Exposure to Asbestos and Lung and Pleural Cancer Mortality Among Pulp and Paper Industry Workers

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We studied the mortality from lung and pleural cancers in a cohort of 62,937 male workers employed for at least 1 year in the pulp and paper industry in 13 countries during 1945 to 1996. Mill departments were classified according to probability and level of exposure to asbestos on the basis of available dust measurements and mill-specific information on exposure circumstances. Thirty-six percent of workers were classified as ever exposed to asbestos. Standardized mortality ratios of lung cancer were 0.99 (95% confidence interval [CI], 0.90 to 1.08) among unexposed and 1.00 (95% CI, 0.90 to 1.11) among ever exposed workers. The number of pleural cancer deaths among unexposed workers was 10; that among exposed workers was 14, most of which occurred among maintenance workers. In internal analyses, a trend in mortality from either neoplasm was suggested for estimated cumulative exposure to asbestos, weighted for the individual probability of exposure within the department and for duration of exposure (relative risk for lung cancer for 0.78+ f/cc-years, as compared with ≤0.01 f/cc-years: 1.44; 95% CI, 0.85 to 2.45; corresponding relative risk for pleural cancer: 2.43; 95% CI, 0.43 to 13.63). Despite a possible nondifferential misclassification of exposure and outcome, this study suggests that the carcinogenic effect of asbestos can be detected among workers employed in industries such as the pulp and paper industry, in which it is not considered to be a major hazard. (J Occup Environ Med. *2002;44:579–584*)

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Exposure to asbestos dust is not considered one of the main occupational hazards in the pulp and paper industry. Other documented exposures with recognized health hazards are more typical to this industry, such as sulfur dioxide and chlorinated compounds.[1–4] Thus, most safety and research evaluations are concentrated on these industry-specific hazards. Employment in the pulp and paper industry entails a variety of exposures, several of which are known or suspected respiratory carcinogens such as formaldehyde, nickel, chromium, and welding fumes.

Some studies have pointed to an excess of pleural cancer (specifically, mesothelioma) among pulp and paper industry workers,[5–8] whereas others have not reported such an excess.[9–11] In other studies, either relevant results were not reported[12–14] or lung and pleural malignancies (*International Classification of Diseases, 9th Revision* [ICD-9], categories 162–163) were not differentiated.[15,16] In several of these studies, the increased risk of respiratory and pleural cancer was at least partly attributed to exposure to asbestos, even though this relationship was ascertained only infrequently.[5,15–17]

Asbestos exposure in the pulp and paper industry is mostly related to particular jobs, such as maintenance (brake shoes of rolling machines), insulation of piping, insulation of recovery or power boilers, or construction.[2,16] Thus, certain subgroups of workers within this workforce are

TABLE 1
Numbers of Male Workers in the Cohort, Person-Years of Observation, and Observed Deaths From Lung and Pleural Cancer, by Exposure to Asbestos and Country

		Never Exposed				Ever Exposed			
				No. of Deaths				No. of Deaths	
Country	Reference*	Subjects	Person-Years	Lung Cancer	Pleural Cancer	Subjects	Person-Years	Lung Cancer	Pleural Cancer
Brazil	–	1,292	19,778	4	–	540	7,177	1	–
Denmark	Rix et al, 1997[11]	6,655	131,152	102	2	1,196	30,548	23	1
Finland	Jäppinen et al, 1987[15] Jäppinen and Pakkala, 1991[19]	2,045	56,560	44	–	4,927	157,084	130	3
France	Wild et al, 1998[20]	3,235	55,936	31	–	1,311	24,044	17	1
Japan	–	1,375	25,867	–	–	487	9,207	1	–
New Zealand	–	2,914	31,797	11	1	3,103	31,829	18	1
Norway	Langseth and Andersen 2000[8]	10,354	252,724	157	4	7,869	207,529	130	7
Poland	Szadkowska-S. et al, 1997[14]	4,983	71,382	19	–	652	10,832	1	–
South Africa	–	233	4,546	–	–	521	9,201	1	–
Spain	Sala-Serra et al, 1996[21]	872	15,372	5	–	176	2,921	–	–
Sweden	Andersson et al, 1998[3]	3,690	73,829	18	3	578	11,980	2	1
UK	Coggon et al, 1997[22]	2,181	50,478	45	–	718	17,527	12	–
US	Henneberger and Lax 1998[23]	378	8,212	14	–	390	9,099	15	–
Total		40,107	797,572	450	10	22,468	528,981	351	14

* If available.

expected to be more heavily exposed than the group as a whole. Among these jobs are maintenance work; power plant work; tasks such as storage, loading, or transportation; and construction work.[4,5,8,16] The purpose of this study was to investigate the mortality from pleural cancer among a large cohort of male workers in the pulp and paper industry from 13 countries, using exposure estimations and mortality data for the period 1945 to 1996.

Methods

The study population included 62,937 male workers employed for at least 1 year in the pulp and paper industry in 13 countries during the period 1945 to 1996. In total, 42 mills and 96 departments were included in the study.

The methods for the exposure assessment have been described previously.[2,4,18] Industrial hygienists and engineers from each mill provided detailed information on processes and exposures in each department of each mill, and mill-, department-, and time-specific assessments were performed by an international team of industrial hygienists based on this information and on available measurements, including 1024 measurements of asbestos levels.

Each individual worker was characterized by country, mill, department, and time period, because information on job titles was not available for the entire international cohort. A total of 40,107 workers (64%) were classified as never exposed to asbestos in their jobs, and 22,468 workers (36%) were estimated to have been exposed, at least part of the time, to asbestos during their work in the pulp and paper industry (ever exposed). The group of nonexposed contributed 797,572 person-years of observation, and the group of ever exposed contributed 528,981 person-years (Table 1).[3,8,11,14,15,19–23]

Several indices of exposure were derived. Prevalence of exposure refers to the proportion of workers in a particular department who, according to the industrial hygienists' estimation, were exposed to asbestos on an average workday during a certain time period. The categories of prevalence of exposure were (1) less than 5% (weight 0.025), (2) 5% to 50% (weight 0.25), (3) 51% to 95% (weight 0.75), and (4) over 95% (weight 0.975) of exposed workers in the department concerned.

Intensity of exposure refers to the mean level of exposure averaged over the work year among asbestos-exposed workers; it was classified as (1) 0.001 f/cc, (2) 0.01 f/cc, or (3) 0.10 f/cc. Duration of exposure was calculated as from the first assignment in a department with asbestos exposure and summarized over all periods of employment in departments where exposure to asbestos existed. Duration of exposure was categorized into quartiles.

Cumulative exposure is the sum of the products (intensity × duration) for all employment periods in exposed departments; weighted cumulative exposure is a similar index that also includes prevalence of exposure. These indices were expressed in f/cc-years and categorized into quartiles. Assessment of exposure to other agents occurring in the pulp and paper industry, including sulfur dioxide and formaldehyde, was conducted according to a similar approach.

TABLE 2
SMRs, by Exposure to Asbestos*

Cause of Death	Never Exposed			Ever Exposed		
	O	SMR	95% CI	O	SMR	95% CI
All causes	6992	0.93	0.91–0.95	5089	0.89	0.86–0.91
All malignant neoplasms	1649	0.92	0.87–0.96	1196	0.92	0.87–0.97
Lung cancer	446	0.99	0.90–1.08	349	1.00	0.90–1.11

* SMR, standardized mortality ratio; O, observed deaths; CI, confidence interval. Cohorts from Brazil and South Africa are excluded.

A follow-up for mortality was conducted in each country according to country-specific procedures. Information on cause of death was obtained from sources comparable with those providing reference rates (typically, death certificates obtained from either central or local archives, or computerized information obtained from nationwide registries).

The main outcome of the study was mortality from lung and pleural cancers, corresponding for lung cancer to codes ICD-7 162–163 (excluding 1622), ICD-8 162, and ICD–9 162; and for pleural cancer to ICD-7 1622, ICD-8 1630, and ICD-9 163. The period of follow-up varied slightly among countries, covering the years 1945 to 1996.

Standardized mortality ratios (SMRs) for all causes, all malignant neoplasms, and lung cancer were calculated as the ratio of the observed numbers of deaths over the expected number of deaths in the cohort and were derived from age- and period-specific national mortality rates. Reference rates were obtained from the World Health Organization Mortality Database (http://www-dep.iarc.fr/cgi-bin/cgisq/who_country.idc). SMRs were not calculated for pleural cancer because reference rates were not available. The 95% confidence intervals for the SMRs were calculated under the assumption that the observed numbers of deaths follow a Poisson distribution. Reference rates were not available for Brazil and South Africa, and these countries were excluded from the SMR analyses.

Relative risks (RRs) were calculated from multivariate Poisson regression modeling, comparing the mortality in a specified exposure category with that in an appropriate reference group. RRs were adjusted for country, age, calendar period, and employment status. For the calculation of RRs, their 95% confidence intervals, and the trend tests (chi-square), the STATA package was used.[24] Results on cancer incidence or mortality for several national components of this cohort have been reported previously (Table 1).

Results

A deficit in overall mortality and in mortality from malignant neoplasms was observed among both exposed and unexposed workers (Table 2). Furthermore, no excess of lung cancer mortality was observed either in workers exposed to asbestos or in nonexposed workers. A total of 14 deaths from pleural cancer was observed in the asbestos-exposed group, of which 13 occurred in workers employed in non–production departments, including maintenance, storage, loading, transport, and construction units. Of the 10 deaths from pleural cancer in the nonexposed group, three occurred among maintenance workers, six among workers employed in departments related to pulp production or paper/paperboard production, and one in construction.

Table 3 reports the RRs of mortality from all neoplasms, lung cancer, and pleural cancer by asbestos exposure. Results for the first two groups are in concordance with the SMR values presented in Table 2. Mortality from pleural cancer, however, is significantly increased among exposed workers. After additional adjustment for exposure to sulfur dioxide and formaldehyde, the RR of lung cancer decreased to 0.78 (95% confidence interval, 0.59 to 1.03), whereas the RR of pleural cancer became unstable because of the correlation between indices of exposure to asbestos and other agents. The RRs for mortality from lung and pleural cancer according to duration of exposure, time since first exposure, and weighted cumulative exposure are presented in Table 4. A trend in pleural cancer mortality was suggested according to weighted cumulative exposure and duration of asbestos exposure. For lung cancer, a trend was suggested for weighted cumulative exposure. Results according to cumulative asbestos exposure not weighted for prevalence of exposure were similar to those reported in Table 4.

Discussion

The rarity of pleural cancer, in particular, mesothelioma, together with its long latency have made the evaluation of the relationship between the occurrence of this tumor and specific occupational exposures quite difficult. To establish meaningful associations regarding occupational exposures and this malignancy, large cohorts and extended periods of follow-up are required. This multinational cohort of pulp and paper workers with more than 1,300,000 person-years of follow-up provides a unique opportunity for such an evaluation. The results suggest an association between estimated exposure to asbestos in this industry and an elevated mortality from pleural and lung cancer.

TABLE 3
RR of Selected Neoplasms for Ever Exposure to Asbestos*

Cause of Death	No. of Unexposed/ Exposed Cases	RR	95% CI
All malignant neoplasms	1656/1202	1.04	0.96–1.12
Lung cancer	450/351	0.95	0.81–1.10
Pleural cancer	10/14	2.53	1.03–6.23

* RR, relative risk adjusted for country, age, calendar period, and employment status (reference category: never exposed); CI, confidence interval.

Asbestos is not a major raw material used in pulp or paper production, although it has been a contaminant of talc, which is commonly used as a filler or to prevent the deposition of pitch in papermaking. In this study, approximately half the mills used talc in paper production, although it is unknown whether the talc was asbestos-contaminated. As in many industries, the more common use of asbestos in the pulp and paper industry has been in insulation of pipes or boilers, or in brake or gasket materials. Insulation with asbestos was almost universal in the industry, including the mills in this study. With the exception of the United Kingdom, where awareness of asbestos exposure started earlier, the pulp and paper industry started to become aware of the hazards of asbestos in the late 1960s through the 1980s, and more than 70% of the study mills instituted asbestos removal programs during this period. We found a deficit in overall mortality and in mortality from malignant neoplasms compared with national reference rates, as has been reported in other studies of pulp and paper workers.[7,13] However, in comparisons within our cohort, we found a suggestion of a dose-dependent increase in lung and pleural cancer mortality associated with asbestos exposure. Similar effects of excess mortality due to asbestos exposure have been reported previously among workers of the pulp and paper industry for pleural cancer, with only marginal or no significant effect for lung cancer.[7]

Exposures in this study were assessed by industrial hygienists, and estimates were made at the level of department, almost always without measurement data from the mill in question, and often with no measurement data from any mill for specific departments. Furthermore, the type of asbestos was unknown. Evaluation of exposure to asbestos was complicated because of its widespread and uncontrolled use. Even though the industrial hygienists identified specific departments within this industry where such exposure was most likely to occur, they could not preclude that exposure did occur in other departments. Therefore, underestimation and misclassification of asbestos exposure are likely to have occurred. Given the cohort study design of the investigation, however, misclassification likely has led to dilution of the true effect of asbestos. Despite these limitations, we found that the exposed group, as a whole, was harboring a greater risk of dying from pleural cancer and that this risk was dose- and time-dependent. Misclassification might have been present in our study, because of the 10 pleural cancers deaths among nonexposed subjects, three occurred in workers in the maintenance, repair, and cleaning departments (no further details were available).

A further source of misclassification stems from the use of the underlying cause of death to measure occurrence of pleural neoplasms, in particular, mesothelioma. It is known that the report of neoplasms on death certificates has limited specificity and sensitivity.[25] As long as this misclassification occurs nondifferentially with respect to asbestos exposure, however, it would contribute further to the underestimation of the association.

The long latency period characteristic of the "natural history" of mesothelioma in asbestos-exposed workers points to the necessity of extending such cohort studies over several decades before the full effects of exposure can be firmly evaluated. In our study, over 520,000 person-years of follow-up in the exposed group were included, with an average follow-up time of 23.5 years per person, but only 43,000 person-years occurred more than 35 years after first exposure. Thus, one can assume that the overall effect of asbestos exposure is not yet fully expressed.

Exposure and outcome misclassifications and the less-than-optimal follow-up period tend to result in underestimation of the effects of asbestos exposure. Thus, when causal relationships are strong, as in the case of mesothelioma, the effect will be ascertained, despite a likely reduction in the statistical strength of the association. On the other hand, causal relationships may be left undetected when, as in the case of lung cancer, they are weaker and more prone to be affected by confounders such as smoking.

A causal relationship between asbestos exposure and lung cancer and mesothelioma is well-established.[26–29] Previous studies have shown an excess of pleural mesothelioma in maintenance workers in the pulp and paper industry.[6,16] Maintenance workers in other industries also exhibit an increased incidence of pleural mesothelioma[5,29]; this finding is not surprising, considering the nature of their tasks and the tendency to apply safety practices primarily to regular production staff. On the other hand, maintenance workers in the cohort might have been employed in similar tasks in industries other than pulp and paper, thus experiencing additional exposure to asbestos.

Occupational asbestos exposure accounts for the majority of me-

TABLE 4
RR of Lung and Pleural Cancers for Duration of Ever Exposure, Years Since First Exposure, and Weighted Cumulative Exposure to Asbestos*

	Lung Cancer			Pleural Cancer		
	n	RR†	95% CI	*n*	RR‡	95% CI
Years of exposure						
1–3§	89	1.00		3	1.00	
4–15	123	1.20	0.85–1.69	4	1.11	0.24–5.13
16–34	108	1.18	0.82–1.71	3	0.80	0.15–4.28
35+	27	1.05	0.60–1.83	4	3.54	0.66–18.8
Test for linear trend, *P* value		0.62			0.28	
Years since first exposure						
1–24§	120	1.00		3	1.00	
25–35	119	1.02	0.73–1.42	5	1.75	0.36–8.53
36–43	68	1.09	0.73–1.62	3	1.34	0.21–8.57
44+	44	0.88	0.55–1.40	3	2.06	0.30–14.3
Test for linear trend, *P* value		0.62			0.57	
Weighted cumulative exposure (f/cc-years)						
≤0.01§	111	1.00		3	1.00	
0.02–0.09	131	1.19	0.85–1.66	4	1.16	0.25–5.37
0.10–0.77	80	1.44	0.97–2.13	4	1.66	0.34–8.23
0.78+	25	1.44	0.85–2.45	3	2.43	0.43–13.63
Test for linear trend, *P* value		0.07			0.29	

* RR, relative risk; CI, confidence interval.
† RR adjusted for country, age, calendar period, employment status, and exposure to sulfur dioxide, and formaldehyde.
‡ RR adjusted for country, age, calendar period, and employment status.
§ Reference category.

sothelioma cases.[29,30] Thus, the diagnosis of mesothelioma (or the death from pleural cancer) in a worker should be viewed as a sentinel event, pointing to the need to obtain a comprehensive occupational history to elucidate possible occupational and nonoccupational asbestos exposures in the past. Such investigations could further identify worksites or jobs in which asbestos exposure (expected or unexpected) could be encountered.[31–33] The identification of new hazardous exposure circumstances should lead to appropriate preventive measures to protect the populations at risk.

In conclusion, our findings suggest an effect of asbestos exposure in the pulp and paper industry that is more than negligible, and a particularly high risk for maintenance workers to die from pleural cancer. These findings underscore the importance of the asbestos awareness and reduction programs undertaken in most of the industry in recent years and the need to support these programs with data such as these on the risk of asbestos-related cancers among specific subgroups.

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