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Low-Dose Exposure to Asbestos and Lung Cancer: Dose-Response Relations and Interaction with Smoking in a Population-based Case-Referent Study in Stockholm, Sweden

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This population-based case-referent study investigated the lung cancer risk associated with occupational exposure to asbestos, focusing on dose-response relations and the interaction with tobacco smoking. Incident cases of lung cancer among males aged 40–75 years in Stockholm County, Sweden, were identified from 1985 to 1990. Referents were selected randomly within strata (age, inclusion year) of the study base. Questionnaires administered to subjects or their next of kin gave information on occupations, tobacco smoking habits, and residences. Response rates of 87% and 85% resulted in 1,038 cases and 2,359 referents, respectively. Occupational exposures were assessed by an industrial hygienist. Lung cancer risk increased almost linearly with cumulative dose of asbestos. The risk at a cumulative dose of 4 fiber-years was 1.90 (95% confidence interval (CI): 1.32, 2.74), higher than that predicted by downward linear extrapolation from highly exposed occupational cohorts. The relative risk (exp(beta)) for a transformed dose variable ln(fiber-years + 1) was 1.494 (95% CI: 1.193, 1.871) per unit of exposure. The joint effect of asbestos and smoking was estimated to be 1.15 (95% CI: 0.77, 1.72) times that predicted from the sum of their individual effects and 0.31 (95% CI: 0.11, 0.86) times that predicted from their product, indicating a joint effect between additivity and multiplicativity. *Am J Epidemiol* 2002;155:1016–22.

asbestos; case-control studies; lung neoplasms; occupational diseases; occupational exposure; smoking

Evidence for the carcinogenicity of asbestos has been accumulating since the 1950s, leading many western countries to ban asbestos. However, asbestos is still mined, and asbestos products are manufactured and used in many parts of the world. In 1996, the quantity of asbestos mined in the world was estimated as 2,290,000 metric tons (1). Although both the International Agency for Research on Cancer (2) and the World Health Organization (3, 4) have classified asbestos as carcinogenic to humans, regardless of fiber type, a debate is still ongoing about the hazards from asbestos exposure, especially regarding low-dose exposure to chrysotile (5). The hazards associated with exposure to low levels of asbestos in the general environment, emitted from asbestos industries or ventilation systems, are also extensively debated because of sparse epidemiologic data on dose-response relations in the low-dose range (6–8).

A synergistic effect between tobacco smoke and asbestos in the causation of lung cancer was indicated by an early study of US insulation workers (9). A later and larger cohort study of US insulators showed that the joint effect of asbestos and tobacco smoke followed a multiplicative pattern; that is, the risk for those workers exposed to both asbestos and tobacco smoke equaled the product of the risk associated with each factor (10). However, later studies have indicated joint effects ranging from supramultiplicative (11, 12) to intermediate between additive and multiplicative (13, 14). Most systematic reviews have found a marked heterogeneity in the magnitude of the joint effect (15–17), although one review considered the present data indicative of multiplicativity (18). Differences in study design, asbestos types, exposure levels, or choice of cutoffs in the exposure variables explained the observed heterogeneity only partially (17).

In this context, the difference between the concepts of biologic as opposed to statistical interaction should be emphasized. Statistical interaction is evaluated as departure from a specified statistical model (in the case of logistic regression, as departure from multiplicativity), whereas biologic interaction commonly is defined as a deviation from additivity (19). Several quantitative measures have been proposed to evaluate interaction, among them the synergy index (20).

On the basis of an assumed multiplicativity between asbestos exposure and smoking, it has been emphasized that it is especially important for asbestos-exposed persons to quit smoking, since cases of lung cancer induced by both exposures (due to the interaction) would be prevented, along

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Abbreviations: CI, confidence interval; TLV, threshold limit value.

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with those induced by smoking alone. This concern has led to the formation of smoking prevention programs for the asbestos exposed (21).

The relative lack of direct data on the lung cancer risk from low doses of asbestos, and the ambiguity over the nature of the effect of concurrent exposure to tobacco smoke, led us to investigate this issue in a population-based case-referent study of lung cancer among men in Stockholm, Sweden, that included individual data on occupational history, coded for asbestos exposure by an industrial hygienist; lifetime smoking history; and other data (22). The study provided a good opportunity to examine the effects of low-level exposure to asbestos; before asbestos was banned in 1974, only use of asbestos products occurred in the Stockholm area, and there was no mining or large-scale manufacturing of such products, leading to comparatively low exposure levels.

MATERIALS AND METHODS

We conducted a population-based case-referent study. The study base, methods of exposure assessment and analysis, as well as basic findings on six occupational exposures (diesel exhaust, other combustion products, asbestos, oil mist, metal dust, and welding fumes) were presented earlier (22). The methods are briefly summarized here, and we provide a more detailed description of the classification of asbestos exposure. Methods and findings regarding air pollution in the general environment have been published separately (23, 24).

Study subjects

The study population comprised all men aged 40–75 years who were residents of Stockholm County at any time between 1985 and 1990 and who had lived outside the county for no more than 5 years during the period 1950–1990. All cases of lung cancer (*International Classification of Diseases,* Seventh Revision, code 162.1) diagnosed from January 1, 1985, to December 31, 1990, were identified from the regional cancer register of Stockholm County.

Referents were selected randomly from computerized registers of the population of Stockholm County and were frequency matched to cases on age (5-year groups) and year of inclusion in the study (1985–1990). Two referent groups were selected. The first, "population referents," was selected with no restrictions from all men alive at the end of each respective inclusion year. The second, "mortality-matched referents," was frequency matched to cases with regard to vital status as of December 31, 1990 (in addition to age and inclusion year) and was selected from those men alive at the beginning of each inclusion year. Because of the high mortality rate among lung cancer patients, the second referent group was included to evaluate reporting bias that might arise from the imbalance in the proportion of persons alive when data were collected for cases and referents. The deceased referents were selected from persons who had not died from diseases related to tobacco smoking. The analyses for both occupational and environmental exposures indicated no large difference in risk when the population-based or mortality-matched referents were included (22, 24), and both referent series were combined for the present analyses.

A postal questionnaire was sent to study subjects or, for deceased subjects, their next of kin. The questionnaires were supplemented by telephone interviews if answers were incomplete. The response rate was high for both cases (87 percent) and referents (85 percent). A total of 1,038 cases and 2,359 referents were included in the analyses.

The study was approved by the ethics committee of the Karolinska Institutet in Stockholm.

Exposure data

The questionnaire asked about lifetime occupational history, residential history beginning in 1950, lifetime smoking habits, and some other potential risk factors for lung cancer. Occupational history included company name and location, occupation, and work tasks for each work period with a duration of at least 1 year.

The intensity and probability of exposure to asbestos during every work period was assessed from the questionnaires by a senior industrial hygienist, blinded to the case-referent status of study subjects. The exposure assessments were based mainly on a large survey of asbestos exposure conducted at Swedish workplaces in 1969–1973. The survey involved over 2,400 samples at 35 workplaces, representative of 70–75 percent of the total quantity of asbestos imported by Sweden at that time (25). Samples were taken by using the membrane filter method and were analyzed by phase contrast microscopy using the criteria specified by the American Conference of Governmental Industrial Hygienists in 1973 (26). In addition, findings from smaller studies, both published and unpublished, were also used. Changes in asbestos levels over calendar periods were accounted for in the estimations, especially the large decrease in exposure levels that occurred when asbestos was banned in 1974.

Time-period-specific annual arithmetic average levels of exposure to asbestos were classified by using a four-level scale, with cutoffs related to the Swedish threshold limit value (TLV) in 1993 (0.30 fibers/ml). Cutoffs at 1/10, 1/3, and 1/1 of the TLV level resulted in the following classes: less than 0.03 fibers/ml ("unexposed"), 0.03–0.09 fibers/ml, 0.10–0.29 fibers/ml, and more than or equal to 0.30 fibers/ml. The probability that a person had experienced the intensity assigned for each period was assessed by using four classes based on the estimated exposure prevalence for each occupation/job task: 0, 20, 50, or 85 percent. For some work periods, it was equally relevant to assign a high-intensity but low-probability code or a low-intensity but high-probability code for asbestos exposure; under these circumstances, we gave preference to a high probability. Cumulative exposure was calculated as the product of intensity, probability, and duration of exposure, summed over all work periods during the occupational history and expressed as fibers $\times$ ml^{-1} $\times$ years (fiber-years).

Data analysis

The relative risks and 95 percent confidence intervals for developing lung cancer were estimated by using unconditional logistic regression. All analyses were adjusted for matching of the referents (age group and year of inclusion) by use of indicator variables.

Relative risks were adjusted (by using indicator variables) for occupational exposure to diesel exhaust, combustion products (22), historical environmental air pollution from road traffic, and a proxy for indoor radon levels in each dwelling since 1955 (24). Smoking was accounted for by use of four indicator variables signifying former smokers (≥2 years since stopping) and current smokers smoking on average 1–10, 11–20, and more than 20 cigarettes a day or the corresponding quantity of tobacco. In addition, continuous variables were used to adjust for amount of time since stopping smoking and, for current smokers, intensity of smoking (to avoid residual confounding arising from the relatively wide smoking intensity categories in the indicator variables). Analyses that might be confounded by exposure to asbestos were adjusted by using an indicator variable for exposure above or below a cutoff at 0.9 fiber-years, the median cumulative exposure among exposed referents (22).

The joint effect of asbestos and tobacco smoke was evaluated in terms of departure from additive or multiplicative models. Departure from multiplicativity was investigated by including an interaction term in the logistic regression model; departure from additivity was evaluated from the confidence interval of the synergy index (in the dichotomized analysis only) according to methods described by Hosmer and Lemeshow (27). An SAS software program developed by Lundberg et al. was used (28).

RESULTS

Of the cases, 20.0 percent were ever exposed to asbestos for at least 1 year, and the corresponding proportion for referents was 14.4 percent. The cases and referents had had 10,441 work periods of at least 1 year's duration. The codes for intensity and probability of asbestos exposure assigned to these work periods are shown in table 1. Generally, the cumulative doses of asbestos were low, ranging from zero (or environmental background levels) to a maximum of 20.4 fiber-years.

The numbers of cases and referents per combination of exposure class for asbestos and tobacco smoke are presented in table 2. The number of persons who had high doses of both tobacco smoke and asbestos was low, and, for analysis of interaction, the two highest dose groups for both exposures were combined. All groups were retained when the variables were investigated one by one. Former smokers were excluded from the analyses of interaction.

The relative risk of lung cancer increased monotonically with cumulative dose of asbestos. Figure 1 shows the point estimates and 95 percent confidence intervals for the categorized cumulative dose of asbestos (the same classes as those in table 2). The point estimates indicated a dose-response curve that did not follow an exponential pattern, which would correspond to a straight line in figure 1, when a log scale was used for the y-axis. Instead, the risk at high doses was lower than that predicted by an exponential model and was close to that predicted by a linear model. To fit the multiplicativity inherent in the logistic model (29), doses were transformed by using a logarithmic transformation: dose = ln(fiber-years + 1). The resulting continuous risk curve is shown as a solid line in figure 1, and the dotted

TABLE 1. Cross-tabulation of all 10,441 work periods for male cases and referents, subdivided by intensity and probability of exposure to asbestos, Stockholm, Sweden, 1985–1990

Probability (%)	Intensity (fibers/ml)				
	0–0.02	0.03–0.09	0.10–0.29	≥0.30	All intensities
0	9,659				9,659
20		85	10	3	98
50		260	42	1	303
85		252	103	26	381
All probabilities	9,659	597	155	30	10,441

TABLE 2. Numbers of male cases and referents (cases/referents), cross-tabulated by cumulative dose of asbestos and tobacco smoking habits, Stockholm, Sweden, 1985–1990

Asbestos exposure (fiber-years)	Average exposure per class (fiber-years)	Never smokers	Former smokers	Current smokers: no. of cigarettes smoked/day (average in g/day)				Total
				1–10 (7.7)	11–20 (16.5)	21–30 (24.6)	>30 (31.3)	
Unexposed	0	26/620	215/724	112/262	276/299	152/98	49/17	830/2,020
>0–0.99	0.56	4/51	29/67	14/20	25/35	21/12	2/3	95/188
1–2.49	1.51	3/26	18/29	10/19	30/24	8/5	1/1	70/104
2.5–4.49	3.44	1/4	7/10	1/7	14/5	2/2	0/0	25/28
≥4.5	8.80	2/4	1/10	5/4	3/0	5/1	2/0	18/19
Total		36/705	270/840	142/312	348/363	188/118	54/21	1,038/2,359

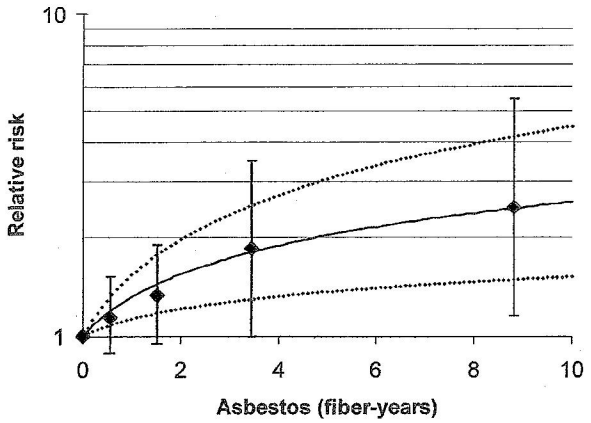

FIGURE 1. Relative risk of lung cancer and cumulative dose of asbestos for men in Stockholm, Sweden, 1985–1990. Diamonds and error bars indicate point estimates and 95% confidence intervals of the relative risks for categorized cumulative asbestos doses plotted at the position of the arithmetic average dose within each class (refer to table 2 for a definition of classes). The solid line indicates the relative risk and the dotted lines the 95% confidence interval for a continuous dose variable obtained by using the transformation ln(fiber-years + 1). The relative risk (exp(beta)) for the transformed dose variable was 1.494 (95% confidence interval: 1.193, 1.871) (refer to the text). Relative risks were adjusted for age group, selection year, residential radon, tobacco smoking, environmental nitrogen dioxide, diesel exhaust, and combustion products.

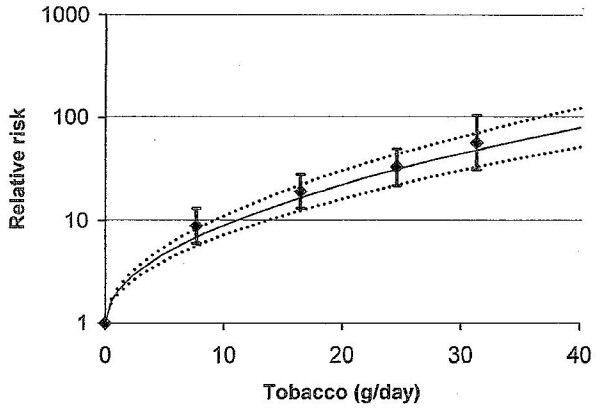

FIGURE 2. Relative risk of lung cancer and tobacco smoking among men in Stockholm, Sweden, 1985–1990. Former smokers were excluded. Diamonds and error bars indicate point estimates and 95% confidence intervals of the relative risks for categorized tobacco doses (g/day) plotted at the position of the arithmetic average dose within each class (refer to table 2 for a definition of cutoffs). The solid line indicates the relative risk and the dotted lines the 95% confidence interval for a continuous dose variable obtained by using a regression model based on the following dose transformation: square root(g/day). The relative risk (exp(beta)) for the transformed variable was 1.999 (95% confidence interval: 1.865, 2.142). Relative risks were adjusted for age group, selection year, residential radon, environmental nitrogen dioxide, diesel exhaust, combustion products, and asbestos.

lines represent the 95 percent confidence interval. The relative risk (exp(beta)) for the transformed variable was 1.494 (95 percent confidence interval (CI): 1.193, 1.871) per unit of exposure. The fitted risks were very close to those obtained for the categorical variable. At any cumulative dose, the risk predicted by the model may be obtained graphically from figure 1 or calculated in the following way: The relative risk at a cumulative dose of x fiber-years = $1.494^{\ln(x+1)}$. At this dose, the 95 percent confidence interval may be obtained by substituting 1.193 and 1.871 for 1.494. For example, at 4 fiber-years, the risk was $1.494^{\ln(4+1)} = 1.90$ (95 percent CI: 1.32, 2.74).

The risk associated with asbestos exposure was also calculated separately for never smokers and current smokers. The exp(beta) for the transformed dose variable (ln(fiber-years + 1)) was 1.345 (95 percent CI: 1.024, 1.767) for current smokers and 2.848 (95 percent CI: 1.486, 5.458) for never smokers. Substituting a dose of 4 fibers-years into $1.345^{\ln(\text{fiber-years}+1)}$ produced a relative risk of 1.55 for current smokers and $2.848^{\ln(4+1)} = 5.38$ for never smokers at this dose level.

As expected, lung cancer risk was strongly influenced by tobacco smoking (figure 2). The risk of lung cancer for those smoking more than 30 cigarettes a day or the corresponding quantity of tobacco (on average 31.7 g) was more than 50 times higher than that for lifelong nonsmokers. For smoking, the categorical data indicated a dose response in between linearity and exponentiality. Use of either the dose (grams per day) directly or a logarithmic transformation (ln(g/day + 1)) gave a poor fit. Instead, the risk was modeled by taking the square root of the number of grams smoked per day, which provided a reasonably good fit to the categorized data (figure 2).

The risks of lung cancer for combinations of asbestos dose and tobacco smoking habits are shown in table 3. Exposure to asbestos was associated with an increased lung cancer risk for both current smokers of different quantities of tobacco and lifelong nonsmokers. The dose response did not increase monotonically in all smoking strata, probably because of low numbers, as indicated by the wide confidence intervals.

The degree of synergy between tobacco smoke and asbestos can be evaluated crudely by comparing the relative risks shown in the four corner cells of table 3. If tobacco smoke and asbestos have a joint effect that follows multiplicativity, the relative risk given in the cell combining the highest dose of asbestos and tobacco smoke would equal the product of the risk for nonsmokers highly exposed to asbestos and smokers in the highest smoking category but not exposed to asbestos (20): $45.4 \times 10.2 = 463.1$. The observed risk is considerably lower, 80.6, indicating that the joint effect is less than multiplicative. The observed risk is not much in excess of that predicted by using an additive model (20): $45.4 + 10.2 - 1 = 54.6$.

Statistical tests of the nature of the joint effect of tobacco smoke and asbestos were performed in models in which both dichotomized and continuous variables for asbestos and smoking were used. In the dichotomized analysis, asbestos exposure of more than or equal to 1 fiber-year was compared with no exposure, and current smokers were com-

TABLE 3. Relative risks* of lung cancer in relation to exposure to asbestos and tobacco smoking, using unexposed to both agents as referents, for men in Stockholm, Sweden, 1985–1990

Asbestos exposure (fiber-years)	Never smokers		Current smokers (no. of cigarettes smoked/day)					
			1–10		11–20		>20	
	RR	95% CI†	RR	95% CI	RR	95% CI	RR	95% CI
Unexposed	1		10.5	6.7, 16.6	23.3	15.2, 35.8	45.4	28.6, 71.9
>0–0.99	1.8	0.6, 5.5	18.1	8.2, 40.4	17.0	8.8, 32.7	38.5	17.7, 83.4
1–2.49	2.7	0.7, 9.5	12.1	5.1, 29.3	29.8	15.1, 58.6	36.8	11.9, 113.7
≥2.5	10.2	2.5, 41.2	13.56	4.6, 40.0	86.2	28.8, 258.2	80.6	20.2, 322.0

* Relative risks (RRs) were adjusted for age group, inclusion year, residential radon, environmental nitrogen dioxide, diesel exhaust, and combustion products.
† CI, confidence interval.

TABLE 4. Relative risks* of lung cancer, interaction terms, and synergy index for men in Stockholm, Sweden, 1985–1990

	Asbestos exposure				Asbestos exposure			
	None		≥1.0 fiber-years		None		≥2.5 fiber-years	
	RR	95% CI†	RR	95% CI	RR	95% CI	RR	95% CI
Never smokers	1		4.2	1.6, 11.1	1		10.2	2.5, 41.2
Current smokers	21.8	14.4, 32.8	28.6	19.9, 48.3	21.7	14.3, 32.6	43.1	20.1, 88.6
			Point estimate	95% CI			Point estimate	95% CI
Interaction term in multiplicative model			0.31	0.11, 0.86			0.20	0.04, 0.89
Synergy index			1.15	0.77, 1.72			1.41	0.65, 3.04

* Relative risks (RRs) were adjusted for age group, inclusion year, residential radon, environmental nitrogen dioxide, diesel exhaust, and combustion products. Former smokers, and those exposed to asbestos in the interval 0 to <1.0 or 0 to <2.5, respectively, were excluded from the analysis.
† CI, confidence interval.

pared with lifelong nonsmokers (table 4). This analysis supported a less than multiplicative effect, with a relative risk of 0.31 (95 percent CI: 0.11, 0.86) for the interaction term. The synergy index was 1.15 (95 percent CI: 0.77, 1.72), indicating a joint effect close to additivity. Similar conclusions were reached when asbestos exposure equal to or higher than 2.5 fiber-years was contrasted to none, as shown in the right-hand part of table 4.

A model based on the continuous variables for asbestos and smoking, presented in figures 1 and 2, produced an interaction term of 0.85 (95 percent CI: 0.73, 0.99). Again, this value indicates a submultiplicative joint effect.

Only six cases who did not smoke had a cumulative asbestos dose of more than or equal to 2.5 fiber-years. The potential impact of misclassification of smoking habits was assessed by recoding one of these six cases as a former smoker. This recoding changed the interaction term in the model above from 0.31 to 0.37 (95 percent CI: 0.13, 1.09), which is not formally statistically significant but still indicates a submultiplicative joint effect.

The risk estimates differed only slightly with regard to reference group. The relative risk for asbestos exposure of more than or equal to 2.5 fiber-years versus nonexposure was 1.84 (95 percent CI: 1.00, 3.38) when the population referents were used and 2.00 (95 percent CI: 1.08, 3.67) with the mortality-matched referent group.

Referents were frequency matched to cases with regard to age group and year of inclusion in the study. When there are very low numbers in some strata, unconditional regression may yield biased results. Conditional regression analysis was performed to investigate this possibility; the 42 combinations of seven age groups and six inclusion years were used to define the matched sets, and the analyses presented in table 3 were repeated. Nearly identical results were obtained.

DISCUSSION

The present study is one of few investigating risk estimates for lung cancer in relation to low-dose exposure to asbestos. The study incorporated individual estimates of cumulative dose of asbestos as well as individual data on tobacco smoking, other occupational exposures, residential radon, and environmental traffic-related air pollution.

Our study showed an obvious excess risk of lung cancer in association with occupational exposure to asbestos. The risk per fiber-year observed, based on a population in which the level of exposure was low, was much higher than that predicted by downward linear extrapolation from studies of highly exposed cohorts (30, 31). Dose-response calculations based on such cohorts show a large variability in risk per unit of exposure (fiber-year), depending on asbestos types,

industry types, and populations studied (30). However, there is some agreement that the risk in high-dose ranges is linearly related to cumulative dose of asbestos, as described by the following equation: relative risk = $1 + k \times$ (fiber-years), where $k = 0.01$ for chrysotile asbestos (31). Chrysotile asbestos is by far the most common type of asbestos used in Stockholm. This equation has also been adopted by the US Environmental Protection Agency (32), although it is known that available epidemiologic data show both higher and lower values for the constant k (1, 30). At 10 fiber-years, the equation predicts a relative risk of 1.10 for lung cancer, whereas our study indicated a risk of 1.5–4.5 at this exposure level (figure 1). Our findings contrast with those from a study of environmental exposure to asbestos, which suggested that downward linear extrapolation overestimated the risk at low doses (33). Our study provides no information on the risk at higher cumulative doses and has a reasonable precision for doses up to about 5 fiber-years.

Since asbestos and tobacco smoke seemed to have a less-than-multiplicative joint effect, any calculation of a common relative risk associated with asbestos in a population will depend on the proportion of smokers. Steeper asbestos dose-response curves will be obtained for populations with few smokers than for populations with a high proportion of smokers. However, in our study, the risk per exposure unit for smokers only was higher than that predicted by extrapolation from highly exposed cohorts with mixed smoking habits: at a cumulative dose of 4 fiber-years, the relative risk was 1.55 for smokers in our study, considerably higher than the 1.04 predicted from studying highly exposed cohorts. Thus, our finding of a steeper dose-response curve cannot be explained by a low proportion of smokers in our study base.

Analysis of the joint effect of asbestos and tobacco smoking indicated a submultiplicative but slightly more than additive joint effect. This result is consistent with those of many, although not all, studies on this topic (15–17). The early findings of multiplicativity among US insulators (10) has led to a focus on preventing smoking by asbestos-exposed or formerly asbestos-exposed persons (21). Although this focus is well warranted because of the preventive effect on future lung cancer risk, it is questionable whether the number of extra cases of disease prevented by focusing on asbestos-exposed persons is particularly large in view of the present findings.

Variations in exposure between workers within job tasks, incomplete information on earlier exposure levels, and errors in work histories all contribute to misclassification of exposures. To a large extent, occupational histories were obtained from cases' next of kin because of the short survival time of lung cancer patients. A slightly higher risk estimate was obtained by using the mortality-matched referents instead of the population referents, which indicates that asbestos exposures may have been somewhat underestimated when proxy information was used for occupational histories. In this respect, the risk estimate obtained when the mortality-matched referents were used may be more valid than that for the population referents, because of the similarity with the cases in the proportion of proxy information used. Since differences were small, data for all referents were retained in the analyses to increase statistical power. Exposure was classified by an industrial hygienist blinded to the case-referent status of study subjects, arguing against differential misclassification at this stage of the exposure assessment.

The exposure assessment method used in our study, which was based on "expert judgment," has been shown to be reliable and more valid than self-assessment methods (34, 35). Inclusion of data on work tasks and industry type increased the precision of exposure estimates in contrast to assessments based on job titles only (36). Errors in exposure classification that differed systematically between cases and referents seem unlikely. Systematic and uniform under- or overestimations of exposure cannot be ruled out, since exposure assessments relied on external exposure data. However, these data were from a period (1969–1973) relevant because it occurred before asbestos was banned in Sweden, and the data also account for a latency of 15–20 years from exposure period until observation of risk. Even if some misclassification of earlier exposure levels cannot be ruled out, it does not seem probable that it could explain the much higher risk per fiber-year found in this study.

The methods used for sampling (membrane filter) and analysis (phase contrast microscopy) are still specified for compliance with TLVs (37). No large systematic differences due to analytical methods seem probable.

Our study is one of few investigating the relative risk of lung cancer in the low-dose asbestos exposure range using individually assessed exposures and individual data on important confounders. We found a clear excess risk of lung cancer at low-dose levels and that linear extrapolation from high exposure levels underestimates the risk at low doses. Even if this finding has some indirect support from other population-based case-referent studies (38–41), data also exist indicating the opposite (33). Further studies seem warranted before the shape of the dose-response curve in the low-dose range can be estimated reliably.

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