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NONOCCUPATIONAL EXPOSURE TO CHRYSOTILE ASBESTOS AND THE RISK OF LUNG CANCER

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ABSTRACT

Background Heavy industrial exposure to asbestos causes lung cancer and mesothelioma, but it remains unknown whether much lower environmental exposure to asbestos also causes these cancers. Nevertheless, regulatory agencies, including the Environmental Protection Agency (EPA), have assessed the risk of lung cancer by extrapolating known risks from past industrial exposure to asbestos to today's much lower environmental asbestos levels (roughly 100,000 times lower). We also tested the EPA's model for predicting the risk of asbestos-induced lung cancer in a population of women with relatively high levels of nonoccupational exposure to asbestos.

Methods Mortality among women in 2 chrysotile-asbestos–mining areas of the province of Quebec was compared with mortality among women in 60 control areas, and age-standardized mortality ratios were derived. With the help of an expert panel, we estimated past exposure to asbestos among women in the mining areas and used these data with the EPA's model to predict the relative risk of lung cancer. We then compared this prediction with the observed mortality ratios.

Results On the basis of the estimated exposure in the asbestos-mining areas, a relative risk of death due to lung cancer of 2.1 was predicted by the EPA's model, amounting to about 75 excess deaths from lung cancer in this population. By contrast, we calculated a standardized mortality ratio of 1.0 and a standardized proportionate mortality ratio of 1.1 ($P>0.05$), suggesting that there were between 0 and 6.5 excess deaths from lung cancer among the women with nonoccupational exposure to asbestos. Seven deaths from pleural cancer were observed (relative risk, 7.63; $P<0.05$).

Conclusions We found no measurable excess risk of death due to lung cancer among women in two chrysotile-asbestos–mining regions. The EPA's model overestimated the risk of asbestos-induced lung cancer by at least a factor of 10. (N Engl J Med 1998; 338:1565-71.)

ASBESTOS is a commercial group of strong, ductile, and fire-resistant mineral fibers. These properties, which differ among different mineralogic types of asbestos, strongly affect its in vivo persistence and toxicity.[1,2] Chrysotile asbestos, which constitutes about 99 percent of airborne asbestos fibers in the general environment, is cleared much more rapidly from the lung than amphibole asbestos.[3,4]

It has been recognized for several decades that exposure to asbestos at high levels, as was common among asbestos workers in the first half of this century, can cause lung cancer and mesothelioma of the pleura and peritoneum.[5] Among asbestos workers, nearly all mesotheliomas are induced by exposure to asbestos, whereas most lung cancers are attributable to smoking. Yet because mesothelioma is so rare, asbestos-induced cases of lung cancer greatly outnumber cases of mesothelioma among asbestos workers.[5-12]

In the 1980s, after labor-union campaigns and governmental regulations had greatly reduced occupational exposure to asbestos, public attention turned to environmental exposure.[13] Pressed to recommend preventive regulations and remedial measures, public health authorities assessed the risks of asbestos-induced cancers in the general population on the basis of occupational data.[5-12] The validity of such estimates of risk has been questioned for several reasons.[14-22] Extrapolations were made to environmental exposure to asbestos at levels that were 1/100,000 of those to which workers had been exposed in the past. The amphibole content of airborne dust containing asbestos (aerosols) is much lower in the general environment now than in historical occupational settings. In addition, past studies of occupational

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exposure to asbestos were methodologically limited, dose–response estimates varied by a factor of 1000 among studies, and estimates of the risk of asbestos-induced cancer have not been validated in nonoccupationally exposed populations.

We tested the Environmental Protection Agency's (EPA's) dose–response model for asbestos-related lung cancer in a population exposed to asbestos at levels intermediate between those encountered by asbestos workers and those encountered by today's urban populations. A small region of the province of Quebec, Canada, produced most of the world's asbestos until 1954 and remains the world's largest exporter of asbestos. Between 1891 and 1980, asbestos-dust emissions and fallout were usually visible. Asbestos aerosols were similar mineralogically to those found in cities today; more than 98 percent were chrysotile.[23] Our study was restricted to women in order to exclude most asbestos workers.[24] In contrast to previous studies of general populations,[25-31] we estimated levels of exposure to asbestos in order to quantify the relation between asbestos and lung cancer. We used data obtained from death certificates, which are adequate to study the risk of lung cancer but not that of mesothelioma.[32-34] Mesotheliomas are currently being investigated in a separate study.

METHODS

The study comprised three distinct components: a mortality study to measure the actual relative risk of death due to lung cancer and other causes, a historical exposure assessment, and a risk assessment to predict the relative risk of lung cancer on the basis of the exposure assessment and the EPA's risk model. We assumed, as in the EPA's risk-assessment model, that the risk of death due to lung cancer was nearly identical to the risk of lung cancer — a commonly accepted approximation for diseases in which survival is short.

Mortality Study

We determined the number of deaths that occurred between 1970 and 1989 among women at least 30 years of age who lived in 2 chrysotile-asbestos–mining areas or 60 reference areas in the province of Quebec. An area was defined as a group of contiguous municipalities with a total population of at least 4500. The areas where the population was exposed to asbestos were Thetford Mines (population, 29,095 in 1981) and Asbestos (population, 14,225); these two areas comprised eight towns, of which three (Thetford Mines, Black Lake, and Asbestos) contained nearly all the asbestos mines and mills. The residents of these areas lived within 10 km of a mine or mill, and 80 percent lived within 4 km. Among the other 65 areas in Quebec, 4 large urban centers and 1 shipbuilding area were excluded. The remaining 60 reference areas were spread across the province and had populations ranging from 8000 to 41,000 (total population, 1,375,370 in 1981).

To compute the relative risk of death due to specific causes in the asbestos-mining areas, we compared the observed numbers of deaths with the numbers expected on the basis of the rates in the unexposed areas. Since there was migration in and out of the asbestos-mining areas during the period of observation, the study population actually consisted of different people each year. The annual population numbers, which we used as denominators for mortality rates, were based on Canadian census data. Over the entire observation period, among women 30 years of age or older, there were 221,375 person-years in the asbestos-mining areas and 8,629,630 person-years in the reference areas.

The numerators for our calculations came from Quebec's mortality registry; we obtained the death certificates of women 30 years old or older who died from 1970 to 1989 in Quebec Province. The municipality where each woman resided at the time of her death was used to assign the death to an asbestos-mining area, to an unexposed reference area, or to a municipality excluded from the analysis.

The conventional standardized mortality ratio and standardized proportionate mortality ratio were estimated for the two asbestos-mining areas separately and together, as compared with the reference areas. Both measures are ratios of the numbers of observed deaths in the population under study to the expected numbers, with adjustment for age and calendar year. For the standardized mortality ratio, the expected number is based on the absolute mortality according to cause in the reference population. For the standardized proportionate mortality ratio, the expected number is based on the proportion of all deaths in the reference population that are due to each cause. The confidence intervals for the standardized mortality ratios were computed with use of Byar's approximation; the confidence interval for each standardized proportionate mortality ratio was computed with use of an approximation of the standard error of its natural logarithm.[35]

Estimates of Exposure to Asbestos

To predict the risk of lung cancer according to the risk model, we estimated the population's average cumulative exposure to asbestos, which is the product of the intensity and the duration of exposure. These two components were estimated separately for each of three possible types of exposure: neighborhood exposure, resulting from emissions from asbestos mining or milling in the towns' outdoor air; household exposure, resulting from dust brought home by asbestos workers; and occupational exposure. We present here a brief summary of the rather complex process of assessing exposure, described in detail elsewhere.[36]

Neighborhood Exposure

Our objective was to estimate historical levels of asbestos in the mining towns and to derive time-weighted average exposure levels for the "average" female resident. Information on airborne asbestos levels in the asbestos-mining towns was obtained from continuous measurements of dust made by a government agency beginning in 1972; annual measurements of asbestos fibers in the air, made by the asbestos industry since 1974; and two recent surveys.[23,37] To derive estimates of exposure for earlier periods, we took the following steps to obtain evidence:

Annual production volumes were computed for each asbestos-mining town from 1900 to 1984.

Detailed information about determinants of asbestos pollution going back to 1900 was obtained — specifically, the classes of fibers produced, controls on emissions, location of mining or milling sites and tailing piles in relation to inhabited areas, urbanization, topographic maps, and the directional distribution of winds.

The relation among levels of airborne dust, annual asbestos production, and dust controls was estimated for each mining town for the period from 1972 through 1984, and extrapolations were made back to 1900.

The frequency and intensity of past visible asbestos deposition and the distance of residences from mines and mills were estimated on the basis of the responses of a representative sample of 817 elderly female residents to a survey.

The volume and characteristics of asbestos dust currently retained by the plants' dust-emission filtration systems were entered into

a standard aerosol-dispersion model to estimate airborne asbestos levels in the town of Asbestos, Quebec, before the onset of dust controls in the 1950s.

We analyzed the relation between the lung burden of asbestos and the histories of occupational exposure among 89 Quebec miners and millers studied at autopsy by Sébastien et al.[38] We then applied that relation to the lung burdens of 22 deceased residents of the mining area who had no occupational exposures to asbestos, as reported by Case and Sébastien,[39] to estimate past exposure levels.

We then asked an international panel of five experts on the measurement of exposure to asbestos to consider the evidence. After evaluating the data critically, the panel estimated average neighborhood exposure levels in the three main mining towns for four key years (1945, 1960, 1974, and 1984), which cover the important phases in the implementation of dust-emission control. The panel also provided guidelines for estimating yearly average levels from 1900 to 1989, based on the values for the key years and on town-specific asbestos-production levels (Fig. 1). Average annual ambient levels were estimated to have peaked at 1 fiber per milliliter or more (this value reflects the number of fibers longer than 5 μm and visible on optical microscopy per milliliter of air) between 1940 and 1954 and to have been above 0.2 fiber per milliliter from about 1905 to about 1965. The panel thought that the true values were unlikely to lie below 33 percent or above 300 percent of their best estimates, thereby providing subjective plausibility ranges. Furthermore, it was estimated that the three main towns were 7 to 20 times more polluted than the five other municipalities in the two asbestos-mining areas.

Household Exposure

Seventy percent of the women in the asbestos-mining areas had each lived in the same household as an asbestos worker,[24] but there were very few data regarding indoor exposure. We estimated indoor exposure on the basis of the results of autopsies of 10 residents who had lived with asbestos workers. Using data on the relation between the lung burden of asbestos and lifetime exposure to asbestos among workers, we calculated that the asbestos lung burden of those 10 residents had resulted from indoor asbestos levels that were roughly 0.3 fiber per milliliter higher than the outdoor levels. This estimate was consistent with the meager documentation on indoor asbestos levels (0.1 to 6.0 fibers per milliliter) in the homes of asbestos miners in Quebec,[37] in the homes of chrysotile-asbestos miners elsewhere,[40] in urban buildings polluted with asbestos,[41-45] in homes in naturally contaminated areas of the world,[46-51] and in an experiment with clothes contaminated with asbestos dust.[52]

Occupational Exposure

From our survey in the area, we estimated that about 5 percent of local women had worked in the asbestos industry or had mended bags used for shipping asbestos. A large occupational study in the local asbestos industry estimated that the few female workers had worked in less dusty jobs than male workers and had accumulated less than 50 fiber-years per milliliter (fiber-years are calculated by multiplying average annual exposure by years of exposure).[53] We used this value to estimate cumulative exposure for the proportion of person-years spent by the population in work in the asbestos industry.

Duration of Exposure

In 1989, we interviewed 817 elderly female residents of the asbestos-mining areas about their lifetime residential and employment histories and those of the persons they had lived with. This inquiry gave us information about the numbers of person-years of residence in the area, residence with an asbestos worker, and asbestos-related work for women of different birth cohorts in each of the asbestos-mining areas.

Cumulative Lifetime Exposure

For each woman in the 1989 survey, the lifetime cumulative neighborhood exposure was estimated by multiplying years of exposure by the estimated asbestos levels for each year and town in which she had lived. Cumulative household and occupational exposure was computed in the same way but adjusted for discontinuous exposure. We extrapolated values for the cumulative exposure of the women we surveyed to the entire exposed population and the study period (1970 through 1989) by assuming that the women interviewed in 1989 were representative of the entire population with regard to their history of exposure.

Table 1 shows the estimated cumulative exposure for the population in the asbestos-mining areas according to the type of exposure. Neighborhood exposure represented about 65 percent of the study population's average cumulative exposure, household exposure about 30 percent, and occupational exposure about 5 percent. The estimated average cumulative level of exposure was 25 fiber-years per milliliter. Considering the range of plausible values around the expert panel's neighborhood-exposure estimates, the greater uncertainty of the household-exposure esti-

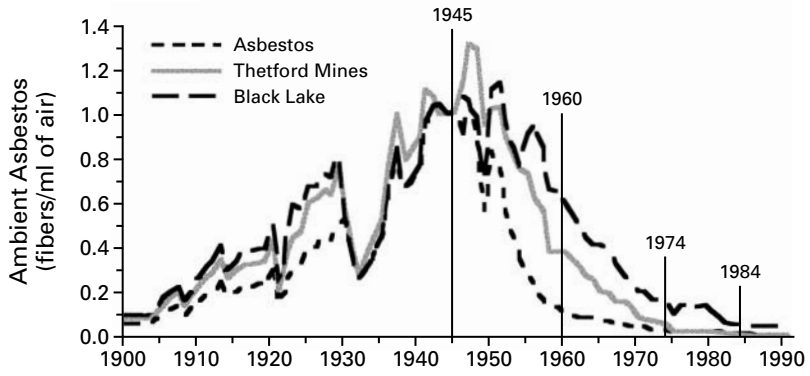

Figure 1. Mean Ambient Asbestos Levels in Three Asbestos-Mining Towns in the Province of Quebec, 1900 through 1989, Based on Estimates by an Expert Panel.

Asbestos levels are expressed as the numbers of fibers longer than 5 μm and visible on optical microscopy per milliliter of air. The vertical lines indicate the years for which the panel estimated asbestos levels (1945, 1960, 1974, and 1984); other values were interpolated on the basis of local asbestos production volumes.

TABLE 1. AVERAGE CUMULATIVE LIFETIME EXPOSURE OF THE POPULATION IN THE ASBESTOS-MINING AREAS, ACCORDING TO TYPE OF EXPOSURE, 1970 THROUGH 1989.*

TYPE OF EXPOSURE	ESTIMATED CUMULATIVE EXPOSURE
	fiber-yr/ml
Neighborhood exposure	16.0
Household exposure	7.8
Occupational exposure	1.2
Total cumulative exposure	25.0
Subjective plausible range of exposure†	5–125

*Values shown are averages for women 30 years of age or older who were living in the two asbestos-mining areas during the follow-up period, with adjustment for the duration of exposure. Values are expressed in fiber-years per milliliter of air, calculated by multiplying years of exposure by the average exposure level, and reflect cumulative round-the-clock exposure (1 fiber-year per milliliter is equivalent to 4.2 fiber-years per milliliter of cumulative exposure calculated for workers exposed 40 hours per week).

†The subjective plausible range provides for errors in estimating past environmental and household exposure levels and for errors in sampling and measuring in our exposure-history survey. The lower limit of 5 fiber-years per milliliter corresponds, for example, to 50 years of exposure to asbestos at a level of 0.1 fiber per milliliter (the actual mean ambient airborne-asbestos level in the area in 1974); the upper limit of 125 corresponds, for example, to 50 years of exposure to 2.5 fibers per milliliter — a relatively low exposure level in local asbestos-mining and asbestos-milling industries before 1960.

mates, and the uncertainty in our extrapolation from the sample of women surveyed in 1989 to the entire population in the asbestos-mining areas, we determined a subjective plausible range extending from 20 percent to 500 percent of this estimate.

Estimates of Risk

The dose–response model used by the EPA expresses the relative risk of lung cancer in a population as a linear function of its average cumulative exposure to asbestos,[5] as follows:

$$R = 1 + K_L \cdot \bar{X},$$

where K_L is the toxicity gradient, or the increase in the relative risk of lung cancer for each additional fiber-year per milliliter of cumulative exposure, $\bar{X}$ is the estimate of mean cumulative occupational exposure based on a workweek of 40 hours, and R is the risk of lung cancer in an exposed population as compared with that in a comparable unexposed population with similar smoking habits (we used the standardized mortality ratio and the standardized proportionate mortality ratio as estimates of this relative risk).

The EPA's estimate of K_L (0.01) is the geometric mean of relative-risk gradients estimated on the basis of data from 11 occupational studies.[7] The model requires that the exposed and reference populations have similar smoking habits, regardless of the smoking habits of workers in the original cohort studies. According to the model, a continuous exposure of 168 hours a week is equivalent to 4.2 40-hour workweeks of exposure to the same level of airborne asbestos. We applied this model to the exposure level estimated for the populations in the asbestos-mining areas to predict its relative risk of lung cancer.

RESULTS

Given the estimated average cumulative exposure of the population in the asbestos-mining areas (Table 1), the EPA model predicted a relative risk of lung cancer of 2.05 (plausible range, 1.21 to 6.25).

Table 2 shows the standardized mortality ratios and standardized proportionate mortality ratios for death from selected causes in the exposed population. The standardized mortality ratio in the two asbestos-mining areas combined was 0.91 for death from all causes (2242 deaths observed) and 0.92 for death due to all cancers (595 deaths observed). There were 71 deaths due to lung (or bronchial) cancer among the exposed women. The standardized mortality ratio for lung cancer was 0.99 (95 percent confidence interval, 0.78 to 1.25), whereas the standardized proportionate mortality ratio was 1.10 (95 percent confidence interval, 0.88 to 1.38). The confidence intervals barely overlapped with the plausible range of the relative risk predicted from the EPA's model.

The difference between the expected number of deaths, based on rates in the reference population, and the observed number of deaths yields an estimate of the excess number of deaths in the exposed population. Applying the relative risk predicted by the EPA's risk-assessment model to the same expected numbers, it is possible to derive the number of excess deaths that would be predicted by the model. Table 3 shows these computations. Depending on whether one bases the computation of expected numbers on the standardized mortality ratio or the standardized proportionate mortality ratio, the risk-assessment model predicts between 68 and 75 excess deaths from lung cancer, whereas we observed 0 to 6.5. Thus, the EPA's risk-assessment model overestimated the mortality attributable to asbestos by a factor of at least 10 ($68 \div 6.5$).

There were, however, two significant elevations in risks associated with residence in the asbestos-mining areas. The standardized mortality ratio for pleural cancer was 7.63 (95 percent confidence interval, 3.06 to 15.73), and the standardized mortality ratio for asbestosis was 23.49 (95 percent confidence interval, 2.64 to 84.83).

DISCUSSION

Regulatory policies regarding asbestos are influenced by estimates of the risk of lung cancer and mesothelioma attributable to environmental exposure to asbestos. Such estimates are controversial because they rely on unverified assumptions and imprecise data. In this study, the EPA's model overestimated the risk of asbestos-induced lung cancer among women who lived in chrysotile-asbestos–mining areas between 1970 and 1989 by at least a factor of 10. Such risk assessments may also overestimate the risk of asbestos-induced lung cancer in other populations with nonoccupational exposure.

Our units of observation were clusters of towns, not individual residents, since it was not feasible to identify a large cohort of individual residents and ascertain their exposure levels and vital status. The ap-

TABLE 2. STANDARDIZED MORTALITY RATIO (SMR) AND STANDARDIZED PROPORTIONATE MORTALITY RATIO (SPMR) FOR DEATH FROM SELECTED CAUSES AMONG WOMEN IN THE ASBESTOS-MINING AREAS, AS COMPARED WITH MORTALITY AMONG WOMEN IN THE REFERENCE POPULATION, FROM 1970 THROUGH 1989.*

CAUSE OF DEATH	NO. OF DEATHS	SMR (95% CI)	SPMR (95% CI)
All causes	2242	0.91 (0.87–0.95)	1.00 (—)
Circulatory diseases	1087	0.89 (0.83–0.94)	0.98 (0.94–1.02)
Respiratory diseases	104	0.81 (0.66–0.98)	0.89 (0.73–1.08)
Asbestosis	2	23.49 (2.64–84.83)	24.10 (6.06–95.81)
All cancers	595	0.92 (0.85–1.00)	1.02 (0.96–1.10)
Digestive cancer	205	0.96 (0.83–1.10)	1.06 (0.93–1.21)
Oral cancer	4	0.68 (0.18–1.74)	0.75 (0.28–2.00)
Breast cancer	120	0.88 (0.73–1.06)	0.97 (0.82–1.15)
Genital cancer	64	0.85 (0.65–1.08)	0.93 (0.73–1.18)
Urinary cancer	19	0.84 (0.51–1.32)	0.94 (0.60–1.46)
Lymphatic or hematopoietic cancer	42	0.78 (0.56–1.05)	0.85 (0.63–1.15)
Respiratory cancer	82	1.06 (0.84–1.32)	1.17 (0.95–1.45)
Larynx	2	0.64 (0.07–2.32)	0.72 (0.18–2.83)
Lung or bronchus	71	0.99 (0.78–1.25)	1.10 (0.88–1.38)
Pleura	7	7.63 (3.06–15.73)	8.21 (3.92–17.18)

*There were no noticeable differences in mortality between the two asbestos-mining areas for death from any cause, except for the fact that all seven deaths from pleural cancer occurred in the Thetford Mines area. CI denotes confidence interval.

proach we used was nevertheless adequate, because exposures to asbestos differed much more between the exposed and reference populations than within either one. Furthermore, risk estimates such as these are applicable to group averages.

The study populations were dynamic; during the study period, people migrated between asbestos-mining areas and reference or excluded areas. For cultural and linguistic reasons, the population of Quebec was very stable until quite recently. The prosperity of the asbestos-mining areas attracted migrants until 1980. Those who left this area most often moved to large cities that were excluded from this study. Migration patterns would have been similar in the reference areas, albeit with somewhat less in-migration. Migration from exposed to reference areas would not significantly have affected mortality in the reference population, since it greatly outnumbered the exposed population (by 40 to 1). Migration from reference areas to asbestos-mining areas was not substantial, according to our survey of elderly female residents of the asbestos-mining areas. Finally, exposed and reference areas had similar health services, making it unlikely that out-migration from an asbestos-mining area would have been more strongly related to lung cancer than out-migration from reference areas. For these reasons and because of the results of simulations with various plausible assumptions, we concluded that in- and out-migration could not have distorted the relative risk substantially.

Substantial bias due to confounding is unlikely in this study. Both the exposed and the reference populations were small-town homemakers of French-Canadian ancestry (93 percent) who were born in the early part of this century in a society that was culturally and socioeconomically homogeneous until the 1960s. According to the 1987 Quebec Health Survey[54] and our local survey in 1989, the women in the exposed and reference populations were similar in ethnic background, lifestyle, and socioeconomic characteristics. However, the population in the asbestos-mining areas may have smoked slightly less (25 percent were current smokers and 54 percent had smoked at some time) than the women in the reference areas (31 percent and 55 percent, respectively). According to Axelson's method of correcting risk ratios,[55] differences in smoking status should not have distorted the relative risk of lung cancer by more than 7 percent. In view of possible confounding and bias due to migration, and given the low mortality from all causes and from cancer in the asbestos-mining areas, we believe that the best estimate of the relative risk of lung cancer falls between the standardized mortality ratio of 1.0 and the standardized proportionate mortality ratio of 1.1.

The results of the eclectic and varied methods used as the basis for the retrospective estimate of exposure were sufficiently coherent that five experts agreed easily on past levels of neighborhood exposure. Our assessment of exposure was similar to the assessment in historical cohort studies of asbestos

TABLE 3. EXCESS DEATHS FROM LUNG CANCER AMONG WOMEN IN THE ASBESTOS-MINING AREAS, AS COMPARED WITH THE EXCESS PREDICTED ON THE BASIS OF THE EPA'S RISK-ASSESSMENT MODEL.*

VARIABLE	SYMBOL OR FORMULA	BASIS FOR ESTIMATING EXPECTED DEATHS FROM RATES IN REFERENCE AREA†	
		SMR	SPMR
Expected deaths	E	71.4	64.5
Observed deaths	O	71	71
Observed relative risk†	O/E	1.0	1.1
Observed excess deaths	O−E	−0.4‡	6.5
Predicted relative risk†	R	2.1	2.1
Predicted deaths	P=R·E	146.4	132.2
Predicted excess deaths	P−E	75.0	67.7
Ratio of predicted to observed excess deaths	(P−E)/(O−E)	Undefined‡	10.4

*E denotes the expected number of deaths in this population, based on the death rates or proportion of deaths in the reference population, O the observed number, and R the relative risk that is predicted in the population by applying the EPA's model to the estimated exposure level in this population.

†The estimate of the number of excess deaths in the population depends on the number that was expected on the basis of the rates of cancer in the reference population. Since we derived two versions of the expected number — one based on the standardized mortality ratio (SMR) and one based on the standardized proportionate mortality ratio (SPMR) — the excess numbers corresponding to each of these calculations are shown. Observed deaths and predicted relative risk are the only variables in this table that do not depend on the expected number of deaths; they are therefore necessarily equal in the two columns.

‡The negative value for O−E was interpreted as an absence of effect (O−E=0), leading to an undefined value for the ratio (P−E)/(O−E).

workers, which also relied on incomplete data and on subjective and imprecise retrospective estimates. These uncertainties and those resulting from the estimation of cumulative exposure on the basis of a survey conducted in 1989 were accommodated by assigning a large plausible range to our best estimate of exposure levels.

There are several possible reasons for the overestimation of the risk of lung cancer by the EPA model. First, the risk in the low-dose range may be less than would be predicted by a linear model. Second, cumulative exposure may be a poor measure of the biologically effective dose of asbestos (the actual dose that contributes to the risk of disease). Third, exposure–risk gradients in occupational studies may have been overestimated because exposure was underestimated, because of confounding by smoking, or because inappropriate reference populations were used. Fourth, chrysotile fibers may be less carcinogenic than amphibole asbestos, which was proportionately more prevalent in the environment of the occupational cohorts used to estimate the dose–response gradient than in the general environment today. Fifth, the relative risk of lung cancer due to asbestos may be lower among nonsmokers than among smokers, contrary to the model's assumption of constant relative risks.[27,56] And finally, the EPA's statistical analysis may have overestimated the dose–response gradient (a recent meta-analysis found the EPA's estimate to be between 4 and 24 times too high).[57]

The results of this study are reassuring with respect to lung cancer, but there were significant excess numbers of deaths due to pleural cancer (seven deaths) and asbestosis (two deaths). The instances of pleural cancer suggest an excess risk of mesothelioma. However, since historical death certificates reflect the incidence of mesothelioma poorly,[33,34] we have launched a separate study based on a province-wide survey of hospital records.

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