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Asbestos standards: Impact of currently uncounted chrysotile asbestos fibers on lifetime lung cancer risk

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Abstract

Background—Current regulations require that asbestos fibers are collected and examined using a light microscope. This method fails to enumerate fibers that are too short or thin to reliably count using a light microscope under normal conditions.

Methods—A cohort of 3054 workers employed at an asbestos textile plant was followed to ascertain causes of death. Exposure was almost entirely chrysotile. Fiber counts were quantified using light microscopy and electron microscopy. The g-formula was used to estimate impacts on lung cancer of policies defined in terms of fiber counts quantified using light and electron microscopy.

Results—Given exposure at the current standard, the estimated lung cancer risk was 7.33%, comparable to the risk expected under a standard of 1 fiber/ml counted using electron microscopy (7.30%). The lifetime risk of lung cancer under a standard of 0.1 fiber/ml counted by electron microscopy was estimated to be 7.10%.

Conclusions—We identify policies defined in terms of electron microscopy-based asbestos exposure metrics that yield comparable, or lower, lung cancer mortality than that expected under the current standard.

Keywords

asbestos; cohort studies; mortality study; lung cancer; occupational diseases

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INTRODUCTION

Despite being a recognized carcinogen, asbestos remains an important occupational and environmental hazard. In the United States and United Kingdom, for example occupational and environmental asbestos exposure is primarily due to the large reservoir of asbestos in infrastructure. However, internationally there is still an important global trade in asbestos, with roughly 2 million metric tons of asbestos purchased each year.¹ Recent estimates suggest that in the United Kingdom asbestos is responsible for 70% of the occupational cancer deaths in the construction industry.² Therefore attention to the adequacy of policies to protect workers and the public from asbestos exposure remains an important task for public health researchers.

Contemporary policies regarding occupational and environmental asbestos exposure require that a sample of air is collected, and the number of asbestos fibers longer than 5 μm in that sample is counted using a phase contrast optical microscope. This counting method using light microscopy dates back more than a half century, and it suffers some important limitations. Notably, under normal conditions it is not possible to reliably count chrysotile fibers that are very short or very thin using a light microscope.³ For example, a long fiber may be invisible under a light microscope if it is very thin. In many settings the vast majority of asbestos fibers in the environment may be of dimensions (e.g. shorter than 5 μm) that are simply not counted using this method.

Methods for counting asbestos fibers using a transmission electron microscope instead of a light microscope have been available for many years but largely used for research purposes rather than routine exposure monitoring and compliance determinations. Large numbers of short and thin fibers that were previously unquantified by light microscopy are readily observed using transmission electron microscopy.⁴ For example, prior studies have examined air samples from public buildings (such as schools, gyms, and kindergartens) and found that for a large proportion of samples, no fibers were counted when using a light microscope but substantial numbers of asbestos fibers were counted when using electron microscopy.^{5,6}

The missed fibers are not necessarily innocuous;⁷ rather they were omitted from regulatory coverage largely as a consequence of the poor ability of the microscopist to reliably quantify these smaller, thinner asbestos particles.⁸ Such considerations are also relevant to consideration of occupational asbestos exposures, such as those experienced by automobile and truck brake mechanics. Those jobs often involve exposure to large numbers of fibers not enumerated by phase-contrast optical microscopy.^{9,10} The phase contrast optical microscopy method measures only a small fraction of total airborne asbestos fiber and the ratio of measured to total fibers is highly variable by fiber type, industry, and process. Moreover, in non-occupational settings, often many fibers that are quantified by light microscopy are not, in fact, asbestos fibers; an electron microscope improves the ability to distinguish between asbestos and non-asbestos fibers.⁴ Consequently, in some settings many of the fibers we do count using the light microscopy method are not asbestos, and conversely many of the fibers we fail to count using the light microscope are asbestos.

Prior analyses, using data for a cohort of workers exposed to chrysotile in a South Carolina asbestos textile plant, found that transmission electron microscope-based exposure was a substantially better predictor of lung cancer and asbestosis mortality than phase-contrast light microscopy-based exposure.¹¹ Such findings suggest important policy implications for evaluating and controlling risks associated with asbestos in the workplace and the general environment, and offer a rationale for greater attention to exposure metrics informed by electron-microscopy.

However, to date, one practical obstacle to using the transmission electron microscopy method of quantification of asbestos is that regulators have noted that it is unclear what level of exposure, as quantified by electron microscopy, would be acceptable as a regulatory basis, because of (a) the larger number of fibers counted by electron microscopy than by the standard phase-contrast light microscopy and (b) the fact that electron microscopy estimates of the total number of fibers may not be well correlated with phase contrast microscopy estimates of fiber counts.¹² In this paper, we identify policies defined in terms of electron microscopy-based asbestos exposure metrics that yield comparable, or lower, mortality due to lung cancer than that expected under the current OSHA standard.

METHODS

Study cohort

The cohort includes 3054 men and women employed in production at an asbestos textile plant located in South Carolina, and who remained at work for at least one month between 1 January 1940 and 31 December 1965 (Dement, Brown et al. 1994; Stayner, Smith et al. 1997). Workers were followed through December 31, 2001 to determine vital status using information from the Social Security Administration, the Internal Revenue Service, state driver's license files, state vital statistics offices, and the National Death Index. Persons who were confirmed as alive on January 1, 1979, with valid Social Security numbers and not shown to be deceased by the National Death Index between 1979 and 2001 were considered to be alive as of 2001. Cause of death information was obtained from death certificates. The primary outcome of interest is death due to lung cancer, defined as deaths for which the underlying cause of death was attributed to cancers of the trachea, bronchus and lung. Information on demographic and employment characteristics was collected from plant records describing date of birth, sex, race, and dates of hire, job or department change, and termination. We excluded workers who terminated employment before age 17.

The study was approved by ethical review committee of the University of North Carolina at Chapel Hill.

Asbestos exposure estimates

The plant began textile production using raw chrysotile asbestos fibers in 1909 and some workers included in this study were employed at the facility prior to start of study follow-up in January 1, 1940. Workers were assigned two exposure metrics for each year of employment at the plant. First, we derived estimates of the number of airborne asbestos fibers as quantified by fiber counting using a phase-contrast light microscope. Asbestos

concentrations by job, department, and calendar time were estimated for each year of employment using 5,952 sampling measurements taken between 1930 and 1975; these sampling measurements were collected by both the older midjet impinger method and by the membrane filter method that were analyzed using light (i.e., phase contrast) microscopy.^{13,14} Textile production operations, which corresponded to physically defined areas of the plant, were considered in deriving operation specific conversion factors that were developed to express impinger dust concentrations as equivalent values quantified using phase-contrast light microscopy.¹⁵

Second, we derived estimates of the number of asbestos fibers in the air that a worker was exposed to, as quantified when an air sample is counted using a transmission electron microscope¹¹. Archived air samples collected at the textile plant were reanalyzed by transmission electron microscopy to estimate asbestos air concentrations. The total number of fibers by job, department and calendar period were estimated. This assessment was performed on a stratified random sample of historical dust samples captured on membrane filters collected in surveys of the SC study plants in 1964-1971. The transmission electron microscope fiber-counting protocol was based on the ISO direct-transfer method.^{16,17} While costs restricted the number of dust samples that could be analysed by electron microscopy, the available data are among the best available for characterizing historical fiber size in an occupational cohort. Estimates of the bivariate (length and diameter) fiber size distribution were derived. These were applied to a matrix of job-, department- and time-specific fiber concentrations estimated by the light microscopy method to generate fiber size-specific estimates of exposure. Descriptions of exposure distributions for this cohort based on phase-contrast light microscopy and transmission electron microscopy methods have been described in detail previously.^{11,18}

Statistical methods

The statistical analysis used a Monte Carlo algorithm for the parametric g-formula.^{19,20} Briefly, the steps needed to estimate lung cancer mortality using this approach are as follows. First, using the observed data, we fitted parametric regression models for lung cancer as a function of covariates and estimated asbestos fiber counts quantified using either light or electron microscopy. We also fitted parametric models for the probability of remaining at work and for the probability of dying from a competing cause. Second, a large Monte Carlo sample is drawn randomly with replacement from the observed participants. Third, the fit of the parametric models in the first step is used to recreate the follow-up experience for each person in the Monte Carlo sample, under the condition that different policies, defined in terms of fiber counts quantified using light and electron microscopy, were applied (i.e., workers' exposures were set to that policy level). Fourth, the survival curve is estimated under each scenario by using the Monte Carlo sample to obtain the cumulative lung cancer mortality through 90 years of age.

Prior work using this cohort applied the g-formula to estimate the impact of exposure standards based on phase contrast microscopy-derived measures of asbestos exposure. The primary focus of the current analysis is to identify policies defined in terms of fiber counts

quantified using electron microscopy that would yield comparable, or lower, lung cancer mortality to that obtained under current OSHA regulations.

A worker entered follow-up for this analysis one month after hire or at age 18 years, whichever was later. A file was created with one record for each person-year of observation from date of entry into the analysis until end of follow-up or administrative censoring of workers alive at age 90 years. Using these data, we fitted the following discrete time regression models: a logistic regression model to predict the probability of remaining employed in a given person-period; a logistic model to predict lung cancer death allowing for a flexible cumulative asbestos exposure-mortality association; and a logistic model for other causes of death (Appendix). The explanatory variables in all models included a cubic polynomial function of age, binary indicators of race and sex, a linear function of calendar year of study entry, and a quadratic polynomial function of cumulative asbestos exposure accrued prior to study entry. The logistic model for employment status included a quadratic spline function of the worker's asbestos exposure in the two prior years. The logistic models for lung cancer and for other causes of death included a cubic polynomial function of the person's cumulative asbestos exposure accrued to that person-period, and indicators for current employment status and employment status in the two prior years.

A consequence of the g-formula approach is the ability to reduce potential healthy worker survivor bias by accounting for employment status as a time-varying covariate affected by prior exposure.²¹ These calculations are based on settings in which exposures were set to a specified policy level. The approach involves a Monte Carlo simulation from the joint distribution implied by the models for employment and mortality. To estimate lung cancer mortality at age 90 years under a specified policy, we used the following process. All individuals are assumed to be employed at the start of follow-up. Starting at period $m=1$, employment status is assigned using the conditional probability estimated from the parametric model for termination of employment. If employed, the person's exposure is set to the level specified by the policy. Next, the probability of lung cancer and competing causes of mortality are estimated based on the joint distribution of exposure and covariates; and, a binary indicator for each outcome is drawn from a Bernoulli distribution with the associated probability. If the individual is still alive at the end of period m , then the process is repeated again for $m=m+1$, until death or until m equals the time at the end of follow-up. Within each person period, we assume the temporal ordering of the component variables assigned to each person-period as follows: fixed covariates, employment status, exposure conditional on being at work, death due to other causes, and lung cancer death. This algorithm yields an estimate of the cause-specific mortality hazards which can be used to estimate the cumulative incidence of lung cancer mortality using a generalization of the Kaplan-Meier estimator.²²

We first calculated cumulative incidence of lung cancer mortality under the current OSHA policy based on light (phase contrast) microscopy methods to quantify asbestos exposure, expressed as fiber/ml. Next, we calculated cumulative incidence of lung cancer mortality under hypothetical policies based on transmission electron microscopy methods to quantify total concentration of asbestos fibers expressed as fiber/ml. We calculated a risk difference by subtracting the cumulative incidence of an index policy from the cumulative incidence

estimated under the current OSHA policy. We identified policies based on electron microscopy that yield comparable lung cancer mortality to that observed under OSHA regulations. As a measure of precision, 95% confidence intervals are computed using standard errors estimated from 200 nonparametric bootstrap resamples. We estimate the number of persons required to follow a hypothetical policy (with reference to the current OSHA standard) to reduce the lung cancer mortality by age 90 years by 1 case as the reciprocal of the estimated risk difference. In a sensitivity analysis, we consider an electron microscopy-based metric defined in terms of counting only fibers $>5 \mu\text{m}$ in length. Most fibers of this length are visible using either a light microscope or electron microscope (although very thin fibers may not be detected and counted by phase contrast microscopy due to limits of resolution by light microscopy).

RESULTS

At study entry, the median age of the cohort members was 24 years; 42% were female and 81% were white. The estimated cumulative lung cancer mortality at age 90 years expected under the 1976 OSHA standard of 2 fiber/ml counted using light microscopy is 9.35%; and, the estimated cumulative lung cancer mortality at age 90 years expected under the current OSHA standard of 0.1 fiber/ml counted using light microscopy is 7.33% (Table I). The risk difference comparing cumulative lung cancer mortality at age 90 years under the 1976 OSHA standard to that expected under the current OSHA standard is 2.02% (95% confidence interval (CI): 0.26%, 3.79%), and the ratio of these risks is 0.78 (95% CI: 0.63, 0.98). In this population, 1 lung cancer death is estimated to be prevented for every 50 workers regulated under the current OSHA standard as compared to the 1976 OSHA standard of 2 fiber/ml, counted using light microscopy.

Next, we calculated cumulative lung cancer mortality under hypothetical standards based upon counting of total asbestos fibers by electron microscopy. A standard of 45 fibers/ml counted by electron microscopy yields 9.41% lung cancer mortality by age 90 years comparable to the 1976 OSHA standard by phase-contrast microscopy. A standard of 1 fiber/ml counted by electron microscopy yields 7.30% lung cancer mortality by age 90 years, comparable to the current OSHA standard. Figure 1 illustrates the expected cumulative lung cancer mortality over ages 20-90 years setting exposure to the 1976 OSHA standard and to the current OSHA standard based on light microscopy and under hypothetical standards of 45 and 1 fiber/ml counted by electron microscopy. An even tighter standard of 0.1 fiber/ml counted by electron microscopy leads to a slightly lower estimated cumulative lung cancer mortality at age 90 years of 7.10% (Table II). The risk ratio comparing cumulative lung cancer mortality at age 90 years under a standard of 0.1 fiber/ml counted by electron microscopy to that expected under the current standard is 0.97 (95% CI: 0.88, 1.07). The risk difference comparing cumulative lung cancer mortality at age 90 years under the current OSHA standard to that expected under a standard of 0.1 fiber/ml counted by electron microscopy is 0.23% (95% CI: -0.52%, 0.97%), suggesting a small, albeit highly imprecise, reduction in risk. We estimate that 1 lung cancer death would be prevented for every 444 workers regulated under a standard of 0.1 fiber/ml counted by electron microscopy as compared to the current OSHA standard of 0.1 fiber/ml counted by light microscopy.

In a sensitivity analysis, we counted only fibers at least 5 μm in length (Table III). Under a hypothetical standard of 0.1 fibers/ml when counting just those fibers at least 5 μm in length by electron microscopy yields 7.21% lung cancer mortality by age 90 years.

DISCUSSION

Over the last forty years OSHA standards for airborne asbestos have fallen from 2 fibers/ml to 0.2 fiber/ml, to the current standard of 0.1 fiber/ml. Exposure at the current OSHA asbestos standard of 0.1 fiber/ml as counted by light microscopy while at work yields a 2% lower risk of lung cancer by age 90 years than that expected given a career in which a worker was exposed at the 1976 OSHA standard of 2 fibers/ml (Figure 1).

The current OSHA standard only regulates asbestos fibers that can be reliably counted when using phase-contrast optical microscopy. However, there are many occupational and environmental settings in which exposures are predominated by shorter asbestos fibers (less than 5 μm in length) and asbestos fibers that are less than approximately 0.25 μm in diameter (i.e. the resolution limit of optical microscopy).³ Of course, if asbestos exposure estimates based upon light microscopy methods were strictly proportional to total exposure to all etiologically-relevant asbestos fibers then a policy that regulated asbestos exposure as measured by light microscopy might suffice to control etiologically-relevant occupational asbestos exposures. However, there is evidence that the proportion of asbestos fibers that are not counted by light microscopy varies by fiber type, work activity, fiber quality, and other conditions. Therefore, workers may have relatively low phase contrast microscopy-based measures of asbestos fiber exposure but high total asbestos exposure due to a large fraction of fibers that are too short or thin to count by light microscopy. Monitoring based on transmission electron microscopy allows enumeration of fibers that are not readily counted using light microscopy.

Using data from the South Carolina asbestos textile cohort study, an important cohort study in the literature on occupational asbestos exposures,^{13,23} we quantified lung cancer mortality under a number of policy choices using the parametric g-formula. Among these policies, we identified policies based on the number of fibers counted using transmission electron microscopy that yield similar lung cancer risk to that expected under the 1976 OSHA standard and the current OSHA standard (Figure 1). A standard of 1 fiber/ml measured by electron microscopy counting of total asbestos fibers yields cumulative lung cancer mortality comparable to that expected under the OSHA standard of 0.1 fiber/ml as quantified by phase contrast microscopy. We calculated the expected reduction in cumulative lung cancer mortality under a hypothetical standard of 0.1 fiber/ml as quantified using an electron microscope, and found that such a standard would be expected to yield a 0.2% reduction in cumulative lung cancer mortality relative to the current standard. This translates into the potential to prevent work-related cancers. We estimated that switching to an electron-microscopy-based standard would result in 1 fewer lung cancer deaths by age 90 years for every 444 workers subject to the regulation, comparing the standard of 0.1 fiber/ml counted by electron microscopy to the current OSHA standard of 0.1 fiber/ml as counted using light microscopy. It is worth noting that calculations under the g-formula provide a method for

quantification of occupational exposure effects in cohort mortality studies that should not suffer a healthy worker survivor bias.^{21,24,25}

These calculations, of course, come with important caveats related to necessary assumptions for valid estimation of the type of average causal effects we report here. To interpret our results as representing the effects of interventions, we must assume no unmeasured confounding. Concerns about such factors, such as cigarette smoking and other occupational lung carcinogen exposures, have been addressed previously.¹³ While there is not strong evidence of such confounding, our estimates of average causal effects require that this assumption holds.²⁶ While such assumptions are challenging to satisfy fully, the information we have for the South Carolina asbestos textile cohort remains among the best available information for epidemiological and policy analyses of asbestos fiber exposures in an occupational cohort for which exposures estimated have been quantified using electron microscopy. Another assumption particular to the parametric g-formula is correct model specification. We used models to describe time-dependent relationships between study covariates and mortality across time. We fit models with flexible terms for time and exposure which allow the data to better inform the model fit at the cost of some precision. While assumptions about model fit are unverified, we have previously shown that this approach can be used to recreate patterns in the observed data.²² This correspondence allows some assurance that our models are not grossly misspecified. Another key assumption is consistency, such that our exposure policies have no meaningful ambiguity with respect to interventions on exposure.^{26,27} That is, compliance with a standard could be met in a number of ways, and the way in which the standard is met should not matter with respect to lung cancer outcomes. A challenge to this arises given that we focus on estimates derived from one facility, with a specific distribution of fibers by length and width.

Some prior research suggests that longer fibers are most relevant to asbestos-associated lung cancer, while a large fraction of the total asbestos quantified by electron microscopy is due to very short fibers.²⁸ We found that a policy that ignores very short fibers yields a very similar estimate of cumulative lung cancer mortality to a policy that does not, at least for the textile industry studied. However, our study is entirely within the same industry, where the ratio of fibers counted using transmission electron microscopy and phase-contrast microscopy is within a relatively narrow range, with variability coming from the various textile departments. This limited our ability to assess the impacts of shorter fibers counted by a transmission electron microscope. Further work is needed to understand the potential benefit of regulations based on transmission electron microscopy, relative to the costs of such an approach, in a wider range of settings for which there is greater variability in the fiber dimensions and in the ratio of fibers counted using transmission electron microscopy and phase-contrast microscopy.

We found that a policy based on 0.1 fiber/ml when counting fibers greater than 5 μm using electron microscopy yields a similar estimate of cumulative lung cancer mortality to that obtained under a policy of 0.1 fiber/ml when counting fibers by light microscopy. This is perhaps not surprising given that most longer fibers can be resolved with both (phase contrast) light microscopy and electron microscopy (although some very thin, long fibers may be missed by the light microscopist). A policy based on a standard of 0.1 fiber/ml

counting total fibers by electron microscopy yields a slightly lower mortality than that obtained under current OSHA standard. While imprecise this may suggest some advantage in reducing total asbestos exposure, regardless of fiber length.

Given the highly variable ratio of phase-contrast microscopy- to transmission electron microscopy-counted fibers in different industries, the results suggest the importance of greater attention to the potential benefits of limiting exposure to currently uncounted asbestos fibers in many industries. For example, in occupational settings such as brake maintenance where the ratio of short to long fibers may be quite high, and environmental settings where almost all fibers may be too short or too thin to count by phase contrast microscopy, attention to the fraction of fibers not quantified by phase contrast microscopy-based counting methods may allow for further reduction of asbestos-related disease. A phase-contrast microscope-based estimate of exposure among brake mechanics of 0.1 fibers/ml may equate to 10 fibers/ml as counted by a transmission electron microscope, or even more. Current regulations based on phase-contrast microscopy allow such exposures to happen undetected. In contrast, application of a 1.0 f/ml standard based on transmission electron microscope in such an occupational setting would substantially reduce exposures to all fibers.

A practical obstacle to using the transmission electron microscopy method of quantification of asbestos is that regulators have noted that it is unclear what level of exposure, as quantified by electron microscopy, would be acceptable as a regulatory basis. In the current paper, using one of the landmark studies of asbestos and lung cancer, we identify policies defined in terms of electron microscopy-based asbestos exposure metrics that yield comparable, or lower, mortality due to lung cancer than that expected under the current OSHA standard. The use of transmission electron microscope-based methods with assessment of all airborne fibers would allow a more consistent measure of exposure and risk across fiber types, industries, and operations where the proportion of fibers included in regulatory assessments is highly variable.

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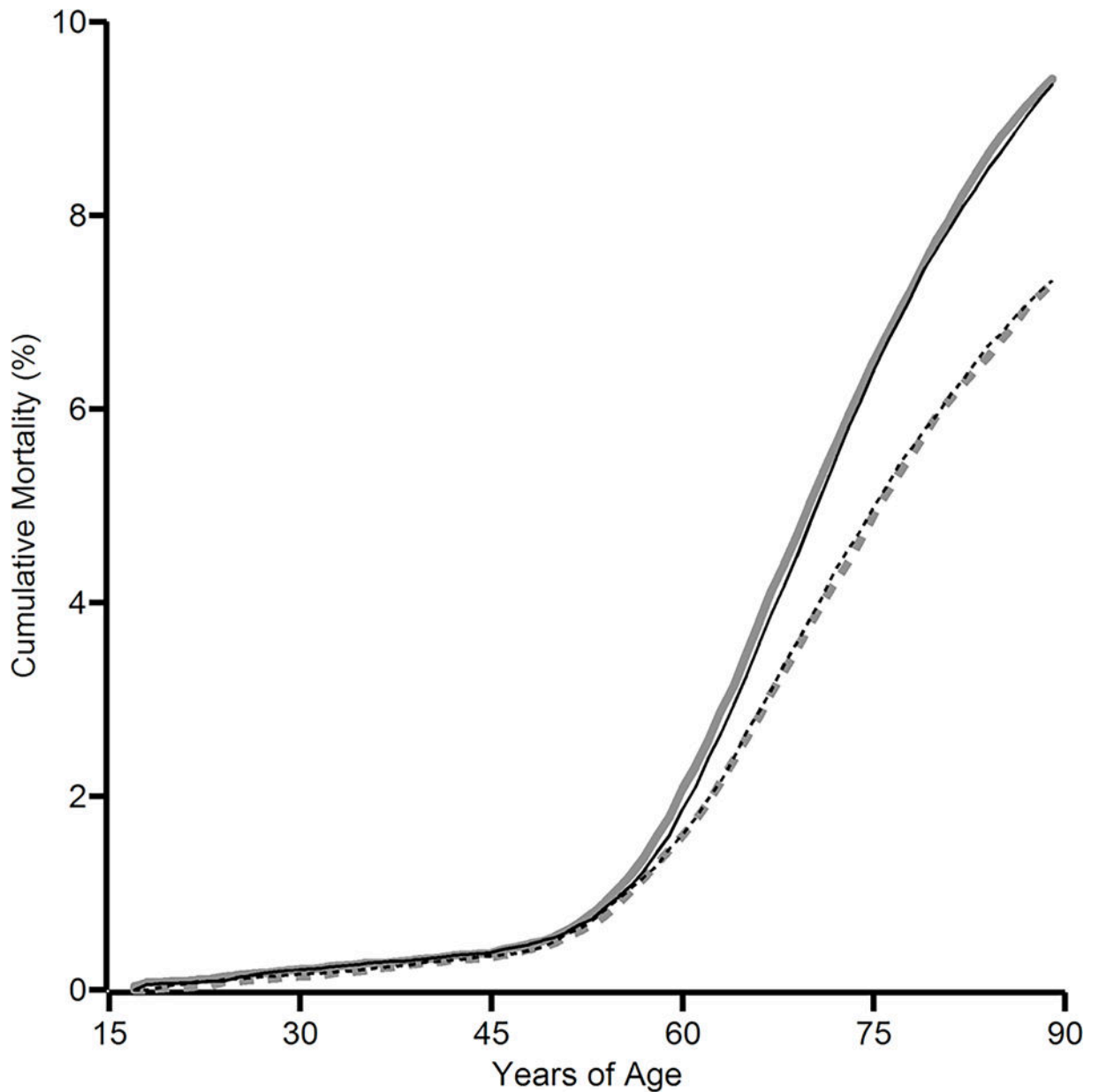


Figure 1.

Cumulative lung cancer mortality (%) by attained age according to asbestos exposure set to the 1976 OSHA standard of 2 fiber/ml as counted by light microscopy (solid black line) and under the hypothetical standard of 45 fiber/ml as counted by electron microscopy (solid grey line), and set to the current OSHA standard of 0.1 fiber/ml as counted by light microscopy (dashed black line) and under the hypothetical standard of 1 fiber/ml as counted by electron microscopy (dashed grey line) among South Carolina asbestos textile workers during follow-up between 1940 and 2001.

Table I

Estimated cumulative lung cancer mortality, expressed as a percentage, at age 70, 80, and 90 years under policies defined in terms of light microscopy counting of asbestos fibers. South Carolina asbestos textile plant cohort, 1940-2008.

Attained age (in years)	Cumulative lung cancer mortality ^a (95% CI)	
	Set exposure to 1976 OSHA standard 2 fiber/ml	Set exposure to 2011 OSHA standard 0.1 fiber/ml
70	4.83 (3.89, 5.77)	3.83 (3.01, 4.65)
80	7.66 (6.35, 8.97)	5.95 (4.73, 7.17)
90	9.35 (7.69, 11.01)	7.33 (5.76, 8.90)

^aExpressed as a percentage, and equivalent to deaths per 100 workers.

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Table II

Estimated cumulative lung cancer mortality, expressed as a percentage, at age 70, 80, and 90 years under policies defined in terms of electron microscopy counting of total asbestos fibers. South Carolina asbestos textile plant cohort, 1940-2008.

Attained age (in years)	Cumulative lung cancer mortality ^a (95% CI)		
	Set asbestos to 45 fiber/ml	Set asbestos to 1 fiber/ml	Set asbestos to 0.1 fiber/ml
70	5.03 (4.19, 5.87)	3.78 (2.94, 4.62)	3.65 (2.79, 4.51)
80	7.77 (6.60, 8.94)	5.95 (4.70, 7.20)	5.76 (4.49, 7.03)
90	9.41 (7.84, 10.98)	7.30 (5.72, 8.88)	7.10 (5.51, 8.69)

^aExpressed as a percentage, and equivalent to deaths per 100 workers.

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Table III

Cumulative lung cancer mortality at age 70, 80, and 90 years under policies defined in terms of electron microscopy counting of asbestos fibers at least 5 μm in length.

	2 fiber/ml	0.1 fiber/ml
Attained age (in years)		
70	3.84%	3.67%
80	6.04%	5.84%
90	7.39%	7.21%

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