

Cancer incidence within a cohort occupationally exposed to asbestos: a study of dose—response relationships

Bénédicte Clin,^{1,2} Fabrice Morlais,¹ Guy Launoy,¹ Anne-Valérie Guizard,³ Brice Dubois,¹ Véronique Bouvier,¹ Nelly Desoubreux,² Marie-France Marquignon,² Claude Raffaelli,⁴ Christophe Paris,⁵ Françoise Galateau-Salle,⁶ Lydia Guittet,¹ Marc Letourneux^{1,2}

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¹Cancers and Populations, ERI3 INSERM, Faculty of Medicine, Caen University Hospital, Caen, France

²Occupational Health Department, Caen University Hospital, Caen, France

³Calvados General Cancer Registry, Caen, France

⁴Occupational Health Department, GISTAF, Condé sur Noireau, France

⁵U954 INSERM, Faculty of Medicine, Nancy University Hospital, Nancy, France

⁶Pathology Department, Caen University Hospital, Caen, France

Correspondence to

Dr Bénédicte Clin, Service de Santé au Travail et Pathologie Professionnelle (Occupational Health Department), C.H.U. (University Hospital) Côte de Nacre, 14033 CAEN Cedex, France; clin-b@chu-caen.fr

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ABSTRACT

Objectives The aim of our study was to analyse the dose—response relationship between occupational asbestos exposure and risk of cancer.

Methods Our study was a retrospective morbidity study based on 2024 subjects occupationally exposed to asbestos, conducted over the period 1 January 1978 to 31 December 2004. Analysis of the dose—response relationship between occupational asbestos exposure, as a time-dependant variable, and risk of cancer was performed using a Cox model. In order to account for the effect of latency, we conducted the analysis with a lag of 10 years.

Results 285 cases of cancers were observed in our cohort. The relative risk of pleuro-peritoneal mesothelioma, lung cancer and colorectal cancer associated with asbestos exposure, adjusted for age as a time-dependant variable and for sex, was correlated with exposure intensity (or average exposure level, AEL). The risk of cancer, whatever the anatomical site, did not increase with the duration of exposure to asbestos.

Conclusion While confirming the established relationship between asbestos exposure and pleuropulmonary and peritoneal cancers, this study also suggests a causal relationship between asbestos exposure and colorectal cancer.

INTRODUCTION

Although the role of asbestos in the development of cancers such as mesotheliomas (pleural, peritoneal, pericardial and testicular/vaginal), primary bronchopulmonary cancers, and laryngeal and ovarian cancers has been established, the relationship between occupational exposure to asbestos and cancers of other anatomical sites, in particular digestive and urogenital cancers, remains controversial.^{1–22}

Even though the industrial use of asbestos is severely controlled or prohibited in most countries, establishing a link between asbestos and various cancers remains a major challenge. Furthermore, confirmation of an association would influence the occupational medical surveillance of exposed individuals, as well as compensation for such cancers.

The aim of this work was to analyse the dose—response relationship between occupational exposure to asbestos (duration, cumulative exposure and intensity) and risk of cancer among a cohort of subjects exposed to asbestos at work. This study had

What this paper adds

- The role of asbestos in some cancers has been established, but its role in other cancers, in particular digestive and urogenital cancers, remains controversial.
- The study of a potential link between asbestos and cancer remains a major challenge.
- Furthermore, confirmation of such an association would affect occupational medical surveillance of exposed individuals and rules governing compensation for cancer associated with asbestos exposure.
- While confirming the established relationship between asbestos exposure and pleuropulmonary and peritoneal cancers, our study also suggests a causal relationship between asbestos exposure and colorectal cancer.
- These results could lead to changes in the medical surveillance and medico-legal management of colorectal cancers in subjects occupationally exposed to asbestos.

two particular advantages: information on cancer incidence and anatomical site from cancer registries and data on occupational exposure derived from an employment exposure matrix developed within the employing organisation and based on workshop measurement data.

MATERIALS AND METHODS

Population

As described in a previous study on the incidence of digestive cancers within the same cohort, the study subjects consisted of individuals who had worked in an asbestos reprocessing plant in southern Calvados (Normandy).²³ Asbestos was used in this plant to produce textiles and friction materials. The company was established in 1928 and specialised in asbestos spinning and weaving and in the manufacture of clutch mechanisms (through impregnation) and asbestos-based friction materials (brake pads). During World War II, asbestos-related activities were suspended due to lack of raw materials. After the company re-opened in 1945, it rapidly expanded from 1946 to 1949 with the acquisition of three new factories, which also manufactured

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asbestos-based textiles. These textiles contained approximately 20% crocidolite asbestos. In 1961, the company's fifth and last factory was established and manufactured chrysotile asbestos-based friction materials. Replacement fibres were used from the 1980s (rock wool, glass wool, ceramic and plastic fibres), with the use of asbestos ceasing in 1997 when the manufacture or transformation of asbestos fibres was banned in France.

All subjects alive in 1978 who had worked for at least 1 year in the plant, either before and/or after 1978, and had lived in Calvados for all or part of the study period, were included.

Data collection

Detailed information on the professional history and occupational exposure of each subject in the cohort was available in files held by the company occupational health department. Data on occupational exposure to asbestos included the following information: date of first employment, date of departure from the company, exposure sector (textile/friction), type of asbestos handled (chrysotile alone or mixed chrysotile/amphibole), duration of asbestos exposure, cumulative exposure index (CEI) for asbestos at career end expressed in fibres/ml×years and average exposure level (AEL) expressed in fibres/ml, calculated according to the company's own employment exposure matrix. This matrix was based on dust concentration measurement data collected by the company since 1959.²⁴ Analysis of the company's dust concentrations was based on data from 'dust concentration archives', a compilation of all available measurements performed in the company.

The first dust concentrations were measured using an ARM (Avy-Raillère-Martin) device, which provided the total number of particles per litre of air. The apparatus was equipped with a soluble filter and a differential air pressure gauge with adjustable airflow and vacuum extraction. A second instrument (CASELLA) was used to conduct measurements from 1973 onwards, using a membrane filter method and phase contrast microscopy, the results being expressed in fibres per ml (with fibres having a length of at least 5 µm, a diameter of less than 3 µm and a length/diameter ratio greater than 3), in agreement with international recommendations. Sampling was performed according to a standard plan, and included measurement of atmospheric fibre concentration and fibre levels at individual work stations, once or twice annually. A conversion factor for data measured by the two devices (ARM and CASELLA) was established based on data measured simultaneously in 1973, enabling ARM results to be converted into fibres per ml. First, the mean values of all samples, for each measurement device, in a given plant during the same period were compared. A conversion factor then was calculated and a global conversion factor obtained from the weighted mean of the conversion factors. Second, simultaneously collected samples for a given work station were compared to each other. Based on 70 measurements taken at the same time by the two devices and using linear regression, a conversion factor was determined. The results obtained using these two approaches were very similar since, in the first case, the conversion factor obtained from the weighted means was 2.07×10^{-4} and, in the second case, simple linear regression resulted in a conversion factor of 1.96×10^{-4} , giving a highly satisfactory correlation ($R=0.812$, $p=0.0001$). The conversion factor finally selected was 2×10^{-4} .²⁴ As no measurements took place before the introduction of the systematic atmospheric sampling mentioned above, dust concentrations needed to be identified for 1928, when the plant opened, and for 1945–1959. Using company archives containing information on its manufacturing history from which dust concentrations before

the installation of ventilation devices in 1960 could be estimated, levels were calculated using linear extrapolation based on the ARM measurements conducted in 1959. From 1977, dust concentrations were limited to 2 fibres/ml. All 1500 available samples were recorded in electronic files by workshop, plant and year, and tables describing general dust concentrations for each plant constructed. Using these tables, cumulative dust concentrations were calculated for each subject based on the year they joined and the year they left each plant. The sum of all exposures was calculated to determine the CEI for asbestos (in fibres/ml×years) at the end of the subject's period of exposure.

For each individual, data were available on the duration of asbestos exposure, the intensity of asbestos exposure or AEL, and the CEI for asbestos (in fibres/ml×years) at the end of the period of exposure.

Since Calvados has had its own digestive and general cancer registries since 1978, all cases of cancer between 1978 and 2004 in cohort subjects and following the period of exposure were known (date of diagnosis, anatomical site, histological type). The incidence of cancer was accordingly estimated for each anatomical cancer site (ICD-O 3 coding). Only primary cancers were taken into account in our study, secondary cancer sites having been excluded. No subjects presented with secondary cancer at the same site. For subjects presenting with primary cancers at different anatomical sites, each cancer was considered independently in our analysis.

All cases of peritoneal and pleural mesothelioma were validated according to the certification procedure of the MESOPATH group (French Mesothelioma Panel), set up in 1972 with the aim of improving pathological confirmation of cases of mesothelioma in France, within the framework of the PNSM (Programme National de Surveillance du Mésothéliome—National Mesothelioma Surveillance Programme).^{25–27} Basal cell neoplasm of the skin was excluded from analysis.

Information on individual civil status (sex, date of birth, place of residence, date of emigration outside the Calvados area), vital status on 31 December 2004 and date of death if deceased, was acquired from the records of Caen University Hospital's occupational and post-occupational pathology department, electoral rolls held by the Préfecture, data obtained from local councils in the subject's place of birth and analysis of data from the Calvados archives. The vital status of 107 subjects (5.3%) on 31 December 2004 could not be ascertained.

Statistical analysis

Individuals participated in the cohort throughout their period of residence within the Calvados area.

The risk of the cancer over time was modelled within the cohort using a Cox model for each cancer site. Patients were censored (but not excluded) at their date of death or date of emigration outside the Calvados area. No subject living outside Calvados at the start of the study moved into the area during the study period. Among the 2024 subjects in the cohort, 285 cancers were diagnosed, 464 subjects died and 457 moved to another area between 1978 and 2004. In addition, 107 subjects for whom vital status was unknown on 31 December 2004 were excluded from analysis. Less frequent cancer sites were grouped together according to anatomical location to enable statistical analysis. Ear, nose and throat (ENT) cancers included cancers of the lip, base of the tongue, other and unspecified parts of the mouth, gum, floor of the mouth, palate, parotid gland, oropharynx, pyriform sinus, larynx and hypopharynx. Cancers of the female genital tract included cancers of the cervix uteri, corpus uteri and ovary. Digestive cancers included cancer of the

oesophagus, stomach, pancreas, small intestine, colorectal cancer, and liver and biliary tract. Only colorectal cancer (25 cases) and oesophageal cancer (22 cases) are mentioned in our final analysis, as the numbers of other cancers of the digestive tract (stomach, small intestine, pancreas) were too small (six, three and six cases, respectively) and would have generated very low statistical power. This was also the case for cancer of the liver and the biliary tract (12 and three cases, respectively).

Description of compiled groups

Variables related to asbestos exposure (duration of exposure, AEL and CEI) were treated as time-dependant variables with a lag of 10 years to account for latency. For a given year 'y', the CEI and duration of exposure were corrected ignoring exposure during the 10 years before year 'y'. The AEL before year 'y' was estimated as the ratio between CEI and duration at year 'y'. These variables were divided into three categories according to tertile of distribution at the end of exposure (exposure duration: category 1 (0; 10 years), category 2 (10; 25 years) and category 3 (25; 48 years); CEI: category 1 (0; 40 fibres/ml×years), category 2 (40; 140 fibres/ml×years) and category 3 (140; 853 fibres/ml×years); intensity of asbestos exposure (or AEL): category 1 (0; 3 fibres/ml), category 2 (3; 9 fibres/ml) and category 3 (9; 107 fibres/ml). Type of exposure (chrysotile alone or mixed exposure involving both chrysotile and amphibole) was also included in the Cox model. The relative risk of pleuro-peritoneal mesothelioma, colorectal cancer, ENT cancers and cancers of the lung, skin, prostate, bladder and kidney, oesophagus and the female genital tract depending on asbestos exposure, was adjusted for age as a time-dependant variable,²⁸ and for sex.

To validate our adjustment for age, we performed sensitivity analysis using age as the time scale, to avoid confounding factors related to the association between age/exposure and risk of cancer.²⁹

In multivariate analysis, for each anatomical cancer site or group of cancer sites, we chose the variables that were significantly associated with cancer risk in univariate analysis, together with age, considered as a time-dependent covariable, and sex. The important colinearity between AEL, CEI, and duration and period of exposure did not allow these three variables to be included together in the multivariate analysis. Thus, we decided to include in the model the variable most closely related to the risk of the two cancers for which asbestos is an known risk factor (pleuro-peritoneal mesothelioma and primitive bronchopulmonary cancer). The statistical significance threshold of trends was set at $p < 0.05$.

RESULTS

The cohort included 2024 individuals, of whom 1604 were men (79.25%) and 420 women (20.75%).

Upon entry into the study, the mean age for men was 39.0 years ($\sigma=13.16$) and for women 39.1 years ($\sigma=13.29$), with a mean length of employment in the company of 18.7 (95% CI 18.2 to 19.3) and 16.6 years (95% CI 15.4 to 17.7), respectively. Subjects worked in various jobs, predominantly in asbestos-based textile or friction material production. Overall, 65.22% of subjects had been exclusively exposed to chrysotile, and 34.74% to chrysotile and amphibole. Of those exposed to chrysotile and amphibole, 58.57% were women and 28.55% men.

Of the 26.33% of subjects who died during the study period, 51.79% had been exposed to chrysotile alone, and to 48.21% to chrysotile and amphibole.

Between 1 January 1978 and 31 December 2004, 285 cases of cancers were observed in our cohort (84.54% of these were in

Table 1 Relative risk of pleuro-peritoneal mesothelioma, lung cancer, colorectal cancer, skin and prostate cancer depending on asbestos exposure, adjusted for age as a time-dependant variable, and for sex, with a lag of 10 years

	Cancers known to be related to asbestos						Other cancers								
	Pleuro-peritoneal mesothelioma			Lung cancer			Colorectal cancer			Prostate cancer			Skin cancer*		
	n	HR (95% CI)	p Value for trend	n	HR (95% CI)	p Value for trend	n	HR (95% CI)	p Value for trend	n	HR (95% CI)	p Value for trend	n	HR (95% CI)	p Value for trend
Exposure duration (years)†															
<10	8	1	0.21	8	1	0.25	4	1	0.44	7	1	0.96	4	1	0.81
≥10 to <25	5	0.67 (0.23 to 1.98)		13	1.22 (0.55 to 2.70)		12	2.48 (0.84 to 7.34)		9	0.55 (0.21 to 1.45)		11	0.63 (0.22 to 1.76)	
≥25 to <48	11	1.98 (0.66 to 5.92)		21	1.74 (0.67 to 4.51)		9	1.46 (0.31 to 6.91)		11	0.95 (0.34 to 2.62)		6	0.90 (0.27 to 3.03)	
Type of fibre															
Chrysotile	9	1	0.14	19	1	0.02	11	1	0.18	16	1	0.50	17	1	0.03
Mixed	15	1.92 (0.80 to 4.68)		23	2.11 (1.12 to 3.97)		14	1.78 (0.76 to 4.18)		11	1.30 (0.60 to 2.85)		4	0.30 (0.10 to 0.91)	
CEI (fibre/ml×years)†															
<40	4	1	0.10	5	1	0.13	1	1	0.09	1	1	0.03	2	1	0.76
≥40 to <140	5	0.83 (0.23 to 3.0)		14	1.05 (0.42 to 2.62)		5	4.19 (0.88 to 19.90)		8	3.82 (0.48 to 30.40)		7	1.48 (0.38 to 5.72)	
≥140 to <853	15	2.27 (0.71 to 7.23)		23	1.89 (0.74 to 4.84)		19	4.60 (0.91 to 23.15)		18	7.00 (0.87 to 56.02)		12	1.34 (0.34 to 5.25)	
AEL (fibre/ml)†															
<3	2	1	0.03	3	1	0.02	1	1	0.02	2	1	0.32	2	1	0.84
≥3 to <9	7	2.23 (0.45 to 10.96)		16	2.59 (0.74 to 9.01)		7	3.86 (0.47 to 31.89)		12	2.11 (0.47 to 9.49)		8	0.98 (0.25 to 3.85)	
≥9 to <107	15	4.19 (0.92 to 19.15)		23	3.99 (1.15 to 13.86)		17	7.20 (0.91 to 56.70)		13	2.34 (0.51 to 10.77)		11	1.10 (0.30 to 4.13)	

*Basal cell tumours of the skin were excluded.

†Time-dependent variable with a lag of 10 years.

AEL, average exposure level; CEI, cumulative exposure index.

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men and 15.46% in women). The table in the online supplementary appendix lists (ICD-O 3 codes) the number of observed cancers for the entire cohort site by site and separately for each sex, together with latency (time to diagnosis since first exposure) and age at diagnosis. Among the bronchopulmonary cancers observed in male subjects, there were 15 squamous cell carcinomas, six small cell carcinomas, six adenocarcinomas, two anaplastic carcinomas, two pseudosarcomatous carcinomas, one bronchiolo-alveolar adenocarcinoma, one acinar cell carcinoma, one non-small cell carcinoma, one neuroendocrine carcinoma, four non-specified and, in women, two adenocarcinomas and one non-specified.

Table 1 gives the relative risk of pleuro-peritoneal mesothelioma and lung, colorectal, skin and prostate cancer depending on asbestos exposure, adjusted for age as a time-dependant variable, and for sex, with a lag of 10 years. When both sexes were considered together, asbestos exposure was significantly associated with three cancers: primary bronchopulmonary cancer, pleural and peritoneal mesothelioma and colorectal cancer. For each of these cancer sites, cancer risk remained significantly correlated with asbestos exposure (assessed using AEL), even after adjustment for age as a time-dependent variable, and for sex. The adjusted relative risks corresponding to the last exposure tertile were 3.99 (95% CI 1.15 to 13.86), 4.19 (95% CI 0.92 to 19.15) and 7.20 (95% CI 0.91 to 56.70) for each cancer site, respectively. The number of years during which subjects were exposed was never significantly associated with cancer risk. The relationship between asbestos exposure and pleuro-peritoneal mesothelioma, and colorectal cancer, was significant when asbestos exposure was expressed in AEL, but not when expressed as CEI. Mixed exposure (involving both chrysotile and amphibole fibres) was associated with an increased risk of colorectal cancer. Mixed amphibole and chrysotile exposure was associated with a significantly elevated risk compared to chrysotile alone. We also observed an increased relative risk of lung cancer among individuals with mixed exposure to both chrysotile and amphibole.

Table 2 lists the relative risks of ENT cancer, and cancer of the bladder and kidney, the oesophagus and the female genital tract depending on asbestos exposure, adjusted for age as a time-dependant variable, and for sex. For these cancer sites, cancer risk was not significantly correlated with asbestos exposure.

Sensitivity analysis using age as the time scale gave very similar results, with smaller hazard ratios and smaller p values (not shown).

DISCUSSION

Our results confirm a dose-response relationship between asbestos exposure and risk of bronchopulmonary cancer and pleuro-peritoneal mesothelioma, and also suggest a dose-response relationship between the intensity of asbestos exposure and the risk of colorectal cancer.

Our study is limited by a low sample size, which affects its statistical power. This might explain why no significant relationship was observed between the level of asbestos exposure and risk for ENT cancer. Nevertheless, this decreased power is compensated for by the detailed and very reliable data collected to assess exposure and measure cancer risk. An employment exposure matrix, specific to the company and based on the measurement of atmospheric fibre concentrations, enabled us to precisely quantify exposure for each subject included in the cohort. Some authors have relied on quantitative data on exposure, but in most published studies, occupational exposure to asbestos has not been so thoroughly reconstructed, due to a lack of precise measurements.^{4 11 16 20 21}

A further major limitation of our study is the absence of individual data on potential confounding factors associated with individual behaviour (eg, tobacco and alcohol consumption, physical exercise, food intake) or with the environment (eg, hours of sunshine, atmospheric pollution). Nevertheless, the possible impact of such confounding factors is limited by the fact that the study was conducted on a cohort of asbestos-exposed workers. Indeed, although one would expect significant differences in the behaviour of exposed workers compared to the general population, any differences between workers with intense exposure and those with low exposure are very probably minor, the latter comprising the reference group for the estimation of relative risk.

Moreover, it should be noted that since one of our inclusion criteria was that subjects had to be alive in 1978, there may be a selection bias related to the 'healthy worker effect'. This bias concerns subjects who had worked in the company before 1978, some of whom began work during the highest exposure period

Table 2 Relative risk of ear, nose and throat (ENT) cancer and cancer of the bladder and kidney, the oesophagus and the female genital tract depending on asbestos exposure, adjusted for age as a time-dependant variable, and for sex, with a lag of 10 years

	ENT cancer			Bladder and kidney cancer			Oesophageal cancer			Female genital tract cancer		
	n	HR (95% CI)	p Value for trend	n	HR (95% CI)	p Value for trend	n	HR (95% CI)	p Value for trend	n	HR (95% CI)	p Value for trend
Exposure duration (years)*			0.86			0.38			0.82			0.47
<10	3	1		3	1		6	1		6	1	
≥10 to <25	16	1.45 (0.58 to 3.64)		9	1.62 (0.47 to 5.62)		10	1.57 (0.58 to 4.24)		6	0.60 (0.19 to 1.90)	
≥25 to <48	8	0.60 (0.11 to 3.20)		5	1.07 (0.28 to 4.03)		6	0.40 (0.04 to 3.58)		4	0.66 (0.16 to 2.74)	
Type of fibre			0.21			0.09			0.22			0.68
Chrysotile	21	1		12	1		16	1		6	1	
Mixed	6	0.55 (0.22 to 1.41)		5	0.32 (0.08 to 1.22)		6	0.55 (0.21 to 1.44)		10	0.81 (0.29 to 2.23)	
CEI (fibre/ml×years)*			0.14			0.66			0.61			0.77
<40	5	1		3	1		3	1		3	1	
≥40 to <140	14	0.55 (0.22 to 1.38)		5	1.17 (0.26 to 5.22)		11	2.57 (0.81 to 8.10)		9	1.54 (0.47 to 4.96)	
≥140 to <853	8	0.44 (0.14 to 1.38)		9	1.40 (0.29 to 6.70)		8	0.79 (0.19 to 3.24)		4	0.79 (0.19 to 3.20)	
AEL (fibre/ml)*			0.12			0.50			0.81			0.50
<3	6	1		2	1		3	1		5	1	
≥3 to <9	16	1.01 (0.40 to 2.51)		7	3.63 (0.44 to 30.20)		10	1.58 (0.43 to 5.79)		2	0.41 (0.08 to 2.16)	
≥9 to <107	5	0.40 (0.12 to 1.31)		8	2.88 (0.33 to 25.45)		9	1.02 (0.26 to 4.00)		9	1.36 (0.43 to 4.34)	

*Time-dependent variable with a lag of 10 years.

AEL, average exposure level; CEI, cumulative exposure index; ENT, ear, nose and throat.

prior to 1970. This could have led to an underestimation of cancer risk associated with the highest exposure, due to insufficient knowledge of cancers occurring before 1978 and the fact that these subjects had a smaller share of the cohort's total person-years. Furthermore, the oldest subjects entering our study, who had the highest exposure to asbestos, had a lower probability of developing the cancers of interest, due to an increased risk of prior death due to other diseases. Furthermore, the existence of local cancer registries enabled us to access comprehensive data on cancer incidence within the cohort, thus ensuring the reliability of information on diagnosis and cancer site; this was not the case in previously published mortality studies, which were often impaired by cancer classification errors.^{2 3 8} Moreover, all cases of peritoneal and pleural mesothelioma were validated by an expert pathologist from a national panel of experts, thus verifying classification.

Since a dose-response relationship between asbestos exposure and bronchopulmonary cancer or pleuro-peritoneal mesothelioma has already been clearly established, our results concerning these cancer sites confirm the reliability of our data. Our study also reveals a dose-response relationship between AEL and colorectal cancer. Results from previous research on the relationship between asbestos and colorectal cancer are conflicting and, recently, experts from the WHO International Agency for Research on Cancer Monograph Working Group stated that proof of such a relationship was 'limited'.¹ Although a study by Albin *et al*⁸ revealed a dose-response relationship between cumulative exposure to asbestos and colorectal cancer among asbestos-cement workers, currently available epidemiological data do not firmly establish such a causal relationship, as concluded by the collective INSERM expertise in a report published in 1997.²² Moreover, a review of the literature published in 2007 by Gamble *et al*, focusing on the relationship between asbestos exposure (either from inhalation or ingestion) and gastrointestinal cancers, reached the same conclusion.¹³ The particular relevance of this review lies in the fact that it attempted to document a potential dose-response relationship by comparing the risk of colorectal and/or colon cancer observed in different published cohorts with the risk bronchopulmonary cancer and mesothelioma recorded in those same cohorts. The risk of colorectal cancer was increased in cohorts with a standardised mortality ratio greater than 4 for bronchopulmonary cancer; however, no significant difference was observed based on reported mesothelioma risk. In our study, we observed an increased relative risk of colorectal cancer among subjects with mixed exposure to both chrysotile and amphibole. The same findings were reported by Homa *et al*, who suggested amphibole asbestos had a contributory role in the risk of death from colorectal cancer, without formally establishing such a role since no CEI exclusively focusing on this type of asbestos was available to the author.¹¹

Nonetheless, although currently available epidemiological data do not allow a causal relationship to be established between occupational exposure to asbestos and colorectal cancer, they do suggest further study on the subject.

CONCLUSION

This study confirms a dose-response relationship between asbestos exposure intensity and pleuro-peritoneal mesothelioma and bronchopulmonary cancer, and suggests a dose-response relationship between asbestos exposure intensity and colorectal cancer.

These results call for further studies in this field with greater statistical power to confirm the observed trends.

Should they be formally established, these results could lead to changes in the medical surveillance and medico-legal management of colorectal cancers in subjects with occupational exposure to asbestos.

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Bénédicte Clin, Fabrice Morlais, Guy Launoy, et al.

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