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

III Etiologic fraction of occupational exposures

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KJUUS H, LANGÅRD S, SKJÆRVEN R. A case-referent study of lung cancer, occupational exposures and smoking: III Etiologic fraction of occupational exposures. *Scand J Work Environ Health* 12 (1986) 210—215. The proportion of lung cancer related to occupational exposure to respiratory carcinogens and other workplace contaminants has been studied in a hospital-based case-referent study of 176 incident cases and 176 referents, recruited from the medical ward of two county hospitals in southern Norway. On the basis of job title and exposure information, three different approaches for the estimation of etiologic fraction were used, all based upon a trichotomous categorization of the exposure variable. Among the definitely exposed subjects, the etiologic fraction for lung cancer related to occupational exposure factors was from 22 to 35 %, increasing to 37—47 % when the "possibly exposed" categories were included. When asbestos was the only factor to be eliminated, the etiologic fraction estimate suggested a 23 % reduction in the lung cancer incidence in the study population. More than 90 % of the lung cancer cases would theoretically have been prevented if smoking had been completely removed. The relative merits of preventing one or several of the study factors simultaneously is discussed.

Key terms: occupational titles, prevention, respiratory carcinogens.

The proportion of cancer attributable to occupational exposure factors has been widely debated in recent years (3, 5, 7, 8, 24). Some of the variance in the different estimates given might be related to different definitions of "attributability" (3, 5, 11, 18), but a more important factor has been a lack of properly designed studies addressing this particular problem (5). Thus the traditional aim of studies in occupational epidemiology up to now has mainly been directed towards identifying occupational risk factors, rather than towards examining their population distributions.

The etiologic fraction (population attributable risk) has been introduced as an appropriate parameter for the quantitation of the disease-producing role of an etiologic factor, and case-referent studies might directly provide the measures required (12, 13, 20). As it has been suggested that 75 % of all occupational cancers among men are lung cancers (5), the proportion of this disease attributable to occupational exposures should be of particular interest. On the basis of a case-referent study of lung cancer from two county hospitals in southern Norway (9, 10), the quantitative importance of occupational exposures for the development of lung cancer has been studied. Etiologic fraction estimates have thus been calculated, with the use of several operational entities for "occupational exposures," partly based upon lifetime occupational-title information and partly upon exposure-based information obtained from interviews and questionnaires.

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Methods

The study relates to 176 incident cases of lung cancer among men and 176 referents matched for age (±5 years), sex, and hospital. The subjects were obtained from Telemark and Vestfold County Hospitals during the five-year period 1979—1983. The main aspects of the design, material, and methods of the study have been presented elsewhere (9). Information on all occupations in a participant's worklife was obtained by blinded personal interview. The occupations were allocated to three exposure categories (OT+ = definite exposure, OT? = possible exposure, and OT− = no exposure) according to possible exposure to respiratory carcinogens and other pollutants in that particular occupation. Etiologic fraction has been calculated for exposure status OT+ and OT? for main occupation (two-digit code) and according to the number of years in definitely (OT+) or possibly (OT?) exposed occupations (five-digit code). Detailed information on asbestos exposure (four grades, based upon intensity and duration of exposure) and exposure to 22 specific agents/processes (relevant exposure for more than three years) was obtained through the interview and a questionnaire. The participants were then classified into three groups according to their exposure status in relation to the 22 factors [E+ = exposure to definite or possible respiratory carcinogens (asbestos, polycyclic aromatic hydrocarbons, nickel, chromium, stainless

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steel welding, hardwood dust, and tunnel/mining exposure), E? = exposure to factors not assumed to be carcinogenic, and E − = no exposure to any of the 22 factors). The etiologic fraction has been calculated for both the E + and the E? categories.

The etiologic fraction for smoking has been based upon the estimated lifetime consumption of tobacco (in kilograms), recalculated as the number of cigarettes smoked per day (1 cigarette = 1 g of tobacco), on the assumption of a 45-year smoking period (the average smoking time among those who had ever smoked).

The estimation of the etiologic fraction has been performed according to principles outlined by Miettinen (13) and Levin (12). In the case of a polytomous determinant, the overall etiologic fraction among all the cases in the study population (EFp) has been calculated as $\Sigma EFe \times CF$, where CF is the case fraction in each category of the determinant and EFe is the etiologic fraction among the exposed. EFe has been calculated as $(RR - 1)/RR$, where RR is the adjusted odds ratio for those exposed in each exposure category compared to those without any exposure. The adjusted odds ratios were obtained from a logistic regression analysis. The 95 % confidence interval estimates (95 % CI) for the EPp have been based upon the standard error given by Walter (21).

Results

On the basis of tables 4 to 6 in a previous paper (9), we have estimated the etiologic fraction of occupational exposures among the exposed (EFe), among all cases (EFp), and the number of "etiologic" cases (EC) using occupational-title information as a basis (table 1). Among the subjects occupationally exposed in their main occupation (OT +), the etiologic fraction (EFe) was 1.3/2.3 = 56.5 %. It follows that 39 of the 69 cases in this exposure category might be considered as "etiologic" cases (EC), and the etiologic fraction among all cases (EFp) was estimated to be 22.2 % (39.0 of 176 subjects). Among the 100 cases with more than 10 years in exposed occupations, 59.7 cases might be attributed to occupational exposure, a calculation which gives an etiologic fraction among all cases (EFp) of 34.0 %. If subjects possibly exposed (OT?) in their main occupation were included, the EFp was 36.9 %, and, if half the years in possibly exposed occupations (½ OT?) were added to the exposure time in OT + occupations, the corresponding etiologic fraction (EFp) of more than 10 years of exposure was estimated to be 45.4 %. All these estimates have been adjusted for smoking habits (three levels) and urban/rural status.

With regard to exposure-based information, asbestos was identified as an important factor among the occupational exposure variables in the present study (10). Fifteen of the 23 cases moderately exposed to asbestos (grade 2) and 16 of the 21 cases heavily exposed (grade 3) were estimated as etiologic cases which might theoretically have been prevented in the absence of such exposure (table 2). Altogether, the etiologic fraction due to asbestos exposure among all the cases was estimated to be 23.0 %.

Correspondingly, the overall etiologic fraction due to smoking five cigarettes/d or more was estimated to be 82.6 %. As there were only two nonsmokers among the cases, an "unclean" reference category (0—4 cigarettes/d) had to be used for this comparison. In a separate analysis, the etiologic fraction (EFp) due to all smoking was estimated to be 92.3 %.

We evaluated the quantitative importance of all 22 agents/processes investigated in the present study by pooling the exposure variables into definite or probable

Table 1. Etiologic fraction (EF) of occupational exposures, based upon occupational title information.

	Number of cases (N = 176)	Risk ratio[a]	EF among exposed (EFe %)	Etiologic cases (EC)	EF among all cases (EFp %)
Main occupation					
Possible exposure (OT?)	63	1.7	41.2	25.9	14.7
Definite exposure (OT +)	69	2.3	56.5	39.0	22.2
Possible (OT?) and definite (OT +) exposure	132	.	49.2	64.9	36.9
95 % confidence interval	.	.	.	.	(16.5—52.9)
Number of years of definite exposure (OT +)					
10—19	38	2.2	54.6	20 7	11.8
20—29	35	2.2	54.6	19.1	10.9
≥ 30	27	3.8	73.7	19.9	11.3
≥ 10	100	.	59.7	59.7	34.0
95 % confidence interval	.	.	.	.	(13.6—54.4)
Number of years of definite exposure (OT +) and half the years in possible exposure (½ OT?)					
10—19	46	2.8	64.3	29.6	16.8
20—29	41	2.2	54.6	22.4	12.7
≥ 30	34	5.6	82.1	27.9	15.9
≥ 10	121	.	66.0	79.9	45.4
95 % confidence interval	.	.	.	.	(29.4—61.4)

[a] Adjusted for smoking habits (three levels) and urban/rural status.

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Table 2. Etiologic fraction (EF) of asbestos exposure and smoking, adjusted for urban/rural status (RR = risk ratio)

Cigarettes per day	Asbestos grade						RR (smoking)	EF among exposed (EFe %)	Etiologic cases (EC)	EF among all cases (EFp %)
	0	1	2	3	1—3	0—3 (total)				
0— 4										
Cases	6	3	—	—	3	9	1.0	0	0	0
Referents	37	10	5	2	17	54				
5— 9										
Cases	8	11	4	4	19	27	2.9	65 5	17.7	10 1
Referents	28	21	3	1	25	53				
10—19										
Cases	40	30	14	13	57	97	9 1	89 0	86 3	49.1
Referents	31	23	3	2	28	59				
20—29										
Cases	11	9	3	4	16	27	16 5	93.9	25.4	14.4
Referents	6	2	—	1	3	9				
≥30										
Cases	6	8	2	—	10	16	90.3	98.9	15.8	9 0
Referents	—	1	—	—	1	1				
≥ 5										
Cases	65	58	23	21	102	167		86.9	145.2	82 6
Referents	65	47	6	4	57	122				(71 4—93.8)
Total										
Cases	71	61	23	21	105	176				
Referents	102	57	11	6	74	176				
RR (asbestos)	1 0	1.2	2.7	4.1	.	.	.	.	.	.
EFe %	0	16.7	63.0	75.6	38.7	.	.	.	.	.
EC	0	10.2	14.5	15.9	40.6	.	.	.	.	.
EFp %	0	5 8	8.2	9.0	23.0	.	.	.	.	.
95 % confidence interval					7.7—38.3		.	.	.	.

Table 3. Etiologic fraction (EF) of all occupational exposures and smoking, adjusted for urban/rural status. (RR = risk ratio)

Cigarettes per day	Exposure status[a]					RR (smoking)	EF among exposed (EFe %)	Etiologic cases (EC)	EF among all cases (EFp %)
	E—	E?	E+	E? and E+	Total				
0— 4									
Cases	1	5	3	8	9	1.0	0	0	0
Referents	18	18	18	36	54				
5— 9									
Cases	6	7	14	21	27	2.8	64 3	17.4	9.9
Referents	12	18	23	41	53				
10—19									
Cases	10	27	60	87	97	8 7	88.5	85 9	48 8
Referents	14	21	24	45	59				
20—29									
Cases	5	6	16	22	27	16.3	93.9	25 3	14 4
Referents	3	2	4	6	9				
≥30									
Cases	1	5	10	15	16	88.0	98.9	15.8	9.0
Referents	1	—	—	—	1				
≥ 5									
Cases	22	45	100	145	167		86.5	144.4	82 1
Referents	30	41	51	92	122				(70 9—93.3)
Total									
Cases	23	50	103	153	176				
Referents	48	59	69	128	176				
RR (E—, E?, E+)	1.0	1.7	2.5						
EFe	0	41 2	60.0	53.8					
EC	0	20 6	61.8	82.4					
EFp	0	11.7	35.1	46.8					
95 % confidence interval				27.0—68.4					

[a] E—: no exposure, E?: ≥ 3 years of exposure to factors not assumed to be carcinogenic, E+: ≥ 3 years of exposure to possible or definite lung carcinogens

carcinogens (E+) and other agents/processes (E?) (table 3). Of the 103 cases exposed to known or probable carcinogens (E+), 60 % were estimated to be etiologic cases. The overall etiologic fraction (EFp) due

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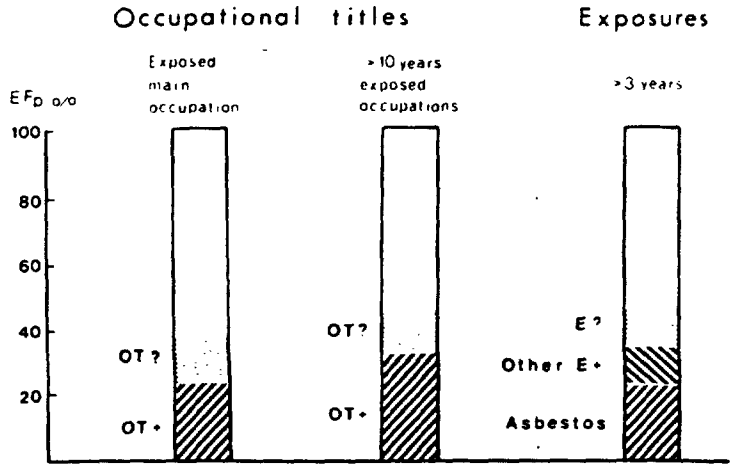
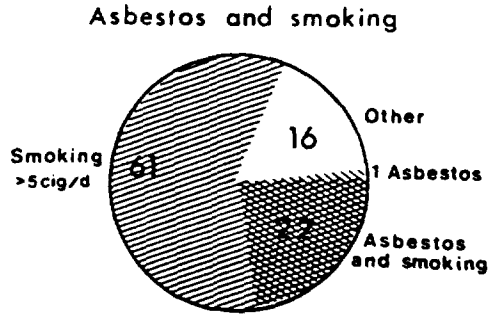


Figure 1. Summary of etiologic fraction (EFp) estimates, based upon main occupation (OT + and OT?), more than ten years in exposed occupations (OT + and ½ OT?) and specific exposure factors. (OT? = possible exposure, OT + = definite exposure, ½ OT? = half the years in possible exposure, E? = exposure to factors not assumed to be carcinogenic, E + = exposure to definite or possible respiratory carcinogens)

to all occupational exposures in this population was 46.8 %, and the corresponding smoking etiologic fraction (>5 cigarettes/d) was 82.1 %.

A comparison of the different estimates of EFp is illustrated in figure 1. For exposure to definite or probable carcinogens (OT + and E + categories), the estimates based upon main occupation, more than 10 years in OT + occupations, and exposure-based information were 22, 34, and 35 %, respectively. When the OT? and E? categories were included, the overall etiologic fraction of all occupational exposures was 37, 45, and 47 % for the three approaches, respectively.

From table 2, the etiologic fraction of the combined exposure to asbestos (grade 1—3) and smoking (>5 cigarettes/d) can be estimated. With the use of the subjects unexposed to asbestos and smoking (0—4 cigarettes/d) as the reference category (6 cases and 37 referents), the combined EFp of asbestos and/or smoking was estimated to be 83.8 %, which is only 1.2 % higher than the etiologic fraction for smoking alone. This relationship is shown in figure 2. Correspondingly, table 3 shows that, when the subjects exposed to any level of smoking (>5 cigarettes/d) and/or occupational exposures (E + and E?) were contrasted with the unexposed (1 case and 18 referents), the combined EFp was estimated to be 94.4 %. It follows that 12.3 % of all the cases were theoretically preventable by the elimination of the occupational factors only (94.4 − 82.1 %), 47.6 % (94.4 − 46.8 %) by intervention on smoking habits only, and 34.5 % (94.4 − 47.6 − 12.3 %) by intervention either on smoking or on occupational exposures. The estimates are subject to large sampling errors, however, based as they are on only one unexposed nonsmoking case.



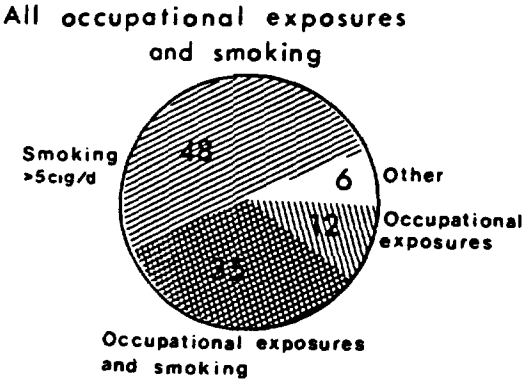


Figure 2. Etiologic fraction of combined exposure to smoking (>5 cig/d) and asbestos exposure and to smoking (>5 cig/d) and all occupational exposure factors (E + and E?), respectively. (cig = cigarettes)

Discussion

To estimate the fraction of disease that may be avoided by reducing or eliminating the population exposure to a given etiologic agent is a prerequisite for the evaluation of disease-preventing strategies. However, in spite of the educational appeal of etiologic fraction estimates, these measures must be interpreted with caution. If the etiologic fraction is equated with the expected change in disease load following the reduction

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or complete removal of a risk factor, it presupposes a causal relationship between the factor and disease, and not merely a statistical association. The complex situations which arise when this index is estimated in the presence of several risk factors and their combinations warrant further caution in its interpretation (15, 19, 22, 23). However, as far as the estimates given in the present study represent causal relationships, they might contribute to the discussion of the proportion of lung cancer which might be due to occupational exposures, and which thereby could theoretically be preventable.

As "occupational exposures" is an inaccurate description of exposure to a multitude of specific agents during a working career, the estimates of the fraction of a disease due to "occupational exposure" are highly dependent upon the definition and categorization of the exposure variable. By the use of both title-based and exposure-based occupational information, we have utilized a trichotomous exposure variable, with an intermediate category of possibly exposed subjects (OT? and E?). On the basis of the definitely exposed categories only, the three different approaches gave estimates of EFp in the range of 22—35 %. When the "possibly exposed" were included in the exposed category, as suggested by Berrino (2) and Walter (23), the data indicated that from 37 to 47 % of the lung cancers in this study might have been preventable if all occupational exposures were eliminated.

Previous estimates of the etiologic fraction of lung cancer due to occupational exposures have been in the range of 5—36 % (1, 6, 14, 16, 17). Most of these estimates were based, however, upon more crude measures of the exposure variable, obtained through postal questionnaires (6) or interviews of next of kin (1, 16, 17). Mainly by using personal interviews, Pastorino et al (14) have estimated the proportion of lung cancer due to occupational exposures among 211 cases and 351 referents in an industrialized area in northern Italy. Their study, which has many design aspects in common with the present one, estimates the etiologic fraction of possible and probable exposure to defined lung carcinogens at 33.0 %, rising to 41.7 % when nonspecific occupational exposures are included.

With regard to the external validity of the present study, the area in which the study was performed is considered somewhat more industrialized than the average for the country. In a recently performed nationwide cohort study of 12 000 Norwegian men, census-based information of main occupational title was allocated to corresponding exposure groups as in the present study (G Kvåle et al, "Occupational Exposure and Lung Cancer Risk," submitted for publication). They found an etiologic fraction of 26 % due to occupational exposure (OT + and OT?) after adjustment for age, region, urban/rural place of residence and smoking, and one of 20.5 % after further adjustment for socioeconomic class. Through the application of the figures for exposure prevalence in that study to our data, the etiologic fraction estimate of 36.9 % in the present study was reduced to 29.3 %. This figure was further reduced to 27.9 % if the EFp was based upon the exposure status of occupational title (two digits) of all 1.5 million economically active men of 16 years of age or more in Norway in 1970 (4). These figures suggest that the exposure frequencies observed among the referents in the present study are higher than in the general Norwegian population and that the estimates of the proportion of lung cancer related to occupational exposures in other parts of the country might be somewhat lower.

A major proportion of the lung cancer assumed to be due to occupational exposures in the present study is related to asbestos exposure (figure 1). Thus, if asbestos were eliminated, the etiologic fraction estimate would suggest a 23 % reduction in the lung cancer incidence of this population. Although asbestos may have been in more common use in the study area than in other parts of the country, the figure is high compared to other estimates (5, 7). The more-detailed exposure characterization in the present study may have contributed to this high figure.

However, the greatest preventable effect from intervening in one single factor is obviously the elimination of tobacco exposure. Reducing smoking to ≤ 5 cigarettes/d would theoretically have eliminated more than 80 % of all lung cancers in the present study, and only 8 % of all cases would have been left in the absence of smoking at all levels.

A further question, however, is that of the relative merits of preventing one or several factors simultaneously. It is important to point out that the individual EFp estimates of two factors contributing to a multifactorial disease are not invalidated, although their sum exceeds 100 %, and each estimate must be interpreted as a measure of disease reduction if the factor in question were the first to be eliminated (22). In figure 2, it is shown that the preventive effect of reducing smoking to less than 5 cigarettes/d is reduced from 83 to 48 % if occupational exposures are removed first. The opposite strategy seems even less attractive from a public health point of view, where very little is gained in addition by removing occupational exposures after the successful elimination of smoking, as opposed to removing smoking alone.

In conclusion, the present study indicates a relatively large proportion of lung cancer which might be prevented by the elimination of occupational exposures. The effect of preventing smoking would be dramatic.

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