Published in final edited form as:

Epidemiology. 2014 March ; 25(2): 246–254. doi:10.1097/EDE.0000000000000045.

Estimating the effect of cumulative occupational asbestos exposure on time to lung cancer mortality: Using structural nested failure-time models to account for healthy-worker survivor bias

Ashley I. Naimi¹, Stephen R. Cole^{1,*}, Michael G. Hudgens², and David B. Richardson¹

¹ University of North Carolina at Chapel Hill, Gillings School of Global Public Health, Department of Epidemiology, Chapel Hill, NC 27599-7435

² University of North Carolina at Chapel Hill, Gillings School of Global Public Health, Department of Biostatistics, Chapel Hill, NC 27599-7420

INTRODUCTION

The goal of many epidemiologic studies is to estimate the effect of a time-varying exposure on time to an outcome of interest. In such studies, exposure effect estimates are often prone to time-varying confounding. A time-varying confounder is a variable (*i*) whose values change over time, (*ii*) that influences exposure at subsequent time-points, and (*iii*) is associated with the time to the outcome of interest. When a time-varying confounder is also related to prior exposure values, standard methods such as Cox regression will fail to consistently estimate the total (i.e., direct and indirect) effect of exposure on the outcome of interest.¹⁻⁴ In particular, while standard methods may resolve confounding bias, the net bias may be increased upon adjustment due to collider stratification (Figure 1).⁵⁻⁷

Moreover, additional problems arise when there are no exposed or no unexposed individuals within a given stratum of a time-varying confounder. This results in a violation of the positivity assumption, which formally requires an exposure probability bounded away from zero and one in all confounder strata at all time-points.⁸⁻¹⁰ A canonical example of such time-varying confounding with a positivity violation is the healthy worker survivor bias.¹¹⁻¹³ This bias arises in situations where employment status is associated with the outcome of interest (Figure 1). In such a scenario, the effect of an occupationally-based exposure on the outcome of interest may be confounded by employment status, while employment status may be affected by prior exposure (Figure 1). In addition, individuals who leave employment often have no chance of incurring work-based exposure at subsequent time points, resulting in a violation of the positivity assumption. Because individuals who leave active employment are no longer exposed, and employment status may be associated with exposure at prior time-points, consistent exposure effect estimates cannot be obtained using standard analytic techniques.^{3,14-16}

* Correspondence: Epidemiology, CB7415, University of North Carolina, Chapel Hill, NC 27599, 919-966-7415 cole@unc.edu.

Conflicts of Interest: None

While standard methods provide inconsistent estimates under the healthy worker survivor bias, g-estimation of a structural nested accelerated failure time model provides consistent exposure effect estimates under such conditions.^{1,3,17,18} To date, only one prior study used structural nested models to account for the healthy worker survivor bias, in which an occupational exposure metric that was originally measured on a continuous scale was dichotomized.¹⁹ One (separate) study has implemented structural nested models to estimate the effect of erythropoietin dose (on a continuous scale) on mortality in patients with end stage renal disease.²⁰ No studies have used structural nested models to account for the healthy worker survivor bias in the relation between a continuous occupational exposure and mortality. The purpose of this paper is: (i) to describe the application of structural nested accelerated failure time models with a continuous exposure variable using data from a cohort of 2,564 asbestos textile factory workers followed for lung cancer mortality during 100,765 person-years between 1940 and 2001; and (ii) compare effect estimates obtained using this method to those obtained using more standard analytic techniques.

METHODS

Study Cohort

The South Carolina Chrysotile Asbestos study was an occupational cohort study of the relation between workplace asbestos exposure and lung cancer mortality over a 60-year period. The cohort consisted of 3,072 individuals who worked in the plant for at least one month between 1 January 1940 and 31 December 1965.²¹ Of the 3,072 individuals, 508 had been working in the plant prior to 1 January 1940, and were excluded from the study, leaving a total of 2,564 individuals followed for 100,765 person-years. Workers were followed for vital status and cause of death. Follow-up ended at death, loss to follow-up, or administrative censoring on 31 December 2001. Date of birth, sex, and race (Caucasian versus non-Caucasian) were ascertained from company personnel records. This study was conducted on de-identified existing records and therefore deemed not human subjects research.

Mortality Ascertainment

Vital status through 1978 was determined using information from the Social Security Administration, Internal Revenue Service, the US Postal Mail Correction Service, state driver's license files, and state vital statistics offices.^{21,22} Between 1979 and 2001, the United States National Death Index (NDI) was used to obtain vital status. Workers that were confirmed alive on 1 January 1979 and not shown to be deceased by the NDI between 1979 and 2001 were considered to be alive as of 2001. Workers lost to follow-up before 1 January 1979 were censored at the date they were last known to be alive. Prior to 1979 death certificates were obtained from the state vital records offices and the underlying cause of death was coded by a qualified nosologist. The NDI provided underlying causes of death from 1979 onwards. All deaths were coded according to the revision of the International Classification of Diseases (ICD) in effect at the time of death. Lung cancer mortality was defined as ICD-8 and ICD-9 codes 162-163, and ICD-10 codes C33-C34.

Asbestos Exposure Assessment

Ambient asbestos concentrations were estimated for the years 1940 and 1977 (inclusive; no individuals were employed at the facility under study after 1977) using 5,952 sampling measurements taken between 1930 and 1975 analyzed using phase contrast microscopy.²³ To create a job/task exposure matrix, the factory was divided into nine exposure zones corresponding to physically well-defined areas. Jobs within each exposure zone were assigned to one of four uniform job categories based on the tasks associated with that job. Average asbestos concentrations in the ambient air surrounding nine exposure zones were estimated using a job and calendar time specific exposure matrix.²³ These estimates were linked to individuals using detailed job histories based on personnel records collected by the company beginning in 1930, compiled and microfilmed by the US Public Health Service in 1968, and updated, digitized, and quality controlled in 1978.²⁴ Each day during the years in which the individual was not employed was assigned a zero asbestos exposure. Each day during the years in which the individual was employed was assigned a job and calendar period specific ambient asbestos concentration in units of chrysotile fibers longer than five μm per mL air. Following previous research,^{21-23,25-27} annual exposure levels, in units of 100 fiber-years/mL, were calculated as the average number of fibers to which a given individual was exposed per day in a given year times the number of days exposed in that same year, divided by 100×365 .²⁵

Statistical Methods

The information from the cohort provided a data vector $O \equiv \{Y, \delta, \bar{X}_t, \bar{W}_t, \mathbf{L}\}$ for each of the $i = 1$ to 2,564 study participants. We let $Y = \min(T, C)$ denote the years from study entry to lung cancer mortality (T ; $\delta = 1$) or censoring due to deaths from other causes, dropout, or study completion (C ; $\delta = 0$). We assume non-informative censoring conditional on measured covariates and illustrate how to account for it in Appendix 1 (for standard methods) and 2 (for structural nested models). We let overbars denote a variable's history. For instance, $\bar{X}_t$ denotes the set of annual exposure values, in units of 100 fiber-years/mL, representing an individual's exposure status over the course of follow-up, up to year t . Similarly, we let $\bar{W}_t$ denote the set of indicators of whether the individual was actively employed at the facility under study over the course of follow-up up to time t . For example, for an individual who left employment mid-year in their 3rd year on study over five years of follow-up, $\bar{W}_4 \equiv \{W_0, \dots, W_4\} = \{1, 1, 1, 0, 0\}$. Finally, $\mathbf{L}$ is a vector of time-fixed covariates consisting of age at study entry (age), birth year (byr), and binary indicators for gender (female = 1) and race (non-Caucasian = 1).

We assess the relation between occupational asbestos exposure and lung cancer mortality using two modeling strategies: a standard parametric accelerated failure time model (AFT) and a structural nested AFT model. Both models estimate the ratio of survival time quantiles (e.g., median) for a 100 fiber-year/mL increase in cumulative occupational asbestos exposure, lagged by 10 years. Survival time ratios (relative times) were chosen as measures of the effect of asbestos exposure, 95% confidence intervals as measures of precision, and confidence limit ratios²⁸ as measures of efficiency. We opt for relative times rather than

hazard ratios due to the inherent selection bias associated with the latter.²⁹ We lagged the exposure by 10 years to account for an empirical induction period³⁰ based on prior literature.^{21,31} Specifically, we defined a cumulative exposure metric with a 10-year lag as $A_t = \sum_{j=0}^{t-9} X_j$ if $t \geq 9$, and $A_t = 0$ otherwise. For all models, we used time from entry into the study as the timescale. In all models, age at study entry, birth year, and pre-entry exposure were entered as restricted quadratic splines with knots at the 5th, 28th, 50th, 73rd, and 95th percentiles of the variable's distribution.³²

We specified a standard parametric AFT model^{33(p425)}, which we write as:

$$F^{-1}\{P(T \leq t | \mathbf{Z}_t = \mathbf{z}_t)\} = \int_0^t \exp(\beta' \mathbf{z}_u) du \quad \text{Model 1}$$

where $F^{-1}\{\cdot\}$ is the inverse of a Weibull cumulative distribution function and $\mathbf{Z}_t$ is a vector of covariates containing the exposure and measured confounders. We parameterized this Weibull model with a shape parameter σ and a location parameter $\phi \equiv \beta' \mathbf{z}_t$. In this model the exponentiated β coefficient for A_t can be interpreted as the associational survival time ratio for a 100 fiber-year/mL increase in A_t , adjusting for all other covariates in the model. For example, $\exp(\beta)$ can be interpreted as the ratio of the (e.g., median) survival time for individuals exposed to $a + 100$ fiber-years/mL of cumulative asbestos relative to a fiber-years/mL of cumulative asbestos. Parameters for Model 1 were estimated using maximum likelihood accounting for right censoring and time-varying covariates.³⁴ Technical details are provided in Appendix 1. Even with a model adjusting for all relevant confounders, the maximum likelihood estimator will be inconsistent for the exposure effect when the conditions under which the healthy worker survivor bias may occur are present.¹⁻³

We also specified a structural nested AFT model as

$$T^{\bar{0}} = \int_0^T \exp(\psi A_u) du \quad \text{Model 2}$$

where $T^{\bar{0}}$ is the potential survival time that would have been observed under no exposure. In this model, exponentiated ψ is the causal survival time ratio for a 100 fiber-year/mL increase in A_t . In contrast to the survival time ratio for a unit increase in A_t obtained from the standard AFT model (Model 1), the estimand for a structural nested AFT model is a ratio of potential survival times for a unit difference in A_t . The parameter ψ for Model 2 was estimated using g-estimation, with inverse probability weights to account for right censoring due to drop out or competing risks.¹⁻³ Technical details are provided in Appendix 2. Assuming a correctly specified structural nested model (Model 2) and no unmeasured confounding (Equation A2.1), this g-estimator will be consistent for the exposure effect, whether or not the healthy worker survivor bias is present.¹⁻³ We used SAS release 9.3 for all analyses (SAS Institute, Cary, NC).

RESULTS

Table 1 presents study characteristics for 2,564 individuals. Median age at entry into the study cohort was 23 years, with 42% female, and 20% non-Caucasian. Over the course of

100,765 person-years of follow-up, 15% of person-years were spent at work, and 13% were classified as exposed to any asbestos. Among exposed person-years, median asbestos exposure over follow-up was 2.9 (quartiles: 1.3, 5.0) fiber-years/mL. Over the course of follow-up, median cumulative exposure was 1.7 (quartiles: 0.0, 8.2) fiber-years/mL. Furthermore, 89% of individuals (2,285/2,564) left active employment alive, with the remaining 11% either lost to follow up ($n = 236$), or having died of lung cancer ($n = 4$) or a competing cause of death ($n = 39$) while classified as actively employed. An additional 14 individuals were lost to follow up after leaving active employment, for a total of 250 individuals (9.7% of 2,564) lost to follow-up. A total of 142 individuals (5.55 of 2,564) were classified as having died due to lung cancer.

For a 100 fiber-year/mL increase in cumulative asbestos, the Weibull AFT model adjusting for gender, race, birth year, baseline exposure, and age at study entry yielded an estimated survival time ratio of 0.88 (95% confidence interval: 0.83, 0.93). Further adjustment for work status yielded an estimated survival time ratio of 0.89 (95%: 0.82, 0.96). These models yielded confidence limit ratios of 1.12 and 1.17, respectively.

Figure 2 displays the plot of the Z-statistics described in Appendix 2 for each value of $\tilde{\psi}$.

The structural nested AFT model yielded an estimated survival time ratio of $\exp\{-\hat{\psi}\} = 0.57$ per 100 fiber-year/mL increase in cumulative exposure to asbestos, with 95% bootstrap confidence intervals of (0.33, 0.96) and a confidence limit ratio of 2.91. Test and slope based 95% confidence intervals (see Appendix 2) yielded similar results. The survival time ratio obtained from the structural nested model is 35% stronger than both Weibull AFT models (Table 2). Compared to the fully adjusted parametric model, the structural nested model was 60% less efficient as determined by 95% bootstrap confidence intervals.

DISCUSSION

Using structural nested accelerated failure time models, we estimated that an increase in 100 fiber-years/mL of work-based cumulative asbestos is associated with a 43% shorter time to lung cancer mortality. This was in contrast to an estimated 12% and 11% shorter time to lung cancer mortality obtained from the work status unadjusted and work status adjusted parametric accelerated failure time models, respectively.

There are competing explanations for the differences we observed in the results from standard and structural nested models. First, the differences may be attributable to the healthy worker survivor bias. Second, structural nested models are semi-parametric: non-parametric with respect to both the distribution of the baseline survival time,³⁵ and the functional form of the relation between relevant confounders (e.g., age and birth year) and lung cancer survival time;³⁶ and parametric (Model 2) with respect to the functional form between cumulative asbestos exposure and lung cancer survival time. Standard parametric AFT models, on the other hand, assume *a priori* that the baseline survival times follow a specified distribution (e.g., Weibull), and assume a parametric form for the relation between all covariates (exposure and confounders) and the outcome. In theory, part of the observed difference may be due to residual confounding caused by mis-specification of measured

confounders.^{37(p198)} With structural nested models, one typically adjusts for confounding by modeling the exposure as a function of measured confounders (see Appendix 2). With a common exposure, one can leverage the available information to specify a flexible model for confounding (by including, for example, splines, fractional polynomials, and 1st and higher order interactions). In contrast, standard regression models typically adjust for confounding by modeling the outcome as a function exposure and measured confounders. With a less common outcome, model stability can become problematic with flexible confounder specification.

Indeed, in the asbestos cohort study data, we were able to obtain convergence while adjusting the structural nested model (using g-estimation) for all baseline confounders with all 1st and 2nd order interactions. Using the standard parametric AFT models, we could only adjust for all baseline confounders and select 1st order interactions (i.e., the maximization algorithm failed to converge to a unique solution when all 1st and 2nd order interactions were included). Nevertheless, removing interaction terms from the structural nested model that were not in the parametric model yielded negligible changes in the estimated survival time ratio, thus ruling out residual confounding as a possible explanation of the differences between our two modeling strategies.

Given the distinctions between standard and structural nested accelerated failure time models, it can be argued that the parameter estimates from structural nested models would be preferable: (i) better confounder control is always desired when the goal is unbiased point estimation; (ii) semi-parametric methods make less restrictive assumptions about the supposed mechanisms that generated the data; and (iii) structural nested models can account for time-varying confounding when the positivity assumption is violated (as with the healthy worker survivor bias).

On the other hand, compared to the parametric models, confidence intervals for the parameter from the structural model were much larger, as can be seen in Table 2. This is the expected result of the fact that: (i) semi-parametric methods are known to be less efficient than their correctly specified parametric counterparts;³⁸ (ii) the simple robust variance estimator used in our exposure model is conservative;¹⁷ (iii) the chosen functional form of the potential outcomes in our exposure model (see Appendix 2) is known to result in an efficiency loss;² and (iv) artificial censoring, required for consistent estimation of structural nested model parameters when administrative censoring is present (see Appendix 2), reduces the effective number of events.²⁰

Any statistical method must rely on several identifiability assumptions to make valid inferences. In particular, we assume no unmeasured confounding.^{2,39} In our case, we did not have information on individual smoking status, socioeconomic position, or intermittent time off work, which is a limitation of the current study.

In addition, we assume counterfactual consistency, which states that for a given individual, the potential outcome that would have been observed under the observed exposure is, in fact, the observed outcome.⁴⁰⁻⁴⁴ This assumption is better satisfied with an exposure contrast that can be construed as an intervention.⁴⁰⁻⁴² In our study, we defined the exposure

as the cumulative number of chrysotile asbestos fibers longer than $5\mu\text{m}$ per milliliter of air to which an individual was exposed in an asbestos textile factory, in units of 100 fiber-years/mL. Our exposure contrast can be thought of as one that compares the survival time under some arbitrary level of cumulative exposure over time t , to the survival time that would have been observed under a cumulative exposure level $t + 100$ (i.e., a 100 f-y/mL increase). Such a change in the exposure value could ostensibly be achieved through a number of interventions such as, for example, a change in the amount of venting in the workspace.

We further assume no interference and correct model specification. The former assumption implies that no individual's potential outcome is influenced by another individual's exposure value,⁴⁵ which is likely in our setting. For standard AFT models, the latter assumption requires a correctly chosen: (i) distribution for baseline survival time; (ii) link function relating the outcome to the model covariates; and (iii) the functional form of all covariates involved. For the structural nested model, the latter assumption requires only a correctly specified link function, and a correct functional form of the relationship between cumulative asbestos exposure and time to lung cancer mortality (or a meaningful projection thereof⁴⁶).

Finally, the positivity (or experimental treatment assignment) assumption is a central requirement for valid causal inferences using observational data. Positivity requires exposed and unexposed observations in all confounder strata at all time-points.⁸⁻¹⁰ The healthy worker survivor bias results in a systematic (as opposed to random) violation of positivity:¹⁶ individuals who have terminated active employment *cannot* be exposed to work-based asbestos.

Systematic positivity violations can be problematic for two reasons. First, it is possible that the data contain information that can be used to make valid causal contrasts, but due to a lack of positivity, some methods fail (while other methods succeed) to estimate such contrasts. For example, inverse probability weighting (IPW) estimators of the parameters of a marginal structural model (MSM) are not consistent when the positivity assumption is violated.^{16,47} Other MSM estimators (g-computation,⁴⁸ augmented-IPW,⁴⁹ or targeted maximum likelihood estimators⁵⁰), or other methods (parametric g-formula¹⁴ or g-estimation of a structural nested model¹⁷) can provide consistent (i.e., unbiased) estimates, even under positivity violations. On the other hand, positivity violations may be such that there is no relevant information upon which one can make a valid causal contrast.^{10,51-53} In such a scenario, researchers must take care to avoid using methods that will provide point estimates for a causal contrast that is unsupported by data, of little meaning or public health relevance, or both. In our specific case, we are estimating the effect of a 100 fiber-year/mL change in work-based cumulative asbestos exposure on lung cancer survival. Because the probability of being exposed conditional on measured confounders is bounded away from zero and one, this contrast is supported by the data.

Using structural nested AFT models, we assessed the relation between cumulative asbestos exposure and lung cancer mortality while accounting for the healthy worker survivor bias. The example demonstrated that standard and structural nested models provided different effect estimates. The structural model yielded a survival time ratio that was 35% stronger

than the estimates from the parametric models. This is suggestive of bias in previous analyses with these data, and the magnitude is such that it underscores importance of accounting for healthy worker survivor bias in this setting. Our exploration of these relations is further strengthened by the use of a large cohort with well-characterized mortality and under 10% loss to follow-up over a 60-year period. When the healthy worker survivor bias is suspected, researchers should opt for appropriate methods, such as structural nested models, to obtain unbiased estimates of the effect of a work-based exposure on a health-related outcome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank Steven B. Wing, and M. Alan Brookhart for comments on earlier versions of the manuscript. We thank Marshall M Joffe and Erica EM Moodie for expert advice.

Sources of Funding: Drs. Naimi, Cole, and Richardson were supported in part through NIH-NCI grant R01CA117841. Dr. Naimi was supported by a Doctoral Research Award from the Fonds de Recherche en Santé du Québec

APPENDIX 1: Technical details for the time-varying Weibull AFT model

For observation time $Y = \min(T, C)$, we assume that conditional on measured confounders, the event time T is independent of censoring time C . We let $f_Y(y)$ and $S_Y(y)$ denote the probability density and survival functions for $Y \sim \text{Weibull}(\phi, \sigma)$, defined as:

$$f_Y(y) = \frac{1}{\sigma y} \exp\{-\phi y\} y^{\frac{1}{\sigma}} \exp\left\{\exp(-\phi y) y^{\frac{1}{\sigma}}\right\}$$

and

$$S_Y(y) = 1 - \Gamma\left\{\exp(-\phi y) y^{\frac{1}{\sigma}}\right\}$$

respectively, where $\phi_y = \beta'z_y$, and where $\Gamma\{\cdot\}$ is the CDF for a generalized gamma distribution defined in Cox et al.³⁴ For the Weibull AFT model accounting for right censoring and time-varying covariates, each individual's contribution to the log-likelihood is

$$L_i(\phi_y, \sigma) = \left\{ \prod_{y=0}^{\lfloor Y_i \rfloor} \frac{S_Y(y; \phi_y)}{S_Y(\lfloor y-1 \rfloor; \phi_y)} \right\} \left\{ \frac{f_Y(y; \phi_y)}{f_Y(\lfloor y \rfloor; \phi_y)} \right\}^{\delta_i} \left\{ \frac{S_Y(y; \phi_y)}{S_Y(\lfloor y \rfloor; \phi_y)} \right\}^{(1-\delta_i)}$$

where $\lfloor \cdot \rfloor$ denotes the floor function (e.g., $\lfloor 5.7 \rfloor = 5$), and $a \wedge b = \min(a, b)$. In this equation, the product is taken over integer values of y because annual measures were taken.

Thus, all individuals contribute to the first term in the likelihood, lung cancer deaths ($\delta_i = 1$) contribute to the second term, and censored observations ($\delta_i = 0$) contribute to the third term.^{54(p220)} We fit this model using a SAS NLMIXED program provided by Cox et al³⁴ to estimate parametric survival models with time-varying covariates.

APPENDIX 2: G-estimation

The g-estimation algorithm is premised on the assumption of no unmeasured confounding.^{2,39} This assumption states that, at time t , and conditional on past confounders and exposure history, the exposure received is independent of the potential outcomes. No unmeasured confounding implies

$$E\left\{X_t | \bar{X}_{(t-1)}, \mathbf{V}_t, T^a\right\} = E\left\{X_t | \bar{X}_{(t-1)}, \mathbf{V}_t\right\}, \quad T > t \quad \text{Equation A2.1}$$

where $E\{\cdot\}$ denotes the expectation operator, $\bar{X}_{(t-1)}$ is the exposure history up to and including time $t - 1$, and $\mathbf{V}_t$ is a vector of time-fixed and time-varying covariates that renders the assumption of no unmeasured confounding as close to true as possible (in our case, the time-fixed variables in $\mathbf{L}$ and time-varying W_t). This assumption implies that the exposure allocation mechanism can be thought of as a sequentially randomized (or nested) process: roughly speaking, within strata defined by the joint distribution of $\left[\bar{X}_{(t-1)}, \mathbf{V}_t\right]$ over all time points, exposure allocation occurs at random (or, equivalently, is independent of the potential outcomes).

The g-estimation algorithm is then implemented as follows:

- i. Specify a model for Equation A2.1.
- ii. Specify a set of parameter values denoted $\tilde{\psi}$ that are likely to span the effect of interest with an appropriate increment to carry out a line search (e.g., 0 to 2 by 0.05) that will be used to estimate ψ .
- iii. For each value of $\tilde{\psi}$, use Model 2 to impute T^0 , which we re-write as $T(\tilde{\psi})$ to make the dependence on ψ clear. Thus, $T(\tilde{\psi})$ the potential survival time under no exposure for each value of $\tilde{\psi}$.
- iv. For each value of $\tilde{\psi}$, use the imputed survival times $T(\tilde{\psi})$ to test whether exposure at time t is conditionally independent of the potential outcomes given $\bar{X}_{(t-1)}, \mathbf{V}_t$. We can test this independence using a Wald, score, or likelihood ratio test. A set of 41 $\tilde{\psi}$ values (0 to 2 by 0.05) returns 41 different test statistics, denoted $Z(\tilde{\psi})$.
- v. Using a *modus tollens* argument, we can obtain our parameter estimate: Assuming no unmeasured confounding holds, the value of $\tilde{\psi}$ for which the test statistic $Z(\tilde{\psi}) = 0$ is the value at which we have imputed to correct set of potential

outcomes for each individual in our study. Therefore, the estimator $\hat{\psi}$ is set equal to the $\tilde{\psi}$ at which $Z(\tilde{\psi}) = 0$.

Slope-based estimated standard errors for $\hat{\psi}$ can be computed as $\sigma_s = \left(d^{-2}\right)^{\frac{1}{2}}$, where d is the numerical derivative of the test statistic $T(\tilde{\psi})$ evaluated at $\hat{\psi}$. This derivative may be estimated by the slope of a local linear regression of $\tilde{\psi}$ on the $Z(\tilde{\psi})$ statistic.⁵⁵

Alternatively, a bootstrap estimate of the standard error of $\hat{\psi}$ can be obtained as the standard deviation of the set of 200 bootstrapped estimates $\{\hat{\psi}_1^*, \dots, \hat{\psi}_{200}^*\}$. Each bootstrap estimate can be obtained by fitting Model 2 to a random sample of size $N^* = 2,564$ (where * denotes a bootstrap resample) drawn, with replacement, from the original 2,564 data vectors O .⁵⁶

Finally, assuming $Z(\tilde{\psi}) \sim N(0, 1)$, test-based upper and lower 95% confidence intervals for $\hat{\psi}$ can be computed by the values of $\tilde{\psi}$ that correspond to $Z(\tilde{\psi}) = \pm 1.96$.

For our data, asbestos exposure for each year on study (X_t) followed a complex zero-inflated distribution. To simplify the analysis, we categorized this continuous exposure into 11 groups (one category for $X_t = 0$, and deciles for $X_t > 0$) and specified a proportional odds model⁵⁷ for Equation A2.1, which was implemented with PROC GENMOD, as:

$$\text{logit} \left[\frac{\pi_{m+1} + \dots + \pi_{11}}{\pi_1 + \pi_2 + \dots + \pi_m} \right] = \alpha_{0m} + \alpha_1 I(\text{nonCaucasian}) + \alpha_2 I(\text{female}) + \alpha_{f1} f_1(\text{year}) + \alpha_{f2} f_2(\text{byr}) \\ + \alpha_{f3} f_3(\text{age}) + \alpha_{f4} f_4(C) + \alpha_g g(X_{t-1}) + \alpha_h \mathbf{I}^{(1)} + \alpha_i \mathbf{I}^{(2)} + \alpha_5 h \left[Y(\tilde{\psi}) \right] \hat{k}$$

where μ_j , $j = 1$ to 11 is the probability that the continuous exposure value falls in category j ; $I(\cdot)$ is an indicator function; $f_k(\cdot)$, $k = 1, 2, 3, 4$ returns a 1×4 vector of restricted quadratic spline basis functions for argument $(\cdot)$ with knots as defined above; α_{fk} represents a 4×1 vector of parameters for each basis function; C is censoring times (described in the next section) for each individual; $g(\cdot)$ returns a 1×10 vector of fractional polynomial functions for argument $(\cdot)$ of order $\pm 1/3, \pm 1/2, \pm 1, \pm 2, \pm 3$, α_g represents a 10×1 vector of parameters for each polynomial term, and $h(\cdot)$ is a function of the potential outcomes $Y(\tilde{\psi})$ [and not $T(\tilde{\psi})$] and inverse probability of censoring weights $\hat{k}$, all of which are described in subsequent sections. Furthermore, $\mathbf{I}^{(1)}$ and $\mathbf{I}^{(2)}$ represent all first and second order interaction terms between the linear components of each term in the model (except $h \left[Y(\tilde{\psi}) \right] \hat{k}$), respectively. We used fractional polynomials instead of restricted quadratic splines to specify past exposure due to the large number of zero-valued knots obtained with the latter. Including a function of past exposure $g(X_{t-1})$ is required to obtain consistent exposure effect estimates using structural nested models.¹⁷ Including the function of past exposure in our parametric AFT models did not appreciably change the results. Parameters for this estimating equation were estimated using GEE⁵⁸ with an independent working covariance matrix.⁵⁹

Artificial censoring

The potential outcomes imputed by Model 2 are defined as a function of the observation time $Y = \min(T, C)$. In this section, we assume C is the administrative censoring time defined as the difference between the study's administrative end date and date of entry into the study. We handle censoring due to loss to follow up in the next section. If our exposure of interest has an actual effect on survival time, then the survival times of individuals with higher exposures are more (or less) likely to be observed in our study. By using T instead of Y to impute the potential survival time, we create an artificial association between exposure and the potential survival time $T(\tilde{\psi})$, thus violating the assumption of no unmeasured confounding.¹⁸ We use artificial censoring to account for this.^{20,60} To do so, we define a counterfactual censoring time

$$C(\tilde{\psi}) = C \exp\{\tilde{\psi} \times \min[A_t]\} \quad \text{if } \tilde{\psi} \geq 0, \quad \text{and} \quad C(\tilde{\psi}) = C \exp\{\tilde{\psi} \times \max[A_t]\} \quad \text{if } \tilde{\psi} < 0$$

, where $\min[A_t]$ and $\max[A_t]$ refer to the global empirical min and max exposure values (i.e., the min and max values across all person-years in the South Carolina cohort). We then

define a new potential survival time $T^*(\tilde{\psi}) = \min\{T(\tilde{\psi}), C(\tilde{\psi})\}$. This new variable $T^*(\tilde{\psi})$ is the potential survival time only in those individuals whose potential survival times would have been observed under any possible cumulative exposure regime that falls

within the global empirical min and max bounds. Otherwise, $T^*(\tilde{\psi})$ is the potential

censoring time. Because $T^*(\tilde{\psi})$ is a function of the administrative censoring time C , we include C Equation A.2.1 defined above.^{2,61} Finally, in the previous section we referred to $h(\cdot)$ as the functional form of the potential outcomes in our exposure model, which we define

here as $h[T^*(\tilde{\psi})] = I[T(\tilde{\psi}) \leq C(\tilde{\psi})]$. Such a form for the potential outcomes has been shown to affect the efficiency, but not the consistency, of the estimator for ψ .^{2,61} In our study, the effective proportion of failures resulting from artificial censoring over the range of the parameter space defined by $\tilde{\psi}$ was between 3.0% ($n = 86$, $\tilde{\psi} = 2.0$) to 6.0% ($n = 142$, $\tilde{\psi} = 0$, i.e., the actual proportion of failures), with a mean value of 4.9% ($n = 106.46$).

Inverse probability of censoring weights

As with standard parametric AFT models, we assume censoring due to deaths from other causes or loss to follow-up is independent of lung cancer mortality conditional on measured covariates. We use inverse probability of censoring weights to account for right censoring due to drop out or competing risks when fitting a structural nested accelerated failure time model.⁶² For each individual at time t , define

$$\hat{k}_t = \prod_{j=0}^t \frac{\hat{P}(C_j = 0) \times (1 - C_j)}{\hat{P}(C_j = 0 | \mathbf{V}_j)}$$

where

$$\hat{P}(C_j=0|\mathbf{V}_j) = 1/\left\{1+\exp\left[-\left(\hat{\beta}_{0,j}+\hat{\beta}_1 I(\text{nonCaucasian})+\hat{\beta}_2 I(\text{female})+\hat{\beta}_3' f_1(\text{year})+\hat{\beta}_4' f_2(\text{byr})+\hat{\beta}_5' f_3(\text{age})+\hat{\beta}_6' f_4(\text{base})\right)\right]\right\}$$

$$\text{and } \hat{P}(C_j=0)=1/\left\{1+\exp\left[-\left(\hat{\alpha}_{0j}\right)\right]\right\}$$

are based on logistic regression models with parameters estimated using maximum likelihood. Thus, if a person is uncensored in a given year j , k_j is the inverse of the conditional probability of being censored, and is zero otherwise. This inverse probability weight is stabilized by the marginal probability of being censored in year j . For our data, these stabilized weights were not extreme in their distribution, with a mean = 1.00, min = 0.54, and max = 16.59. As denoted in our model for Equation A2.1, we multiply $h\left[T^*\left(\tilde{\psi}\right)\right]$ by k to account for non-administrative censoring. We refer the reader to Witteman et al.^{63(p393)} for an explanation as to how these inverse probability weights account for non-administrative censoring using g-estimation.

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FIGURE 1.

Causal diagram representing the healthy worker survivor bias. We let t index time on study, X represent continuous asbestos exposure, W index employment status, U represent a common cause of W and T , and T index survival time.

FIGURE 2.

Plot of the $Z(\tilde{\psi})$ test statistic by $\tilde{\psi}$ including a horizontal reference line at zero and vertical reference line at $\hat{\psi}$. Gray lines represent results for each of the 200 bootstrap resamples.

TABLE 1

Characteristics of 2,564 individuals in the South Carolina Chrysotile Asbestos cohort at enrollment and during 100,765 person-years of follow-up between 1940 and 2001.

Characteristic ^a	First Year of Follow-up <i>N</i> = 2,564	Entire Course of Follow-up <i>PY</i> = 100,765
Age	23 (20, 31)	22 (19, 28)
Birth year	1922 (1915, 1926)	1922 (1916, 1927)
Female gender, <i>N</i> (%)	1,077 (42%)	42,416 (42%)
Non-Caucasian race, <i>N</i> (%)	512 (20%)	18,305 (18%)
At work, <i>N</i> (%)	2,564 (100%)	15,537 (15%)
Asbestos exposure ^b :		
Any, <i>N</i> (%)	2,314 (90%)	12,781 (13%)
Continuous (<i>X_t</i>) ^c	1.7 (0.9, 3.2)	3.4 (1.6, 5.0)
Cumulative (<i>A_t</i>)	^d	1.7 (0, 8.2)
Deaths (Total)	-	1,522
Lung Cancer Deaths	-	142

* *N*, number

^a Median (Quartiles) unless otherwise stated

^b In units of fiber-years/mL

^c Among person-years with any exposure

^d 10 year lagged cumulative exposure = 0 during first year of follow-up for all individuals on study

TABLE 2

Survival Time Ratios (95% CIs) for the Association Between 10-year Lagged Cumulative Asbestos Exposure for Standard and Structural Nested Model Analyses

Model	Time Ratio	95% CI	CLR
Work Status Unadjusted AFT	0.88	0.83, 0.93	1.12
Work Status Adjusted AFT	0.89	0.82, 0.96	1.17
Structural Nested AFT	0.57	0.33, 0.96 ^a	2.91
		0.32, 1.00 ^b	3.13
		0.17, 0.95 ^c	5.59

^a Bootstrap Wald confidence intervals where $SE(\hat{\psi}) = SD(\hat{\psi}_K^*)$, with $K = 200$ resamples

^b Test-based confidence intervals for $\exp\{-\psi\}$ chosen such that $Z = \pm 1.96$

^c Slope-based Wald confidence intervals with $SE(\hat{\psi}) = (d^{-2})^{1/2}$, where d is obtained from the slope of a local linear regression $\tilde{\psi}$