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ORIGINAL PAPER

Lung cancer in chrysotile asbestos workers: analyses based on the two-stage clonal expansion model

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Abstract
Objective To evaluate the magnitude and temporal pattern of lung cancer risk following exposure to chrysotile asbestos.
Methods I analyzed data on lung cancer mortality in a cohort of asbestos textile workers who were exposed to almost pure chrysotile. Employment history and industrial hygiene data were used to derive asbestos exposure estimates. These data were analyzed within the framework of the two-stage clonal expansion (TSCE) model and the Cox proportional hazards model.
Results Under the TSCE model, the association between chrysotile asbestos and lung cancer mortality was primarily due to an exposure-induced increase in the proliferation of initiated cells. In a setting of protracted exposure to chrysotile asbestos, this model implies that the estimated hazard ratio was at its maximum between ages 40 and 65 years. Cox regression analyses support these conclusions; the estimated excess relative risk per fiber-year/ml was 0.053 (95% CI: 0.023, 0.124) at ages <65 years, while there was minimal evidence of association at older attained ages.
Conclusions The TSCE model fits these data well, accommodating the observed departure from the proportional hazards assumption. These analyses suggest that the effect of chrysotile asbestos exposure on lung cancer risk varies with attained age.

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Introduction

A number of countries have banned the use of all forms of asbestos because of evidence that asbestos causes a range of diseases, including lung cancer, mesothelioma, and asbestosis. However, chrysotile asbestos continues to be used in many countries, primarily as a construction material in the form of chrysotile-cement sheets, pipes, and shingles; it is estimated that about two million metric tons of asbestos were produced each year during the period 2000–2005 [1]. Furthermore, even in those countries where its use has been banned, exposure to chrysotile asbestos may occur as a result of efforts to remediate or remove asbestos containing materials. Given the prevalence of exposure, it is important to accurately characterize the magnitude, and temporal variation, of cancer risk associated with chrysotile asbestos exposure.

The epidemiological literature includes information on cancer mortality in a cohort of Charleston, South Carolina, asbestos textile workers who had relatively pure exposures to chrysotile asbestos and relatively high quality exposure information [2, 3]. Prior analyses of these data employed standardized mortality ratios and relative rate models fitted via Poisson regression methods. The results provide substantial evidence of a positive association between lung cancer mortality and cumulative chrysotile asbestos exposure under a 10-year lag assumption [3–5].

In this paper, I employ a two-stage clonal expansion (TSCE) model for the analysis of associations between occupational exposure to chrysotile asbestos and lung cancer mortality. Temporal aspects of these associations

are further explored via Cox regression models. The use of a multistage model, such as the TSCE, offers a way to incorporate information about exposure rates, and ages at exposure, into exposure-time-response analyses [6]. Such models offer a useful complement to more standard regression models, and may suggest novel insights into the temporal evolution of exposure–response associations.

Methods

This study involves workers employed at an asbestos textile plant located in South Carolina. The plant began producing asbestos products in 1896. Chrysotile asbestos was received from Quebec, British Columbia, and Zimbabwe. The study cohort includes all workers employed in production operations for at least one month between January 1, 1940 and December 31, 1965 [3]. For simplicity in model development and presentation, the analyses in this paper concern the sub-cohort of white male asbestos textile workers.

Vital status was ascertained through December 31, 2001. The outcome of interest, lung cancer mortality, was defined based upon underlying cause of death, coded according to the revision of the International Classification of Diseases (ICD) in effect at the time of death (ICD-5 codes 047B-047F, ICD-6 codes 162 and 163, ICD-7 code 162.0, 162.1, 162.8, 163, ICD-8/-9 code 162, ICD-10 codes C33, C34). The primary exposure of interest was asbestos exposure, expressed in fiber-years per milliliter (fiber-year/ml). Exposure was computed for each worker as the product of the length of employment in each job in a year by the estimated asbestos exposure rate for that job [2].

An analytical data file was constructed with one observation per worker. The file included the worker's age at start of follow-up, age at date of last observation, a binary indicator of death due to lung cancer, and annual asbestos exposure estimates.

TSCE

The TSCE model is a stochastic model intended to correspond to a conceptual model of carcinogenesis involving initiation, promotion, and malignant transformation of a cell [7, 8]. I assume a fixed population, X, of normal stem cells. These cells are susceptible to transformation into an intermediate pre-malignant stage, referred to as initiation, followed by a second transformation resulting in malignant cells (Fig. 1). Initiation occurs at a rate of μ_0, and the rate of malignant conversion is described by the parameter μ_1. Initiated cells may increase in number via cell division or diminish in number via cell death characterized by the parameters α and β, respectively; the net change in the subpopulation of initiated cells may be represented by $\gamma = \alpha - \beta - \mu_1$. Clonal expansion of the subpopulation of initiated cells increases the number of cells at risk of a second transformation, thereby resulting in a malignant cell.

Exposure to an agent may affect one or more of the parameters of the TSCE model. Therefore, initiation, promotion, and malignant conversion rates are each parameterized as $\theta(t)=\theta_0 \times (1 + b_1 \times d(t))$, where θ_0 is the value of the model parameter in the absence of exposure, b_1 is the dose–response coefficient, and $d(t)$ denotes asbestos exposure at age t. Under what I will refer to as a linear-quadratic model, this relationship is given by $\theta(t)=\theta_0 \times \left(1 + b_1 \times d(t) + b_q \times d(t)^2\right)$, with b_1 and b_q referred to as linear and quadratic coefficients of the dose–response relationship.

Estimation of the parameters is achieved by maximum likelihood methods. The likelihood for an individual is defined in terms of the TSCE model hazard function, h, and the corresponding survival function, S. Expressions for the survival and hazard functions of the TSCE with piecewise constant parameters have been described previously [8]. Let us define ts_i as the age at which person i enters the study and tq_i as the age at which the person exits the study. An individual's likelihood is:

$$L = \begin{cases} \dfrac{h(\mathrm{tq}_i) \times S(\mathrm{tq}_i)}{S(\mathrm{ts}_i)}, & \textit{if person is a case}; \\ \dfrac{S(\mathrm{tq}_i)}{S(\mathrm{ts}_i)}, & \textit{otherwise}; \end{cases}$$

thereby accounting for left- and right-censoring in the calculation of an individual's likelihood. The overall likelihood for a model is the product of the individual likelihoods for the members of the cohort.

Allowance for a fixed lag, l, between malignant transformation of a cell and subsequent diagnosis or death due to cancer is implemented by defining $\mathrm{ts}_i' = \mathrm{ts}_i - l$ and $\mathrm{tq}_i' = \mathrm{tq}_i - l$, and then calculating the hazard and survival for the intervals defined by ts_i' and tq_i'. For consistency

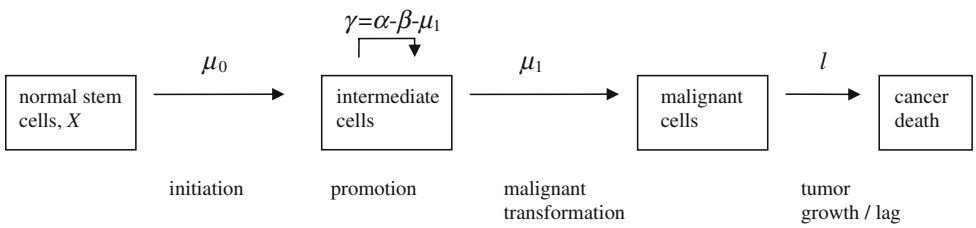

Fig. 1 Pictorial depiction of the two-stage clonal expansion model

with previous analyses of these data, I assumed a fixed 10-year lag assumption. The likelihood function calculation and its maximization were done via the SAS NLMIXED procedure [9].

The baseline rates of transformation and proliferation were estimated first by maximizing the likelihood for the observed outcome using data for the sub-cohort of workers who had <5 fiber-year/ml occupational asbestos exposure. Next, holding these baseline parameters constant, I fit the TSCE model to the entire cohort in order to optimize the exposure–response parameters. A likelihood ratio test (LRT) was used to compare a model in which the dose–response coefficient was allowed to vary freely to a model in which the dose–response coefficient was constrained to be equal to zero. The difference between model deviances, described as a LRT statistic, can be interpreted using a chi-square distribution.

Model fit was assessed by comparing observed and predicted numbers of lung cancer deaths within subgroups of the study population. Predicted numbers of lung cancer deaths were generated by using the estimated parameters for the TSCE model to compute the cumulative hazard for each individual in a group; the predicted number of cases for a given group was the summation of the cumulative hazards of all individuals in that group. Graphs of the predicted hazard ratios were derived by calculating age-specific hazards under specified exposure scenarios.

Cox proportional hazards regression

Cox proportional hazards regression models were fitted to these data via the statistical program PEANUTS, with attained age as the primary time scale [10]. In analyses of cumulative exposure (expressed in 10 fiber-year/ml increments), d, a linear relative risk model, of the form $\lambda = \lambda_0(1 + \beta \times d)$ was fitted, where λ_0 represents the baseline hazard function and β provides an estimate of the excess relative risk per 10 fiber-year/ml. I assumed a fixed 10-year lag; sensitivity analyses were conducted under 5- and 15-year lags. Confidence intervals were estimated via the likelihood method.

As a test of the proportional hazards assumption, a model, $\lambda = \lambda_0(1 + \beta \times d \times a)$, was fitted that included a product term between cumulative asbestos exposure and a time-dependent category variable, a, that is a function of attained age. The category variable, a, was defined such that roughly one-half of the lung cancer deaths occur in each time period, with a boundary point at age 65 years; sensitivity analyses were conducted by specifying this boundary point at age 60 years and 70 years. In order to assess variation in exposure effects with age at exposure, metrics of cumulative exposures accrued at ages <30 years, 30 to <50 years, and ages 50+ years were examined [11]. Each model was compared to a standard model of lifetime cumulative exposure by means of a LRT.

Results

The study cohort included 1,256 white male workers and 116 deaths due to lung cancer. Table 1 shows the distribution of person-time and lung cancer deaths by attained age, year of birth, and cumulative asbestos exposure. The youngest lung cancer death was observed at 46 years of age; the oldest was at 88 years. The median attained age of a lung cancer decedent was 66 years. The median age at entry of a worker into the study was 22 years. The cumulative exposure distribution is skewed to the right.

Baseline model parameters describing initiation, proliferation, and malignant transformation were estimated using data for those workers with cumulative exposure <5 fiber-year/ml (Table 2). There was minimal evidence of an improvement in model fit when initiation, proliferation, or malignant transformation rates were allowed to vary as a

Table 1 Characteristics of a cohort of 1,256 white male asbestos textile workers, South Carolina, 1940–2001

	Lung cancer deaths	Person-years
Attained age		
<50	7	29,292
50 to <55	9	5,335
55 to <60	13	4,777
60 to <65	25	3,875
65 to <70	30	2,947
70 to <75	19	1,844
75 to <80	7	949
80+	6	397
Year of birth		
<1905	14	2,856
1905 to <1910	12	2,727
1910 to <1915	18	4,719
1915 to <1920	20	6,889
1920 to <1925	24	11,112
1925 to <1930	18	8,887
1930+	10	12,224
Cumulative exposure, 0-*year lag* (*fiber-year/ml*)		
<1.5	22	13,223
1.5 to <5	23	14,480
5 to <15	15	8,699
15 to <60	19	7,854
60 to <120	17	3,471
120 to <240	15	1,406
240+	5	280
Total	116	49,416

Table 2 Baseline parameters for a two-stage clonal expansion model for lung cancer mortality among white male asbestos textile workers, South Carolina, 1940–2001

	Description	Estimate (Wald 95% CI)
Fixed parameters	Stem cell population, X	1×10^7
	Lag, l	10 years
Baseline model parameters	α	12.31
		(−0.30, 24.92)
	$\mu_0 = \mu_1$	10.63×10^{-8}
		$(-5.93 \times 10^{-8}, 27.20 \times 10^{-8})$
	γ	0.17
		(0.10, 0.25)

function of year of birth; therefore, birth cohort effects were not included in the baseline model.

Next, a model was fitted in which asbestos affected the rate of initiation, the kinetics of cell proliferation, or the rate of transformation to the malignant state. Inclusion of a term describing a linear effect of asbestos on the initiation rate, μ_0, or the malignant transformation rate, μ_1, resulted in a significant improvement in model fit (LRT = 6.2, 1 d.f. and LRT = 34.7, 1 d.f., respectively). Inclusion of a quadratic term for the effect of asbestos on the initiation rate or the malignant transformation rate led to no additional improvement in model fit when compared to a strictly linear model. The best model fit was obtained via inclusion of a term describing a linear effect of asbestos on the proliferation rate (LRT = 50.2, 1 d.f.); I refer to this as Model 1 (Table 3). A linear-quadratic model for the effect of asbestos on the proliferation rate fitted these data somewhat better than a linear model for asbestos effect on proliferation (LRT = 4.4, 1 d.f.). The quadratic parameter was negative, implying a concave downward exposure–response function.

Including a term for an asbestos effect on initiation to a model that included linear and quadratic terms for the effect of asbestos on cell kinetics led to minimal improvement in model fit (LRT = 0.1, 1 d.f.). Including a term for an asbestos effect on malignant transformation led to a modest improvement in model fit when contrasted to a model that included linear-quadratic terms for an asbestos exposure effect on cell kinetics (LRT = 2.5, 1 d.f.); I refer to this as Model 2 (Table 3).

Table 3 Residual deviances and estimated impact of chrysotile asbestos on parameters for the two-stage clonal expansion model. Lung cancer mortality among white male asbestos textile workers, South Carolina, 1940–2001

	Description	Baseline model	Model 1 Estimate (Wald 95% CI)	Model 2 Estimate (Wald 95% CI)
Asbestos effect	Linear term for asbestos effect on proliferation, γ_1		0.1076 (0.0734, 0.1419)	0.1285 (0.0616, 0.1954)
	Quadratic term for asbestos effect on proliferation, γ_q^a			−0.0029 (−0.0060, 0.0002)
	Linear term for asbestos effect on malignant transformation, μ_{11}^a			0.1821 (−0.1222, 0.4864)
Residual deviance		1440.1	1389.9	1383.0

[a] Applies also to the initiated cells' conversion rate, α

Note the constraint of equality of the spontaneous rates of the first and second mutation ($\mu_0 = \mu_1$) and that the number of susceptible stem cells, X, is fixed at 10^7

Table 4 Number of baseline, observed, and predicted lung cancer deaths by quartile of cumulative asbestos exposure. White male asbestos textile workers, South Carolina, 1940–2001

Quartile (range, in fiber-years/ml)	Baseline Prediction[a]	Model 1 Prediction[b]	Model 2 Prediction[c]	Observed lung cancer deaths
1st (0–1.7)	24.98	25.76	25.81	23
2nd (1.7–5.5)	24.50	25.91	25.95	26
3rd (5.5–25.1)	18.83	21.65	21.49	19
4th (25.1–699.8)	21.39	46.69	48.13	48

[a] Predicted number of deaths based on the model parameters shown in Table 2

[b] Predicted number of deaths based on the model parameters shown in Table 2 and allowing for asbestos exposure effect as shown in Table 3, Model 1

[c] Predicted number of deaths based on the model parameters shown in Table 2 and allowing for asbestos exposure effect as shown in Table 3, Model 2

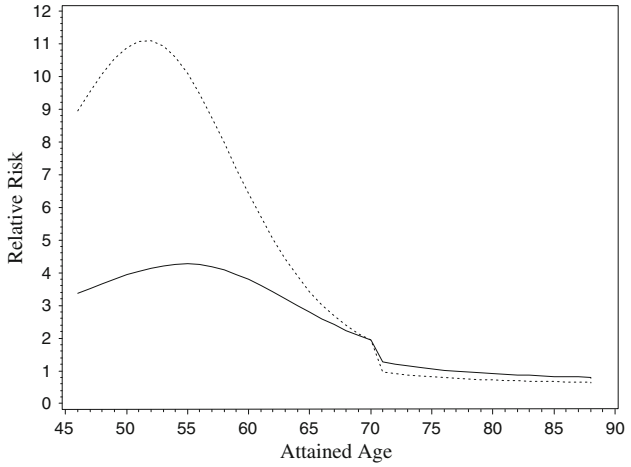

Fig. 2 Lung cancer relative risk by attained age. Predicted impact of asbestos exposure at intensities of 5 (dashed line) and 2.5 fiber/ml (solid line) based upon fitting of the two-stage clonal expansion model (predicted relative risks based on the model parameters shown in Table 2 and allowing for asbestos exposure effect as shown in Table 3, Model 2). Exposure commences at age 20 years and terminates at age 60 years. Ten-year lag assumption

Table 4 reports the baseline, observed, and predicted lung cancer deaths for sub-cohorts defined by quartiles of lifetime cumulative exposure. The predicted number of deaths within each group conforms closely to the observed number of deaths. A comparison of the observed number of deaths to the number expected in the absence of an exposure effect (i.e., the baseline TSCE model) indicates that ~26 of the 116 observed lung cancer deaths are excess cases associated with asbestos exposure.

Figure 2 illustrates the model prediction for the hazard ratio as a function of attained age for a person exposed to asbestos at intensities of 5 and 2.5 fiber/ml, with exposures commencing at age 20 years and terminating at age 60 years. The figure depicts the hazard ratios over the range of attained ages at which lung cancer deaths were observed, suggesting that given protracted exposure to asbestos, the hazard ratio increases with attained age until approximately age 55 years, after which the hazard ratio decreases with attained age.

For comparison, a Cox regression analysis was conducted modeling lung cancer mortality as a function of cumulative asbestos exposure. Model fit was not substantially improved when indicators for birth cohort were included as model covariates; therefore, the baseline model included no covariates. Cumulative exposure, lagged 10 years, was positively associated with lung cancer mortality (Table 5). Cumulative exposure was also positively associated with lung cancer mortality under 5- (ERR = 0.015, 95% CI: 0.007, 0.027) and 15-year (ERR = 0.015, 95% CI: 0.006, 0.029) exposure lag assumptions. As suggested by the TSCE model, there is evidence of interaction between attained age and cumulative asbestos. A model with separate dose–response coefficients for attained ages < 65 and 65 + years fits these data substantially better than a model that implies a constant ERR over all attained ages (Table 5). Consistent with the TSCE model, there is a strong positive association between asbestos exposure and lung cancer at attained ages 46 to <65 years (age 46 years being the youngest observed lung cancer death); there is little evidence of association between asbestos and lung cancer deaths at attained ages ≥65 years. A model with separate dose–response coefficients for attained ages <60 and 60+ years also fits these data better than a model that implies a constant ERR over all attained ages (LRT = 12.8, 1 d.f.), as did a model with separate dose–response coefficients for attained ages <70 and 70+ years (LRT = 4.5, 1 d.f.).

Table 5 Estimated excess relative risk per fiber-year/ml (and associated 95% CI) for lung cancer mortality obtained via proportional hazards regression analysis. Lifetime cumulative exposure under a 10-year lag and within time-windows defined by attained age. White male asbestos textile workers, South Carolina, 1940–2001

	ERR fiber-years/ml (95% CI)
Cumulative exposure	0.015 (0.007, 0.028)
Attained age	
<65 years	0.053 (0.023, 0.124)
65 or more years	0.003 (nd, 0.012)
Test of heterogeneity	
LRT, 1 d.f.[a]	14.0
p-Value	0.0001

[a] LRT comparing a model with two exposure terms to a model with one term for lifetime cumulative exposure

A model that partitions cumulative exposure by age at exposure suggests that there is a positive association between lung cancer mortality and chrysotile asbestos exposures accrued at ages 30 to <50 years (ERR per fiber-year/ml = 0.012, 95% CI: not determined, 0.042) while there is minimal evidence of association with chrysotile asbestos exposures accrued at ages less than 30 years (ERR per fiber-year/ml = −0.006, 95% CI: not determined, not determined) or at age 50 years and above (ERR per fiber-year/ml = −0.018, 95% CI: not determined, not determined). The fit of a model that allows for variation in effect by age at exposure is better than the fit of a model that assumes a time-constant ERR (LRT = 3.2, 2 d.f.); however, a model with variation in effect by attained age fitted these data substantially better than a model that allowed for variation in effect by age at exposure.

Discussion

Prior analyses of lung cancer mortality (in the full cohort of SC asbestos textile workers including females and non-white male workers) reported an estimate of the excess

relative rate per fiber-year/ml chrysotile asbestos of 0.0198 (SE = 0.0050) [3, 4]. The analyses in the present article, conducted within the framework of the TSCE model, suggest substantial variation in the relative risk of lung cancer mortality with attained age (Fig. 2). This observation is also demonstrable in analyses conducted within the framework of the proportional hazards regression model (Table 5). The latter analyses result in an estimate of the excess relative rate per fiber-year/ml chrysotile asbestos of 0.053 (95% CI: 0.023, 0.124) at attained ages less than 65 years and an estimate of 0.003 (95% CI: nd, 0.012) at attained ages of 65 years or older.

This paper illustrates how useful insights into the association between asbestos exposure and lung cancer mortality may be obtained via fitting of the TSCE model. Modeling of the data via the TSCE model encourages the data analyst to produce plots of hazard (and hazard ratio) functions for various exposure scenarios. In addition, it focuses attention on exposure intensities, and their temporal pattern, rather than on a summary metric of cumulative exposure.

Understanding of temporal variation in the relative risk of lung cancer following chrysotile asbestos exposure may be important for worker protection and public health efforts. An accurate assessment of the impact of asbestos exposure on lung cancer risk at the population level requires an accurate characterization of the magnitude of the exposure–response association and its temporal evolution.

Several previous authors have discussed the effects of asbestos exposure on lung cancer risk within the framework of multistage disease models [12–14]. For example, Peto et al. (1982) noted that, lung cancer excess risk rises sharply within 10 years of intense exposure in middle age; and, the relative and absolute risk in old age (when most cases occur) is similar irrespective of age at first exposure [13]. Peto et al. concluded that asbestos acts at a later stage or stages for lung cancer induction. Pearce (1988) and Thomas (1983), discussing the results of fitting the Armitage–Doll multistage model to occupational cohort data for asbestos workers, suggested that the data were generally consistent with asbestos acting at the fourth stage of a six-stage process. The classical Armitage–Doll model, however, does not allow for proliferation of initiated cells (clonal expansion). In contrast, the TSCE model does allow for proliferation, and the analyses in the present paper suggest that the impact of asbestos exposure on clonal expansion rates may be central to describing this association.

The validity of these findings depends, in part, upon the accuracy of the asbestos exposure estimates. A strength of this study, however, is unusually high quality of information with which to estimate historic occupational asbestos exposures. Over 5,900 historical measurements were available to inform exposure classifications in this study, along with information on changes in processes and controls [2]. The validity of these findings also depends upon the absence of substantial confounding. The lack of information on cigarette smoking is a clear limitation. However, prior work suggests that the degree of confounding by lifestyle factors, such as cigarette smoking, will be small in occupational analyses based upon internal comparisons of production workers within a single facility [15, 16]. Cigarette smoking may also be a potential effect modifier of the association between chrysotile asbestos exposures and lung cancer mortality [17]; prior work suggests that the joint effect of these exposures is close to that expected under a multiplicative model [18]. However, the lack of individual level information on smoking history limits the ability to assess such interactions or to evaluate these effects via the TSCE model.

The TSCE model fits these data well and provides useful insights into the temporal variation in the lung cancer mortality hazard rate. Goodness of model fit to a particular data set is not in itself an indication of the validity of a particular theoretical model for the disease process. Nonetheless, cohort analyses within the framework of the TSCE model provide an important complement to more standard regression methods. In particular, the analyses in the present paper imply that the hazard ratio rises, then falls, with attained age, obtaining its maximal value between ages 40 and 65 years. Such findings illustrate the importance of attention to dynamic changes in exposure–response patterns with temporal factors such as attained age. In this cohort, failure to account for variation with attained age in the effect of an increment of asbestos exposure on the relative risk of lung cancer may lead to underestimation of the excess risk of lung cancer in some risk periods (and overestimation of the excess risk of lung cancer in other periods). Further attention should be given to temporal variation in the association between chrysotile asbestos and lung cancer mortality in other populations.

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