, 10—19, ≥20 cigarettes/d).
* $p<0.05$.

Table 9. Simultaneous estimation of occupational exposures, logistic regression.

Exposure factor	Step number						Risk ratio, last step	
	0	1	2	3	4	5		
Smoking	****	×	×	×	×	×	4.4 15.4	(10—19 cigarettes/d) (≥20 cigarettes/d)
Urban/rural status	**	*	○	○	○	○		
Asbestos	***	**	×	×	×	×	2.7	
Rock drilling	*	*	*	*	×	×	2.4	
Quartz	**	*	*	*	○	○		
Cement	**	*	*	*	○	○		
Wood dust	**	**	*	×	×	×	0.5	
Hardwood dust	**	*	*	○	○	○		
Fertilizer production	**	**	*	*	*	×	3.7	
Coke/coal	*	○	○	○	○	○		
Welding/stainless	*	*	○	○	○	○		
Other gases	*	*	○	○	○	○		

Other factors: not significant at step zero ($p>0.05$).
**** $p<0.0001$
*** $p<0.001$
** $p<0.01$
* $p<0.05$
× Factor included in the model.
○ Factor lost significance ($p>0.05$).

ment was made for age, region, smoking, and urban/rural place of residence. Time-related information based upon five-digit job titles, however, as used in the present study, would be a more sensitive method for exposure characterization. With this approach, the risk ratios among those in the highest exposure category increased, particularly when the possible exposure category (OT?) was included (tables 5 and 6).

Occupational exposure was more strongly associated with small cell carcinoma and squamous cell carcinoma than with adenocarcinoma, a finding which corresponds to the results of Stayner & Wegman (32) and Kreyberg (20). It is, however, in contrast to the findings of Vincent et al (34) and Kvåle (G Kvåle, personal communication), who report the strongest association between adenocarcinoma and occupational exposures. Different criteria for the classification of histological subtypes of lung cancer among pathologists, and in particular of adenocarcinoma, may have contributed to some of this apparent discrepancy (31).

The observed risk ratios for several of the separate occupational groups are in accordance with those of other studies (3, 27, 37). Although these data were adjusted for smoking, we are cautious in the inter-

Table 10. Risk ratio for combined exposure to smoking (three levels) and occupational exposure based upon exposure status of the main occupational title and number of years in definitely exposed occupations

	Number of subjects		Risk ratio		95 % confidence interval
	Cases	Referents	Unadjusted	Adjusted[a]	
Main occupation					
No exposure (OT –)					
0— 9 cigarettes/d	12	52	1.0	1.0	
10—19 cigarettes/d	21	23	4.0	4.1	2.5—6.8
≥ 20 cigarettes/d	11	4	11.9	13.2	5.8—30.2
Possible exposure (OT?)					
0— 9 cigarettes/d	11	31	1.5	1.7	0.9—3.0
10—19 cigarettes/d	30	17	7.7	6.8	2.3—20.3
≥ 20 cigarettes/d	22	4	23.8	21.9	5.3—89.5
Definite exposure (OT +)					
0— 9 cigarettes/d	14	24	2.5	2.3	1.3—4.2
10—19 cigarettes/d	44	20	7.9	9.6	3.2—28.5
≥ 20 cigarettes/d	11	1	47.7	30.6	7.5—125.6
Number of years in definitely exposed occupations (OT –)					
< 10 years					
0— 9 cigarettes/d	19	74	1.0	1.0	
10—19 cigarettes/d	36	34	4.1	4.1	2.5—6.8
≥ 20 cigarettes/d	21	8	10.2	14.4	6.3—32.6
≥ 10 years					
0— 9 cigarettes/d	18	33	2.1	2.4	1.5—3.8
10—19 cigarettes/d	59	26	8.8	9.7	3.7—26.0
≥ 20 cigarettes/d	23	1	89.6	34.0	9.3—124.3

[a] Urban/rural status.

pretation given them because of the sparse number of subjects in each group.

This is also the case when the separate occupational exposures are studied (table 8). The interpretation of these data is further hampered by the high interdependence between several of the exposure factors. Exposure to stainless steel welding fumes, together with several other variables initially of statistical significance, lost their significance when smoking and asbestos first entered the model. It is of interest that subjects who reported exposure to rockwool in the present study did not carry any excess risk of lung cancer (RR = 1.0). We have no definite explanation for the "protective" effect of wood exposure in this study (RR = 0.4). The result demonstrates the necessity for cautious interpretation of these data, and the possibility of statistically significant results occurring by chance is also close at hand in this study of multiple exposures (2, 7).

All subjects not exposed to the particular factor under study were used for the risk ratio estimates in table 8, while a "cleaner" reference category consisting of subjects not exposed to any of the factors would be another choice (26, 35). With this latter approach, all the rate ratios increased 50 to 100 %, which gave several additional statistically significant results. Because of the aforementioned limitations in the interpretation of the data, we chose to present the most conservative figures.

For a given level of daily cigarette consumption, the relative risk of lung cancer has been shown to increase with age (12). The constant relative risk observed across the age strata in the present study indicates that this age effect is merely an expression of a cumulative consumption of tobacco (33). The present smoking data suggest, furthermore, that the relative risk is an exponential function of the lifetime tobacco dose; this finding is in accordance with those of previous studies (9, 33).

All histological subtypes of lung cancer showed a dose-response relationship to smoking. This relationship is in accordance with the findings of several other studies (32, 34, 36), but it is in contrast with the results of Kreyberg's study (20), in which adenocarcinoma was shown not to be associated with smoking.

When the rate ratio estimates for smoking and occupational exposures were combined, occupationally exposed heavy smokers carried a more than 30-fold excess risk for lung cancer in comparison to unexposed light smokers (0—9 cigarettes/d). The main factor in these dramatic figures, however, was that of smoking.

As regards the selection of cases, histological verification of the diagnosis was not confirmed for eight of the persons. The results for the separate histological subtypes of cancer do not support the possibility of a "diluted" case group in the present study however.

Furthermore, we have no information which might support the possibility of an exposure-related referral of lung cancer cases to the study hospitals. In Vestfold, however, 73 % of the referents were recruited from the town of Tønsberg and neighboring communities, while only 55 % of the cases came from this region. This occurrence indicates a somewhat larger referral area for the cases than for the referents at this hospital. When urban/rural status was included into the model, the risk ratio estimates among the occupationally exposed was slightly reduced, but the con-

tribution of this variable was statistically nonsignificant for all the associations studied.

Patients admitted to the hospitals because of chronic obstructive lung disease were excluded from the reference series because of the possible association between this condition and occupational exposures (16). Patients admitted to the hospital because of another condition, but who also happened to have chronic obstructive lung disease as a concomitant diagnosis, were not excluded, however, as recommended by Lubin & Hartge (23). Furthermore, as all potential exposures after 1970 were omitted, it seems unlikely that the reference diagnosis in 1979—1983 could have influenced participation in industrial activities in the 1960s.

However, as smoking is associated with cardiovascular disease and a wide variety of other diseases, the effect of smoking on lung cancer might have been underestimated in the present study. The exclusion of 80 subjects with potentially smoking-related diagnoses in the reference group (ICD 410—414 ischemic heart disease, ICD 531—535 stomach disease, and ICD 485—519 other respiratory disorders) did not change the observed risk ratios for smoking. Neither was there any change in the risk estimates for occupational exposures when the smoking-related diagnoses were excluded from the analyses.

With regard to possible bias in the estimation of exposure, occupational title-based information is assumed to be less subject to recall bias than exposure-based information (1, 28). As both job-title information and exposure-based information were available for all the subjects in this study, a retrospective method for evaluating possible recall bias has been used (1). A further study of asbestos exposure among metal workers (code 75), of solvent exposure among painters (code 78), and of fertilizer exposure among chemical process workers (code 83) did not reveal any "protective effect" among the unexposed subjects within the given job categories which could indicate an exaggeration of these exposures among the cases in these particular groups.

The allocation of occupations into different exposure categories will always involve some degree of arbitrarity. For example, if woodwork, which was found to be "protective" in the present study, had been allocated to the OT + instead of the OT? category, the risk ratios would have been 2.0 for both groups when adjusted for smoking (three levels) and urban/rural status. On the basis of an a posteriori judgement, however, woodwork might sooner be placed in the unexposed category, which in turn gives the estimates 2.2 and 2.5 for the OT? and OT + categories, respectively.

Random and independent errors in the estimation of the exposure would furthermore tend to diminish the apparent degree of association between exposure and effect (5). This tendency is even greater when the measure used for confounder control, such as for smoking in the present study, is more reliable than the surrogate measures used to characterize the exposure (21). As multiple categories of exposure were used for both variables based on job titles in the present study, the impact of this error is assumed to be considerably reduced, however, in contrast to studies in which the exposure variable is dichotomized (24).

Although the observed crude risk ratios were somewhat reduced when controlled for smoking at various levels, the results do not suggest smoking as a very strong confounder in the present study. Furthermore, other uncontrolled unknown confounding would need to be strongly associated both with the disease and the exposure variables in order to explain the observed associations (38).

Domestic radon exposure has been suggested as a potential confounder in studies of the association between lung cancer and occupational exposures (10). Although information on building material in main dwellings is a very crude indicator of such exposure, this factor can hardly have confounded the results of the present study, as the vast majority of both the cases and referents had mainly lived in wooden houses.

Several of the occupation and exposure factors allocated to the exposed categories in the present study may not represent a cancer hazard in themselves, eg, exposure to several types of dust and gases. However, such exposure factors may promote the effect of established carcinogens, such as those found in tobacco smoke. If that was the case, one would expect a risk ratio of unity for the occupationally exposed nonsmokers and an elevated risk ratio for the occupationally exposed smokers. The smoking distribution among the cases prevents any meaningful study of this relationship however.

Although interview-based information on occupational exposures is probably more likely to be biased by disease state than information on occupation, the former is obviously to be preferred when the aim is to identify etiologic agents in the workplace. However, such information should be supplemented in future studies by exposure data of a quantitative nature, which would increase the validity of the exposure estimation (22). As to the use of occupational titles in occupational epidemiology, the present study suggests that such information might not only be utilized for hypothesis-generating purposes, but also for quantitative assessments, through the evaluation of the role of a combination of all occupational exposures in the development of a disease. However, a prerequisite for such an evaluation would be detailed information on all occupations held in a lifetime, together with a relevant categorization of the exposure variable.

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