

# The Exposure-Time-Response Relationship Between Occupational Asbestos Exposure and Lung Cancer in Two German Case-Control Studies

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**Background** Numerous studies have been carried out to evaluate the association between lung cancer and occupational asbestos exposure. However, the effects of timing of exposure have not been analyzed thoroughly.

**Methods** Two German case-control studies with data on occupational asbestos exposure histories have been pooled. Duration of work in potentially asbestos exposed jobs and two derived weighted exposure measures are analyzed together with time since last exposure. A spline function is used to model the effect of time since exposure.

**Results** The odds ratios (OR) and corresponding 95% confidence intervals were 1.8 (1.2, 2.7) and 2.4 (1.7, 3.4) for subjects having worked for 3 to 7 years and 8 or more years, respectively, in a job with potential asbestos exposure compared to never-exposed. Based on an evaluation of time since last exposure, the OR decreased significantly to about one-half after more than 20 years since exposure ceased. Using a spline function, applied to workers' complete exposure histories, the effect of an increment of exposure is greatest 10–15 years after that exposure was received.

**Conclusions** In contrast to previous indications, the risk of lung cancer increases soon after asbestos exposure, with its maximum effect from 10 to 15 years after the exposure was received. *Am. J. Ind. Med.* 41:89–97, 2002. Published 2002 Wiley-Liss, Inc<sup>†</sup>

**KEY WORDS:** case-control; lung cancer; asbestos; exposure-time–response; spline; time since exposure

## INTRODUCTION

Asbestos is the single most important factor for occupational cancer in Germany, causing more than 1,000

deaths per year. At its peak in 1965, about 180,000 tons of asbestos were imported to West Germany. Imports of asbestos remained high through the 1970's, then declined sharply to the current level of less than 10,000 tons/year [Brüske-Hohlfeld, 1999].

Although inhaled asbestos is a recognized lung carcinogen, the functional form of the exposure–response relationship, as well as factors that may affect that relationship, have not been well characterized. The form of the exposure–response relationship is particularly important when estimating workers' risks in conjunction with criteria for eligibility in compensation programs [Hillerdal and Henderson, 1997; Steenland and Stayner, 1997].

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Asbestos fibers can be cytotoxic and genotoxic, and can cause proliferative lesions in the lungs, mediated by oxygen radicals and nitrogen oxides. Asbestos fibers can also be phagocytized by macrophages, which release a variety of cytokines and mediators of inflammation that modulate growth and differentiation of the target cells [Vainio and Boffetta, 1994].

This study explores the effects of timing of occupational asbestos exposure on lung cancer risk using data from two case-control studies conducted in Germany from 1988 to 1996. Occupational epidemiological studies often collect complete employment histories on workers, but typically evaluate only cumulative exposure, exposure rate, and time since last exposure. Only rarely do they fully exploit the information in the time-dependent aspects of the employment histories [Thomas, 1983, 1988; Langholz et al., 1999]. In the current study, we assess time-related effects of asbestos exposure by evaluating both the effect of time since last exposure and the effect of time since exposure.

## MATERIALS AND METHODS

### Data Acquisition

To investigate the influence of occupational exposures on lung cancer risk in Germany, we pooled data from two case-control studies [Jöckel et al., 1998; Kreienbrock et al., 2001]. One study was on lung cancer and occupational risk factors and was carried out by the Bremen Institute for Prevention Research and Social Medicine (BIPS) between 1988 and 1993 in Bremen and its environs and the Frankfurt/Main area. The study included 1,004 cases and an equal number of controls. Population controls were randomly drawn from census lists and individually matched on sex, age, and region of residence. Cases included all patients born on or after 1913, of German nationality, with a diagnosis of lung cancer and interviewed within 3 months after diagnosis. The response rate was 69% for cases and 68% for controls.

The second study was on lung cancer and indoor radon exposure and was conducted by the GSF National Research Center for Environment and Health in Neuherberg from 1990 to 1996. It included 2,255 cases and 2,216 controls from the areas of North Rhine-Westphalia, Rhineland-Palatinate, Bavaria and Saarland. Cases had to be less than 76 years old, must be a resident of the study region, had to have lived in Germany for more than 25 years, and interviewed within three months of diagnosis. The response rate among eligible cases was 77%. Population controls satisfying the same age and residency inclusion criteria as cases, were randomly selected from population registries and frequency-matched to cases on sex, age, and region. The response rate for controls was 41%.

In both studies, incident cases of primary lung cancer were included only if the diagnosis was cytologically or histologically verified. Following written informed consent, both cases and controls were interviewed in person by trained interviewers with respect to their occupational exposure, residential history, smoking habits, and other risk factors.

There was a total of 6,479 observations from both studies. We excluded 1,155 females, since few were ever-exposed to asbestos. Among the remaining males, we excluded 115 occasional smokers and 122 pipe/cigar only smokers because of uncertainties in quantifying their tobacco exposure compared to regular cigarette smokers. The data used in the analysis consisted of 5,087 male subjects, 2,652 cases, and 2,435 controls.

### Assessment of Exposures

The studies used similar standardized questionnaires to obtain demographic characteristics, smoking information, and a lifelong job history. The occupational history consisted of all jobs held for 6 months or longer. Controls averaged 2.7 jobs, while cases averaged 2.9.

In total, 20 job-specific supplementary questionnaires (JSQ) were used in addition to the customary job history whenever job titles (e.g., painter, welder), tasks (e.g., insulation), industries (e.g., chemical industry), or circumstances (e.g., use of asbestos in the company) implied exposure to substances which are potentially carcinogenic. Questions with regard to asbestos exposure were addressed in 17 of these JSQs. In addition to types of exposure, participants were asked about duration of exposure in years and days/year. It was then possible to calculate for each subject, the product of years times days/year. Assuming 220 days as one year of asbestos exposure, we defined duration of exposure in years. The intensity of asbestos exposure for each of the possible answers to the questions has been assessed a priori by experienced industrial hygienists as "light", "medium", "heavy", or "unknown" [Ahrens et al., 1993; Orłowski et al., 1993]. Information about the use of protective equipment was only available for the BIPS study and so was not considered in the pooled analysis.

We derived two alternative exposure measures by weighing the duration worked in each of the four categories (light, medium, heavy, unknown), based on  $d = \lambda_l d_l + \lambda_m d_m + \lambda_h d_h + \lambda_u d_u$ , where  $d_l$ ,  $d_m$ ,  $d_h$ ,  $d_u$  were durations in light, medium, heavy, and unknown asbestos-exposed jobs, respectively, and  $\lambda_l$ ,  $\lambda_m$ ,  $\lambda_h$ ,  $\lambda_u$  were weights.

The first alternative measure was obtained from all subjects by deriving risk-based weights using estimates of the logarithm of the odds ratio (OR), i.e., the beta coefficients, from a logistic model which included adjustment factors and four continuous variables: duration in jobs with light, medium, heavy, and unknown levels of exposure

to asbestos. These weights were  $\lambda_l = 1.0$ ,  $\lambda_m = 7.2$ ,  $\lambda_h = 16.2$ , and  $\lambda_u = 21.0$  for light, medium, heavy, and unknown exposures, respectively ( $\lambda_l$  was fixed at 1.0). We called this measure “risk-weighted duration” of asbestos exposure.

A second measure of asbestos exposure used information from a random validity subsample of 485 individuals from the present study. For each individual in the subset, two industrial hygienists estimated the total number of fiber-years (1 fiber-year = 1 work-year  $\times$   $10^6$  fibers/m<sup>3</sup>) on the basis of the detailed job descriptions for each occupation that was held during lifetime, the information from the JSQs and the answers to a simple exposure check-list. These assessments were based on the international literature [Woitowitz et al., 1983], measurement experience of experts and the rules that have been established for the judgment of compensation claims of asbestos related lung cancer [BK-Report, 1994].

Using those individuals in the subsample who were exposed exclusively in one of the four categories, we derived weights by computing the mean fiber-years/year in light, medium, heavy, and unknown asbestos potential jobs. The weights were  $\lambda_l = 0.9$ ,  $\lambda_m = 6.3$ ,  $\lambda_h = 19.1$ , and  $\lambda_u = 12.6$  fiber-years, respectively, and were based on  $n_l = 22$ ,  $n_m = 62$ ,  $n_h = 26$ , and  $n_u = 10$  individuals. These weights were then applied to all subjects in the study to obtain “derived fiber-years” of exposure.

## Statistical Methods

Unconditional logistic regression was used for the analysis. All models were stratified for age (< 50, 50–54, 55–59, 60–64, 65–69,  $\geq$  70) and region (17 categories) as nominal categories. We also adjusted for smoking using categories of years since smoking cessation (0–1, 2–4, 5–9, 10 + years) and the logarithm of cumulative pack-years smoked plus one, i.e.,  $OR = e^{z \log(1+z)} = (1+z)^z$ , where  $z$  denotes pack-years smoked. This power function for pack-years provided a better fit to the data compared to a loglinear function ( $OR = e^{z^2}$ ).

The interaction between asbestos exposure and smoking was evaluated using a geometric mixture model for the joint OR [Lubin and Gaffey, 1988]. The data were consistent with a multiplicative model, while the additive model was rejected ( $P < 0.5$ ). Subsequent analyses used a multiplicative joint association.

Three models were fitted including time since last asbestos exposure (0–4, 5–19, 20–29,  $\geq$  30 years) and either duration of asbestos exposure ( $> 0- < 1$ , 1–2, 3–7, 8 + years), risk-weighted duration ( $> 0-4$ , 5–17, 18–49, 50 +), or derived fiber-years ( $> 0-4$ , 5–17, 18–49, 50 +). We also fitted a model including continuous duration of asbestos exposure and a binary indicator of ever-exposed to asbestos compared to never-exposed.

From each worker’s job history, we determined asbestos exposure for each of 50 years prior to interview. Let  $x(t)$  be an individual’s cumulative exposure to asbestos during the  $t$ -th year prior to interview. Then,  $x(t)$ ,  $t = 5, \dots, 50$ , represents the complete exposure history (excluding a 5-year lag interval), and  $\sum_{t=5}^{50} x(t)$  is the total cumulative asbestos exposure. We set  $\log(OR) = \beta \sum_{t=5}^{50} w(t)x(t)$ , where  $w(t)$  is a year-specific weight defining the contribution of exposure during the  $t$ -th year prior to interview to the OR. The weighted sum  $\sum_{t=5}^{50} w(t)x(t)$ , then represents “effective cumulative exposure”. The product  $\beta w(t)$  is interpretable as the logarithm of the OR for one unit of exposure received  $t$  years in the past. Function  $w(\cdot)$  was estimated using a cubic B-spline. Parameter  $\beta$  and function  $w(\cdot)$  were estimated from the data. For details, refer to the appendix.

Note, that a standard model in cumulative exposure is included in this model by setting  $w(t) = 1$  for all  $t$ . A likelihood ratio test was performed to test if the data are consistent with no variation in the weights, i.e., risk is best characterized by cumulative exposure. Two spline function models were fitted using either continuous duration of asbestos exposure or derived fiber-years, and including a binary indicator of ever-exposed to asbestos.

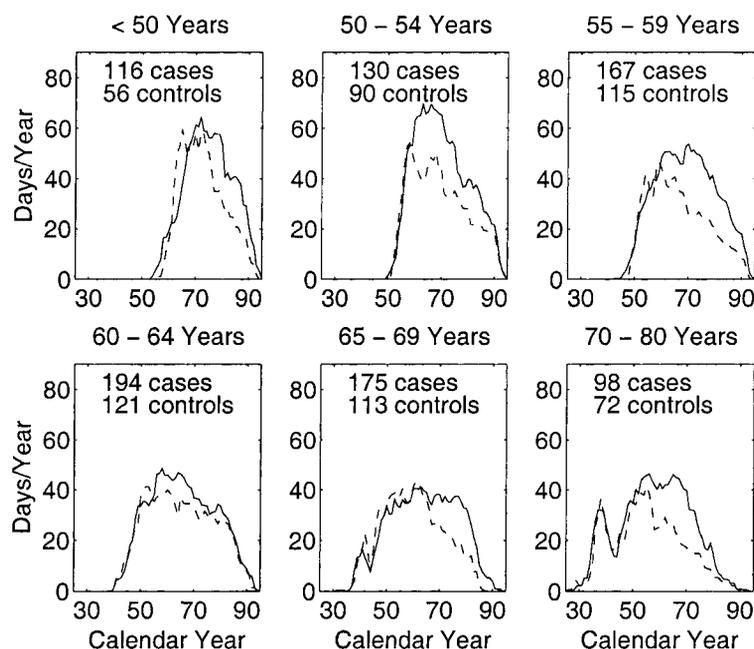
## RESULTS

A total of 880 cases (33.2% of cases) and 567 controls (23.3% of controls) were occupationally exposed to asbestos. Among ever-exposed cases, the mean duration of exposure was 7.1 years, while among controls it was 5.6 years. The maximum duration of exposure was about 50 years.

Only 1.5% of the cases were non-smokers compared to 17.8% of the controls. Only 1.2% of the cases were neither exposed to tobacco smoke nor to asbestos compared to 14.3% of the controls. Among the cases (controls) who smoked, 70 (39) % were current smokers, 14 (48) % stopped smoking 10 or more years ago, and the average amount of tobacco smoked was 38 (24) pack-years. The OR for  $z$  pack-years smoked was  $OR = (1+z)^{0.8}$  relative to never-smokers, and the ORs for 2–4, 5–9, 10 + years since cessation of smoking were 0.82, 0.63, and 0.27, respectively, relative to smokers who stopped smoking two years ago or less including current smokers.

## ORs and Asbestos Exposure

Figure 1 shows mean duration of asbestos exposure by calendar year among ever-exposed individuals. For all age groups, the mean duration reached its maximum (45–65 days/year working in an asbestos-exposed environment) between 1960 and 1970, and then declined with calendar



**FIGURE 1.** Yearly mean duration of asbestos exposure in days among ever-exposed males for cases (solid line) and controls (dashed line) by age group on calendar year scale (19 . . .).

year. Younger individuals had higher mean durations than older workers, and controls had lower mean durations than cases, especially after 1960. Table I gives the ORs for the three measures of asbestos exposure: duration, risk-weighted duration, and derived fiber-years. Among exposed, the ORs increased with duration, although not monotonically. ORs and corresponding 95% confidence intervals (CI) were 1.1 (0.8, 1.5), 1.0 (0.7, 1.4), and 1.3 (0.9, 1.8) for 1–2, 3–7, and 8 years or more of asbestos exposure compared to less than one year. The OR of never-exposed individuals compared to less than one year of asbestos exposure was 0.5 (0.4, 0.8).

The ORs for risk-weighted duration of asbestos exposure and derived fiber-years revealed a stronger increasing trend than the ORs for unweighted duration. The analysis of derived fiber-years showed that the OR and corresponding 95% CI for 18–49 fiber-years, compared to never-exposed, was 1.8 (1.2, 2.6) and for 50 and more fiber-years was 2.6 (1.8, 3.7).

Using continuous duration of asbestos exposure, the proportional increase in the OR per one year was 1.02 (1.01, 1.04). In the same model, the OR for ever-exposed to asbestos compared to never-exposed was 1.3, 95% CI (1.1, 1.6). The significance of the binary indicator parameter suggests that there was a difference between exposed and non-exposed not accounted for by the matching variables, smoking and duration of asbestos exposure, or that there was a marked increase of risk at very low exposures.

## ORs and Exposure Time Patterns

Table I also shows that the ORs significantly declined by about half after 20 years and more since last exposure. Splines offered a more detailed characterization of risks with time. The estimated spline function, which shows the effect of exposure in each year on lung cancer risk, is shown in Figure 2 with duration of asbestos exposure in the upper panel and derived fiber-years in the lower panel. The impact of one year of asbestos exposure reached a maximum at 10–15 years before interview with a four-fold estimated weight for exposures received during that period. Weights declined prior and reached a minimum 30 years before interview. The pointwise 95% CI supported weights greater than one for the period 8 to 17 years before interview and less than one for 25 and more years before interview. The data, however, were also consistent with constant weights, i.e., a standard model in continuous duration that shows no variation with time ( $P=0.1$ ). The spline function based on derived fiber-years was similar in shape. The spline function did not change the estimated OR effect for being ever-exposed to asbestos. The OR  $e^{\beta}$  for one unit “effective exposure”, i.e., for the weighted sum of the yearly exposure increments using the estimated spline function as weights, was also similar to the OR for one year of duration of asbestos exposure. There was no evidence of differing effects with age, as the shape of the estimated spline function was very similar across age groups.

**TABLE I.** OR and 95% CI for Lung Cancer and Three Different Asbestos Exposure Measures Adjusted for Pack-Years and Time Since Smoking Cessation, and Stratified for the Matching Variables Age and Region of Residence

	Cumulative exposure <sup>a</sup>				Years since last exposure			
	I	II	III	IV	0–4	5–19	20–29	≥ 30
Duration								
Cases	228	191	205	256	174	322	165	219
Controls	175	135	140	117	83	152	145	187
OR	1.00 <sup>b</sup>	1.07	0.96	1.27	1.00 <sup>e</sup>	1.02	0.53	0.61
95% CI		0.75, 1.51	0.68, 1.36	0.88, 1.83		0.70, 1.49	0.35, 0.79	0.41, 0.92
Risk-weighted duration								
Cases	199	205	211	265	174	322	165	219
Controls	176	131	136	124	83	152	145	187
OR	1.00 <sup>c</sup>	1.14	1.17	1.55	1.00 <sup>e</sup>	1.03	0.54	0.66
95% CI		0.80, 1.62	0.82, 1.68	1.07, 2.24		0.71, 1.51	0.36, 0.81	0.44, 0.99
Derived fiber-years								
Cases	205	221	203	251	174	322	165	219
Controls	180	141	132	114	83	152	145	187
OR	1.00 <sup>d</sup>	1.25	1.11	1.63	1.00 <sup>e</sup>	1.04	0.54	0.66
95% CI		0.89, 1.78	0.78, 1.59	1.12, 2.37		0.71, 1.51	0.36, 0.81	0.44, 0.99

<sup>a</sup>Cumulative asbestos exposure  $d = \lambda_l d_l + \lambda_m d_m + \lambda_h d_h + \lambda_u d_u$ , where  $d_l, d_m, d_h, d_u$  are years in jobs with light, medium, heavy, and unknown potential asbestos exposure, and  $\lambda_l, \lambda_m, \lambda_h, \lambda_u$  are weights.

Definition of categories:

Duration (total years in jobs with potential exposure to asbestos,  $\lambda_l = \lambda_m = \lambda_h = \lambda_u = 1$ )

I: > 0– < 1, II: 1–2, III: 3–7, IV: 8 +

Risk-weighted duration (weights based on estimates of ORs in the full study,  $\lambda_l = 1.0, \lambda_m = 7.2, \lambda_h = 16.2, \lambda_u = 21.0$ )

I: > 0–4, II: 5–17, III: 18–49, IV: 50 +

Derived Fiber-Years (weights based on validity subsample,  $\lambda_l = 0.9, \lambda_m = 6.3, \lambda_h = 19.0, \lambda_u = 12.6$ )

I: > 0–4, II: 5–17, III: 18–49, IV: 50 +

<sup>b</sup>Reference group, OR of never-exposed vs. reference group: 0.53, 95% CI 0.36, 0.80.

<sup>c</sup>Reference group, OR of never-exposed vs. reference group: 0.62, 95% CI 0.41, 0.93.

<sup>d</sup>Reference group, OR of never-exposed vs. reference group: 0.63, 95% CI 0.42, 0.95.

<sup>e</sup>Reference group.

All continuous trends  $P < 0.05$ .

Example: OR ( $\geq 8$  years duration and  $\geq 30$  years since last exposure vs. never-exposed) =  $1.27 \times 0.61/0.53 = 1.46$ .

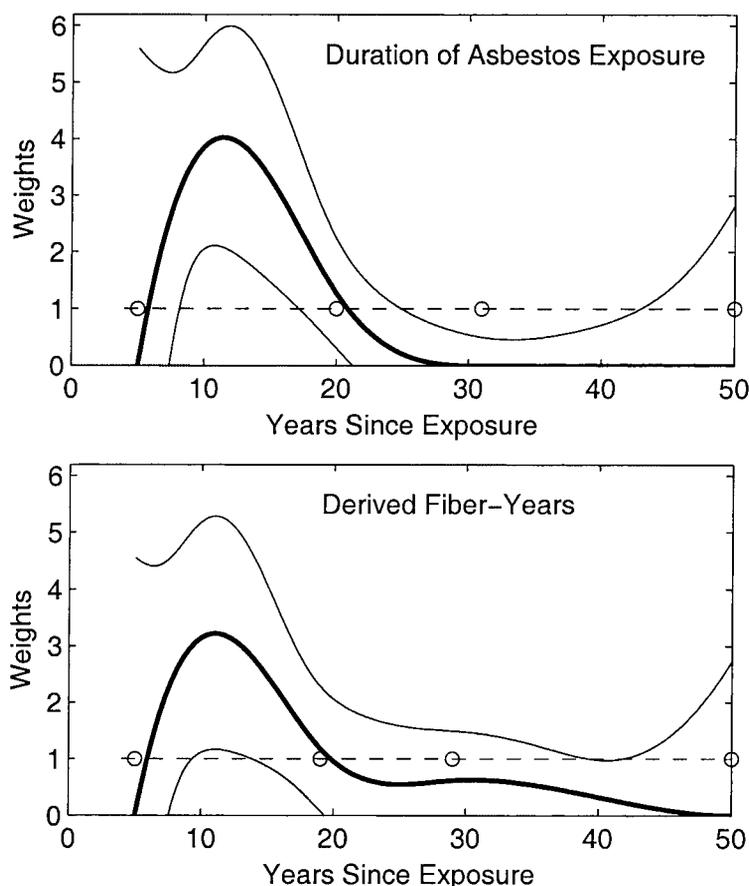
## DISCUSSION

Results for duration of asbestos exposure suggested an increasing exposure–response relationship that was consistent with other studies [Hughes and Weill, 1994; Hillerdal and Henderson, 1997; Steenland and Stayner, 1997]. Our data on asbestos exposure, tobacco smoking, and lung cancer were generally consistent with a multiplicative model as has been reported by others [Vainio and Boffetta, 1994; Hillerdal and Henderson, 1997; Steenland and Stayner, 1997] and rejected an additive model.

This study includes a non-standard approach to study the effect of time since exposure to asbestos in the workplace. The estimated spline function suggests that an indi-

vidual's lung cancer risk following an exposure to asbestos increases for 5–15 years after exposure, then declines, with exposures experienced 12 years before the index date having the greatest effect on risk. Whether the decline continues and risk returns to baseline after more than 25 years remains unclear. However, the spline function model did not fit statistically significantly better than a model in cumulative exposure alone.

Other researchers found that the effect of exposure peaked between 20 and 40 years from onset of asbestos exposure and declined afterwards [Selikoff et al., 1980; Hughes and Weill, 1994; Hillerdal and Henderson, 1997; Stayner et al., 1997]. Our results suggest that the latency period may be shorter. However, the spline function



**FIGURE 2.** Estimated spline functions for profiles of duration of asbestos exposure in years in upper panel and for derived fiber-years profiles in lower panel with pointwise 95% CIs for 5,087 males.

approach allows using time since each yearly exposure compared to time since first exposure, as used in most other studies. Lung cancer occurring a certain time after first asbestos exposure may not necessarily have been caused by the first exposure but by later exposures. This may explain why latency estimated using the spline function is shorter.

Some researchers use a rather long fixed lag time, e.g., 15 years [Jones et al., 1996]. This implies the assumption that asbestos exposures occurring within the lag interval have no effect on the lung cancer outcome. Such an approach prevents a detailed analysis of latency, and is too limiting.

ORs for duration of asbestos exposure exhibited a smaller exposure-response trend than the two derived exposure measures, risk-weighted duration and derived fiber-years. This is likely due to the added intensity information that is included in the two measures, and thus suggests that risk-weighted duration and derived fiber-years were more reflective of the true asbestos exposure among workers. Note that the actual value of risk-weighted duration is not directly interpretable outside these data, unlike

derived fiber-years. The quantitative value of the latter measure is a useful exposure measure, assuming that the subsample from which the weights were derived was representative of all light, medium, and heavy exposure jobs and representative of all workers in the combined studies. We found that the distributions of demographic variables, tobacco use, and asbestos exposure were very similar in the validation subsample and in the general study minus the validation subsample. However, the derived fiber-years measure was based on a small number of observations from the substudy.

The relative contributions to risk from light, medium, heavy, and unknown job categories were similar for the two derived measures. For risk-weighted duration, the ratios of the weights were 1.0:7.2:16.2:21.0 for light, medium, heavy and unknown categories, respectively, while the corresponding ratios for derived fiber-years were 1.0:7.2:21.6:14.3. The similarity in the weights lends credibility to the validity of both measures. The relative magnitude of the weights indicates that one year of exposure in jobs classified as medium and heavy asbestos exposed confers the same lung

cancer relative risk than 7 and 20 years in jobs classified as light exposed, respectively.

It is also noteworthy that the magnitude of the weight for the unknown category for the two derived measures is comparable to the weights in the heavy categories. This suggests that in these two studies workers in jobs with asbestos potential but with unknown intensity are more likely to have been exposed to more than the minimum level of asbestos.

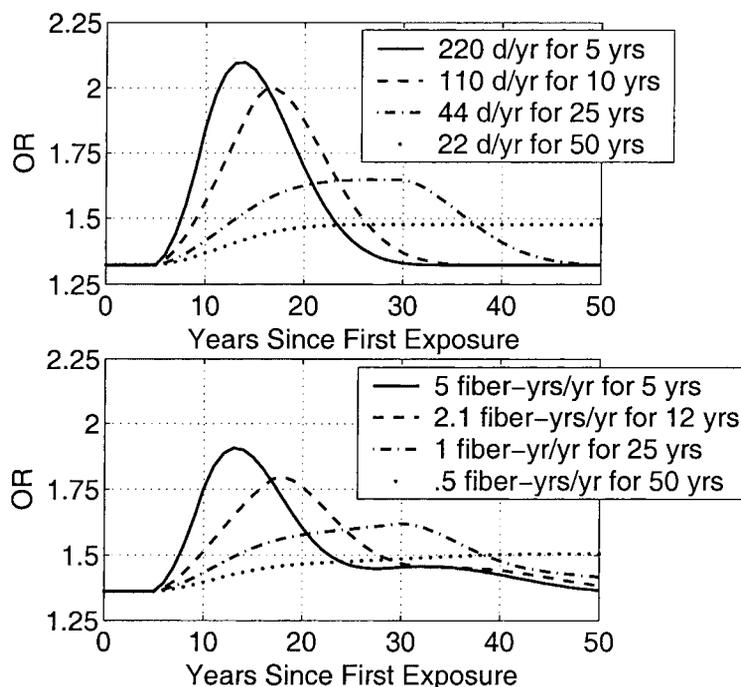
The spline function model allows the analysis of the dependence of lung cancer risk on the specific time pattern of exposure history. The results suggest that two different exposure profiles with the same total exposure may result in different lung cancer risks compared to never-exposed individuals. The more exposure received 5–20 years before the current age (weights larger than one), the higher the risk. Once received, asbestos exposure appears to contribute to a person's lung cancer risk for at least 20 years.

As an example of how the spline function can be used for assessing risks for individual patterns of exposure, Figure 3 illustrates ORs over time for hypothetical exposure histories: 5 years total duration of exposure (upper panel) and 25 derived fiber-years (lower panel) at a constant rate over different periods of time. The figure is directly derived from the estimated spline function. The OR increases with time since first exposure until it peaks, and then decreases. For given cumulative exposure, the maximum OR occurs

earlier after start of exposure when exposure rates are high compared to low exposure rates. Note that after cessation of exposure the OR approaches 1.3, the OR of ever-exposed to asbestos compared to never-exposed.

The results may be affected by uncertainties in exposure data because not all study subjects may have been able to accurately recall their job history during the interview. This is a common problem of occupational epidemiologic studies that have to rely on questionnaire information. However, it can be assumed that job histories of the individuals in this population were fairly stable, which is reflected by an average of less than three jobs per individual. Although we do not have information about jobs shorter than 6 months, those can be assumed to have been rare.

The low response rate in the second study [Kreienbrock et al., 2001] was investigated further. The primary reason for nonresponse was the burden of long-term radon measurements required in the subjects' homes. A telephone interview was conducted among 250 randomly selected nonresponders. Despite the low response rate (21%) in the telephone interview, this substudy found that subjects who participated in the main study were, on average, better educated and younger, and were more often living in rural areas compared to nonresponders. The participating controls, therefore, may be less likely to be exposed to tobacco smoke and probably asbestos than the general population. Since social status was controlled



**FIGURE 3.** OR for a cumulative exposure of 5 years of duration (upper panel, 1 year = 220 work days (d)) and 25 fiber-years (lower panel) at a constant rate over different periods of time vs. never-exposed by years since first exposure.

for by adjusting for smoking, and age was controlled for by matching, the response pattern may not have influenced the results.

In summary, our data provide evidence for a multiplicative association between smoking and asbestos exposure. There was a 2.4-fold increase of risk for subjects having worked for 8 or more years in a job with potential asbestos exposure compared to never-exposed. The OR declines with time since last exposure to about one-half after more than 20 years since last exposure. Although the spline function model was not statistically superior in our data compared to a model including total cumulative exposure, it uses the complete exposure history information and offers a flexible strategy to study the impact of the timing of exposure on the OR. Under the model, there is a shorter latency period than previously assumed, especially for high intensity of exposure. Data were insufficient to draw conclusions on whether risk continues to decline 25 years and more after exposure.

## ACKNOWLEDGMENTS

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## APPENDIX A

### Weight Function Estimation

The weight function  $w(t)$  is modeled as a cubic B-spline according to Hauptmann et al. [2000]. Splines are continuously differentiable piecewise polynomial functions of high flexibility. The segments are separated by knots. In our analysis, the knot positions were chosen such that the study population accumulated approximately constant proportions of its cumulative exposure between two adjacent knots.

The higher the number of knots, the more flexible the spline function. Therefore, the determination of the appropriate number of knots means a compromise between goodness of fit and parsimony of parameterization. The Akaike Information Criterion (AIC), which is the deviance plus two times the number of estimable parameters in the predictor, considers both and was used for model selection.

The likelihood of the model is maximized under the constraints that the weights for year 5 through year 50 before interview are nonnegative and sum to 46, as with standard cumulative exposure. Variance estimation was based on nonparametric bootstrap sampling. Calculations were performed using MATLAB software by The MathWorks Inc. (Natick).

A model with four knots minimized the AIC for both duration of asbestos exposure (knots at 5, 20, 31, 50 years prior to interview) and derived fiber-years (5, 19, 29, 50). The estimated B-spline coefficients were  $(\hat{\theta}_1, \dots, \hat{\theta}_6) = (0, 7.1, 0, 0, 0, 0)$  for duration of asbestos exposure and  $(\hat{\theta}_1, \dots, \hat{\theta}_6) = (0, 5.68, 0, 1.07, 0, 0)$  for derived fiber-years. The corresponding spline functions are presented in Figure 2.

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