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Occupational asbestos exposure and digestive cancers – a cohort study

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SUMMARY

Background
Although the role of asbestos in the genesis of mesothelioma and primary bronchopulmonary cancers has been established, results from studies focusing on the relationship between occupational exposure to asbestos and digestive cancer remain contradictory.

Aim
To determine whether occupational asbestos exposure increases the incidence of digestive cancers.

Methods
Our study was a retrospective morbidity study based on 2024 subjects occupationally exposed to asbestos. The incidence of digestive cancer was calculated from 1st January 1978 to 31st December 2004 and compared with levels among the local general population using Standardized Incidence Ratios. Asbestos exposure was assessed using the company's job exposure matrix.

Results
Eighty-five cases of digestive cancer were observed within our cohort, for an expected number of 66.90 (SIR = 1.27 [1.01; 1.57]). A significantly elevated incidence, particularly notable among women, was observed for peritoneal mesothelioma, independently of exposure levels. A significantly elevated incidence was also noted among men for cancer of small intestine and oesophagus, for cumulative exposure indexes for asbestos above 80 fibres/mL × years. A significantly elevated incidence of cancer of the small intestine was also observed among men having been exposed to asbestos for periods in excess of 25 years and for mean exposure levels in excess of 4 fibres/mL.

Conclusions
This study suggests the existence of a relationship between exposure to asbestos and cancer of the small intestine and of the oesophagus in men.

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INTRODUCTION

The medical consequences of asbestos exposure essentially involve the respiratory tract and include benign pleural pathologies (localized pleural fibrosis, benign pleurisy, diffuse pleural fibrosis and round atelectasis), asbestosis (pulmonary fibrosis caused by the inhalation of asbestos fibres) and malignant pathologies, among which are pleural and peritoneal mesothelioma, together with primary bronchopulmonary cancers.

Although the role of asbestos in the genesis of mesothelioma and primary bronchopulmonary cancers has been established, results from studies focusing on the relationship between occupational exposure to asbestos and digestive cancer remain contradictory (except for peritoneal mesothelioma). Even if the industrial use of asbestos is now prohibited or at least very severely controlled in most nations, the study of a potential link between asbestos and cancer remains a challenge with regard to the risk and the prevention of residual exposure to remaining asbestos. These studies provide the basis of occupational and post-occupational medical surveillance of exposed individuals, together with the modalities concerning the potential compensation for associated cases of cancer.

In 1964 and in 1978, Selikoff put forward the hypothesis of a relationship between occupational exposure to asbestos and certain digestive cancers,[1–3] followed by Miller.[4] Conversely, leading studies carried out since their publication[5–36] do not conclude upon such a relationship. However, most of these studies are based on mortality figures. Very few deal with incidence and among them, none to our knowledge has been conducted based on cancer registry data. Furthermore, in many studies, the reconstruction of occupational exposure is hampered due to a lack of specific data.

Research conducted *in vivo* in animal models and *in vitro* in cellular culture tended to confirm the existence of several mechanisms responsible, either alone or combined, for the carcinogenic effect of asbestos. The first mechanism considered[37] involves the genesis, by asbestos itself, of free radicals responsible for coding DNA lesions in different genes implicated in the initiation and the proliferation of cancers. A further mechanism has been described by other authors:[38] the presence of asbestos fibres could lead to a chronic inflammatory reaction, occurring locally via the abnormal release of free radicals and the hypersecretion of cytokines and cellular growth factors by effector cells. Finally, according to Mossman *et al.*,[39] asbestos fibres are thought to have a co-carcinogenic property, acting as vectors for carcinogens of chemical origin on target cells. However, two essential aspects must be borne in mind: interindividual variations in sensitivity to the toxic effects of asbestos (anti-oxidant system deficiencies, DNA repair system deficiencies) and the influence of the morphological, physical and chemical characteristics of asbestos fibres which condition their biopersistance within the organism[40] (specific toxicity of long, fine fibres for both fibrosis and cancer).

It has now been established that asbestos fibres are mobile and that they disseminate throughout the organism: indeed, following inhalation or ingestion, they are capable of migrating to other organs (directly or via blood and lymph flow).[41] Several authors have reported the presence of large quantities of asbestos fibres and/or asbestosic bodies in histological samples from digestive cancer sites (analysis on a stomach following gastrectomy for epidermoid gastric cancer;[42] biliary tract;[43] oesophageal tissue;[44] colonic mucosa,[45] among subjects occupationally exposed to asbestos). These observations support the hypothesis of the potential responsibility of asbestos in digestive cancers; however, they are insufficient to establish a causal link firmly.

The aim of this work was to analyse the relationship between occupational exposure to asbestos and the incidence of digestive cancer in a cohort of subjects having been exposed to this mineral during their professional activity, by drawing on two specific advantages: on one hand, precise knowledge of the incidence of this pathology via data from a specialized digestive cancer registry and, on the other hand, precise knowledge of the occupational exposure of individuals included in the cohort via the company's own internal job exposure matrix based on workshop data.

MATERIALS AND METHODS

Population

The cohort comprised subjects having worked in an asbestos reprocessing plant located to the south of the department of Calvados in Normandy. Asbestos was essentially used in this plant to produce textile materials and friction lining. All surviving subjects in 1978 having worked for at least 1 year in the plant and

having been resident in Calvados during at least part of the study period were included in the study. The cohort included a total of 2024 individuals, of whom 1604 were men (79.25%) and 420 were women (20.75%).

Upon entry in the study, the mean age was 39.0 years for men (σ = 13.16) and 39.1 years for women (σ = 13.29), with a respective mean period of employment within the company of 18.7 [18.2; 19.3] and 16.6 years [15.4; 17.7]. Subjects worked in a number of different positions, with a predominance for asbestos-based textile and friction lining production. 65.22% of subjects had been exclusively exposed to chrysotile, whereas 34.74% had been subjected to mixed exposure (chrysotile and amphibole). Among the latter, 58.57% were women and only 28.55% were men. These do not add up to 100%.

Among the 26.33% of subjects who died during the study period, 51.79% had been exposed to chrysotile alone compared to 48.21% with mixed exposure.

Data collection

Precise knowledge was available on the professional history and occupational exposure of each subject in the cohort, following consultation of files held in the occupational health department of the company for which they had worked. Data on occupational exposure to asbestos were as follows: date of first employment, date of departure from the company, exposure sector (textile/friction), type of asbestos handled (exposure to chrysotile alone or mixed chrysotile and amphibole exposure), cumulative exposure index for asbestos expressed in 'fibres/mL × years' (CEI), calculated based on the company's own job exposure matrix. This matrix was developed based on dust accumulation measurement data collected by the company since 1959. The retained exposure level for each individual corresponded to the cumulated exposure (in fibres/mL × years) at the end of his/her period of exposure.

As Calvados has its own digestive cancer registry since 1978, all cases of cancer observed between 1978 and 2004 in a subject from the cohort and following his/her period of exposure were precisely known (date of diagnosis, anatomical anatomic site, histological type). The incidence of digestive cancer was consequently estimated for each cancer anatomic site (ICD-O 3 coding). All cases of peritoneal mesothelioma were validated by an expert pathologist from the '*groupe mésopath*', a national college of pathology experts in pleural and peritoneal mesothelioma diagnosis, set up in 1997 with the aim of improving the anatomopathological confirmation of cases of mesothelioma observed in France, within the framework of the PNSM (*Programme National de Surveillance du Mésothéliome* – National Mesothelioma Surveillance Programme).[46–48]

Information on individual civil status (gender, date of birth, place of residence, date of any relocation outside the department of Calvados), vital status at 31st December 2004 and the date of any deaths, was available based on data from consultations at the Caen University Hospital's occupational and post-occupational pathology department, study of electoral roles obtained from the *Préfecture*, letters addressed to local councils in the subject's place of birth and analysis of data from the Calvados departmental archives.

Statistical analysis method

Individuals participated in the cohort throughout their period of residence within the department of Calvados. Deceased subjects, together with those having moved to another department between 1978 and 2004, were excluded from the cohort at the date of their death or relocation. Similarly, the 107 individuals lost to follow-up at 31st December 2004 were excluded from the cohort at the last date at which they were known to be alive. Among the 2024 subjects in the cohort, 464 died and 457 moved to another geographical department from 1978 to 2004. All digestive anatomic sites combined, the total number of person-years was 24513.

The number of expected cancers within the cohort was estimated for each anatomic site based on cancer incidence levels for the period, 1978–2004 standardized for age and for each gender. These cancer incidence levels among the general public from the department of Calvados were calculated using data from the Calvados Cancer Registry and from census data provided by INSEE (National Institute for Statistics and Economic Studies). The authors have used data from the local Calvados Digestive Tumour Registry to obtain the most pertinent reference incidence possible. For oesophageal cancer in particular, the department of Calvados is renowned for having one of the highest incidences in France (three times higher than the national average).[49]

The incidence rates observed within the cohort were compared with those from the local general population

using Standardized Incidence Ratios (SIR). The significance of SIR was tested with a risk α equal to 5%.

Analysis of cancer incidence was performed for two different exposure levels, assessed either using a cumulative exposure index (CEI) expressed in fibres/mL × years, corresponding to the cumulated exposure throughout the subject's professional career or according to exposure duration or to exposure levels in fibres/mL, equal to the CEI ratio and exposure duration. For each evaluation method, two equally numbered groups were formed on either side of the median, which corresponded to 80 fibres/mL × years for the CEI; to 25 years for the duration of asbestos exposure and to 4 fibres/mL for the mean level of exposure to asbestos.

RESULTS

Eighty-five cases of digestive cancer were observed in the population study from 1st January 1978 to 31st December 2004, 87.06% of which were men and 12.94% were women. Among men, 4.61% presented with digestive cancer compared to only 2.62% among women. The vital status at 31st December 2004 remained unknown for 107 subjects (5.3%).

Tables 1 and 2 illustrate, anatomic site by anatomic site, the number of anticipated and observed cancers for the entire cohort and separately for each gender.

Table 1. Number of observed and expected cancers from 1978 to 2004 in the study population (Reference population: population of Calvados)

Localization	Obs (*N*)	Exp (*N*)	SIR [95% CI]
Anal canal	0	0.72	NC
Biliary tract	3	1.57	1.92 [0.38; 5.6]
Colon rectum	24	26.48	0.91 [0.58; 1.35]
Stomach	7	9.77	0.72 [0.29; 1.48]
Liver	13	8.08	1.61 [0.86; 2.75]
Small intestine	3	0.71	4.22 [0.85; 12.34]
Peritoneum	8	0.27	29.65 [12.77; 58.42]
Oesophagus	22	13.75	1.60 [1; 2.42]
Other	0	0.44	NC
Pancreas	5	5.11	0.98 [0.32; 2.29]
Digestive excluding mesothelioma	77	66.63	1.16 [0.91; 1.44]
All digestive	85	66.90	1.27 [1.01; 1.57]

CI, confidence interval; NC, non-calculated.

The three peritoneal mesotheliomas observed among men were all epitheloid; among women, three were epitheloid, one was mixed and the histological type was not specified for the last case.

Among the three cancers of the small intestine observed in men from the cohort, two involved the duodenum and one the ileum. Histological types were as follows: one epidermoid carcinoma (duodenum) and two adenocarcinomas. Among the 22 cancers of the oesophagus observed in men from the cohort, histological types were as follows: one adenocarcinoma, 18 squamous and three indeterminate.

The mean timescale between the date of first employment and the date of cancer diagnosis was 32.7 years (σ = 10.2), both genders combined, the mean timescale among men being 31.8 years (σ = 9.2) compared to 38.2 years (σ = 15.0) among women.

For both genders combined, significantly elevated incidence of all digestive anatomic sites was observed, for all CEIs combined, the SIR being 1.27 [1.01; 1.57]. Significantly elevated incidence of peritoneal mesothelioma was noted in both genders (SIR = 29.65 [12.77; 58.42]). However, after exclusion of cases of peritoneal mesothelioma, the SIR was no longer significant (1.16 [0.91; 1.44]) as indicated in Table 1.

Among men, significantly elevated incidence of peritoneal mesothelioma was observed (SIR = 15.93 [3.2; 46.55]). Significantly elevated incidence of oesophageal cancer was observed (SIR = 1.63 [1.02; 2.48]). As illustrated in Table 2, among women, the over-incidence of peritoneal mesothelioma was significant and was four times more frequent than among men: SIR = 61.30 [19.76; 143.06], non-significantly elevated incidence of liver cancer and colorectal cancer also being noted.

Table 3 provides analysis of results based on the cumulative exposure index for asbestos. In both genders, for cumulative exposure indexes for asbestos inferior or equal to 80 fibres/mL × years, no significantly elevated incidence of digestive cancer was observed, independently of anatomic site and including peritoneal mesothelioma.

For subjects having suffered cumulative exposure in excess of 80 fibres/mL × years, a significantly elevated incidence of peritoneal mesothelioma was observed in both genders, again four times more frequent among women (SIR = 97.66 [31.47; 227.91]), than among men (SIR = 22.63 [4.55; 66.13]).

In men having suffered cumulative exposure in excess of 80 fibres/mL × years, significantly elevated

Table 2. Number of observed and expected cancers from 1978 to 2004 in the study population by gender

Gender	Localization	Obs	Exp	SIR [95% CI]
Men	Anal Canal	0	0.49	NC
	Biliary tract	3	1.22	2.46 [0.49; 7.18]
	Colon Rectum	20	22.62	0.88 [0.54; 1.37]
	Stomach	6	8.76	0.68 [0.25; 1.49]
	Liver	12	7.78	1.54 [0.8; 2.69]
	Small intestine	3	0.61	4.89 [0.98; 14.29]
	Peritoneum	3	0.19	15.93 [3.2; 46.55]
	Oesophagus	22	13.46	1.63 [1.02; 2.48]
	Other	0	0.38	NC
	Pancreas	5	4.37	1.14 [0.37; 2.67]
	Digestive excluding mesothelioma	71	59.68	1.19 [0.93; 1.50]
	All digestive	74	59.87	1.24 [0.97; 1.55]
Women	Anal Canal	0	0.24	NC
	Biliary tract	0	0.35	NC
	Colon Rectum	4	3.86	1.04 [0.28; 2.65]
	Stomach	1	1.04	0.99 [0.01; 5.49]
	Liver	1	0.29	3.41 [0.04; 18.96]
	Small intestine	0		NC
	Peritoneum	5	0.08	61.3 [19.76; 143.06]
	Oesophagus	0	0.3	NC
	Other	0	0.06	NC
	Pancreas	0	0.74	NC
	Digestive excluding mesothelioma	6	6.95	0.86 [0.32; 1.88]
	All digestive	11	7.03	1.57 [0.78; 2.80]

CI, confidence interval; NC, non-calculated.

incidence of digestive cancers was observed, all anatomic sites combined, and for digestive cancers after exclusion of peritoneal mesothelioma. Among men, this exposure level was also associated with significantly elevated incidence of cancer of the small intestine (SIR = 6.93 [1.39; 20.25]) and of the oesophagus (SIR = 1.85 [1.08; 2.96]). Among women having suffered cumulative exposure in excess of 80 fibres/mL × years, over-incidence was exclusively observed in the peritoneum.

Tables 4 and 5 provide analysis of results depending respectively on the duration of asbestos exposure and the mean annual asbestos exposure level. These evaluation methods reveal no further cancerous anatomic site significantly associated with asbestos exposure. Peritoneal mesothelioma remains significantly associated with high exposure to asbestos independently of the exposure evaluation method used (duration of exposure >25 years or mean annual level > 4 fibres/mL), as does cancer of the small intestine among men. Whatever the exposure evaluation method, over-incidence of peritoneal mesothelioma was always higher among women than among men. In women, significantly elevated incidence of peritoneal mesothelioma was observed even for asbestos exposure durations below or equal to 25 years. Conversely, the risk of oesophageal cancer associated with asbestos exposure remained nonsignificant, both according to exposure duration and mean annual exposure.

DISCUSSION

Our results support the hypothesis of a link between exposure to asbestos and the risk of digestive cancer, even if peritoneal mesothelioma is excluded from analysis. However, it must be highlighted that this is only significant in the male group with a cumulative exposure index above 80 fibres/mL × years. Analysis by anatomic site illustrates the hypothesis that increased risk could involve cancer of the oesophagus and of the small intestine in men. These results do not, however, enable a causal link to be firmly established between asbestos exposure and the genesis of digestive cancers. Indeed, available data in our study

Table 3. Number of observed and expected cancers from 1978 to 2004 in the study population and in the reference population, for both genders, according to the cumulative exposure index for asbestos

		CEI ≤ 80 fibres/mL × years			CEI > 80 fibres/mL × years		
Gender	Localization	Obs	Exp	SIR [95% CI]	Obs	Exp	SIR [95% CI]
Men	Anal canal	0	0.15	NC	0	0.34	NC
	Biliary tract	1	0.34	2.96 [0.04;16.45]	2	0.88	2.27 [0.25; 8.18]
	Colon-rectum	4	6.42	0.62 [0.17;1.6]	16	16.2	0.99 [0.56; 1.6]
	Stomach	0	2.48	NC	6	6.28	0.96 [0.35; 2.08]
	Liver	3	2.18	1.38 [0.28;4.02]	9	5.6	1.61 [0.73; 3.05]
	Small intestine	0	0.18	NC	3	0.43	6.93 [1.39; 20.25]
	Peritoneum	0	0.06	NC	3	0.13	22.63 [4.55; 66.13]
	Oesophagus	5	4.27	1.17 [0.38;2.73]	17	9.19	1.85 [1.08; 2.96]
	Other	0	0.11	NC	0	0.26	NC
	Pancreas	0	1.26	NC	5	3.11	1.61 [0.52; 3.76]
	Digestive excluding mesothelioma	13	17.4	0.75 [0.4;1.28]	58	42.3	1.37 [1.04; 1.77]
	All digestive	13	17.5	0.75 [0.4;1.27]	61	42.4	1.44 [1.10; 1.85]
Women	Anal canal	0	0.09	NC	0	0.15	NC
	Biliary tract	0	0.11	NC	0	0.23	NC
	Colon-Rectum	1	1.33	0.75 [0.01;4.17]	3	2.53	1.19 [0.24; 3.47]
	Stomach	0	0.34	NC	1	0.67	1.49 [0.02; 8.31]
	Liver	1	0.1	9.62 [0.13;53.53]	0	0.19	NC
	Small intestine	0	0.04	NC	0	0.06	NC
	Peritoneum	0	0.03	NC	5	0.05	97.66 [31.47; 227.91]
	Oesophagus	0	0.11	NC	0	0.19	NC
	Other	0	0.02	NC	0	0.04	NC
	Pancreas	0	0.25	NC	0	0.49	NC
	Digestive excluding mesothelioma	2	2.39	0.84 [0.09;3.02]	4	4.55	0.88 [0.24; 2.25]
	All digestive	2	2.42	0.83 [0.09;2.98]	9	4.61	1.95 [0.89; 3.71]

CEI, cumulative exposure index; CI, confidence interval; NC, non-calculated.

did not enable us to take potential confounding factors into account, such as alcohol and tobacco consumption or concomitant occupational exposure to other substances. Furthermore, even if our population was monitored over a number of years, its low numbers failed to offer our study high statistical power. In particular, the high number of subjects excluded from the cohort because of relocation outside the geographical department (approximately 25%), contributed to reducing the study's statistical power. The total absence of over-incidence of digestive cancers in women, with the exception of peritoneal mesothelioma, could be explained by this lack of statistical power, the number of person-years among women being 3.38 times lower than among men. Furthermore, we have no data at our disposal on the incidence of cancers within the cohort prior to 1978, the year when the Calvados cancer registries were created. Consequently, a large number of deaths by cancer prior to 1978 among subjects otherwise eligible to join the cohort may have led to an underestimation of cancer incidence. This bias is nevertheless limited by the long latency period associated with asbestos-related cancers. Furthermore, the calculation of person-years proved to be complex as not only the vital status for each employee required to be known but also his/her place of residence and the date of any relocation, subjects having moved from the department of Calvados being excluded from the study as from their departure date. Despite this difficulty, the percentage of subjects lost to follow-up remained low (5.28%). Finally, it was impossible for us to obtain reliable data on tobacco and alcohol consumption, hence rendering account for these established confounding factors for certain digestive anatomic sites (oesophagus) impossible. Nevertheless, if this bias indeed affects comparison of the cohort as a whole with the general population, it has a lesser impact on the differences observed according to exposure levels, increasingly

Table 4. Number of observed and expected cancers from 1978 to 2004 in the study population and in the reference population, for both genders, according to asbestos exposure duration

		Exposure duration ≤ 25 years			Exposure duration > 25 years		
Gender	Localization	Obs	Exp	SIR [95% CI]	Obs	Exp	SIR [95% CI]
Men	Anal canal	0	0.33	NC	0	0.16	NC
	Biliary tract	3	0.81	3.7 [0.74;10.82]	0	0.41	NC
	Colon-Rectum	10	14.9	0.67 [0.32;1.24]	10	7.68	1.3 [0.62; 2.39]
	Stomach	5	5.78	0.86 [0.28;2.02]	1	2.95	0.34 [0; 1.88]
	Liver	10	4.96	2.02 [0.96;3.71]	2	2.8	0.72 [0.08; 2.58]
	Small intestine	1	0.04	2.49 [0.03;13.88]	2	0.21	9.49 [1.07; 34.26]
	Peritoneum	0	0.12	NC	3	0.07	45.86 [9.22; 134]
	Oesophagus	15	8.67	1.73 [0.97;2.85]	7	4.73	1.48 [0.59;3.05]
	Other	0	0.26	NC	0	0.12	NC
	Pancreas	2	2.86	0.7 [0.08;2.52]	3	1.49	2.01 [0.4; 5.87]
	Digestive excluding mesothelioma	46	38.9	1.18 [0.86;1.58]	25	20.6	1.22 [0.79; 1.80]
	All digestive	46	39.1	1.18 [0.86;1.57]	28	20.6	1.36 [0.90; 1.96]
Women	Anal canal	0	0.16	NC	0	0.07	NC
	Biliary tract	0	0.24	NC	0	0.1	NC
	Colon-Rectum	4	2.7	1.48 [0.4;3.8]	0	1.16	NC
	Stomach	0	0.72	NC	1	0.29	3.43 [0.04; 19.06]
	Liver	1	0.2	4.94 [0.06;27.49]	0	0.09	NC
	Small intestine	0	0.07	NC	0	0.03	NC
	Peritoneum	3	0.05	54.55 [10.96;159.38]	2	0.03	75.9 [8.52; 274.03]
	Oesophagus	0	0.21	NC	0	0.09	NC
	Other	0	0.04	NC	0	0.02	NC
	Pancreas	0	0.51	NC	0	0.23	NC
	Digestive excluding mesothelioma	5	4.86	1.03 [0.33;2.4]	1	2.07	0.48 [0.01; 2.68]
	All digestive	8	4.91	1.63 [0.70;3.21]	3	2.1	1.43 [0.29; 4.17]

CI, confidence interval; NC, non-calculated.

significant associations with asbestos being observed in the most exposed groups.

Global over-incidence of digestive cancer within the cohort, without taking account of the mean exposure level and the CEI, was not significant (with the exception of peritoneal mesothelioma). Indeed, certain subjects having worked within the company were not exposed to asbestos (administrative positions...), but were included in the analysis in the same manner as those having been subjected to extensive exposure. Analysis of incidence variations based on the CEI, on the duration of asbestos exposure and on the mean exposure level, has brought to light the over-incidence of certain digestive cancers, hitherto masked by the aforementioned phenomenon.

Our study is original for several reasons. First of all, the existence of a job exposure matrix specific to the company and based on the measurement of atmospheric fibre concentrations enabled us to quantify precisely exposure for each subject included in the cohort. Certain authors have relied on quantitative data on exposure;[12, 25, 34, 35] however, in most published studies, occupational exposure to asbestos has not been so thoroughly reconstructed because of a lack of precise metrological data.[5, 7, 9]

Another originality in our study was the possibility to compare observed digestive cancer incidence levels with those for the local population, which bore great resemblance to the cohort, thanks to the existence of a local specialized cancer registry. The use of this data allowed, in particular, for the local over-incidence of oesophageal cancer described in other studies[49–52] to be taken into account. The use of data from cancer registries ensures the reliability of digestive cancer diagnosis with precise anatomic site; this was not the case in previously described mortality studies.[1, 2, 25, 29] Relying on a specialized cancer registry enabled us to avoid the pitfall of a potentially false estimation of the number of

Table 5. Number of observed and expected cancers from 1978 to 2004 in the study population and in the reference population, for both genders, according to the mean level of asbestos exposure

		Mean level of exposure ≤ 4 fibres/mL			Mean level of exposure > 4 fibres/mL		
Gender	Localization	Obs	Exp	SIR [95% CI]	Obs	Exp	SIR [95% CI]
Men	Anal canal	0	0.08	NC	0	0.41	NC
	Biliary tract	1	0.19	5.37 [0.07;29.86]	2	1.03	1.94 [0.22; 7]
	Colon-Rectum	2	3.58	0.56 [0.06;2.02]	18	19	0.95 [0.56; 1.5]
	Stomach	0	1.38	NC	6	7.36	0.82 [0.3; 1.78]
	Liver	1	1.26	0.79 [0.01;4.42]	11	6.5	1.69 [0.84; 3.03]
	Small intestine	0	0.1	NC	3	0.51	5.86 [1.18; 17.13]
	Peritoneum	0	0.03	NC	3	0.16	19.19 [3.86; 56.07]
	Oesophagus	5	2.37	2.11 [0.68;4.91]	17	11	1.54 [0.9; 2.47]
	Other	0	0.06	NC	0	0.32	NC
	Pancreas	0	0.71	NC	5	3.65	1.37 [0.44; 3.2]
	Digestive excluding mesothelioma	13	9.72	1.34 [0.71;2.29]	58	49.8	1.17 [0.88; 1.51]
	All digestive	13	9.75	1.33 [0.71;2.28]	61	49.9	1.22 [0.93; 1.57]
Women	Anal canal	0	0.05	NC	0	0.19	NC
	Biliary tract	0	0.07	NC	0	0.28	NC
	Colon-Rectum	0	0.77	NC	4	3.09	1.29 [0.35; 3.31]
	Stomach	0	0.2	NC	1	0.81	1.24 [0.02; 6.89]
	Liver	1	0.06	17.28 [0.23;96.13]	0	0.23	NC
	Small intestine	0	0.02	NC	0	0.08	NC
	Peritoneum	0	0.02	NC	5	0.07	76.24 [24.57; 177.91]
	Oesophagus	0	0.06	NC	0	0.24	NC
	Other	0	0.01	NC	0	0.05	NC
	Pancreas	0	0.14	NC	0	0.59	NC
	Digestive excluding mesothelioma	2	1.38	1.45 [0.16;5.23]	4	5.55	0.72 [0.19; 1.84]
	All digestive	2	1.4	1.43 [0.16;5.17]	9	5.62	1.6 [0.73; 3.04]

CI, confidence interval; NC, non-calculated.

digestive cancers occurring within the cohort, which could have been caused by erroneous diagnosis classification, a frequently criticized phenomenon in mortality studies. Indeed, Doll and Peto considered that the association between digestive cancer and asbestos observed in certain studies could have been the result of the erroneous classification of peritoneal mesotheliomas.[33] Moreover, all cases of peritoneal mesothelioma were validated by an expert pathologist from the '*mésopath*' group (national panel of experts), hence avoiding incorrect diagnosis of these neoplasms and potential confusion with nonspecific peritoneal carcinosis.

The presence of eight cases of peritoneal mesothelioma in the study population (SIR = 25.04 [10.78; 49.33]) confirmed the significantly elevated incidence of these cancers for both genders. The existence of higher over-incidence of peritoneal mesothelioma among women than among men concords with another French study in which comparable results were obtained (8% of mesotheliomas in men and 26% in women were of different anatomic site from the pleura),[53] and with an American study[54] having compiled all cases of peritoneal mesothelioma from 1973 to 1984 and in which the percentage of cases in women was higher than in men. These results confirm the relationship between this type of neoplasm and asbestos exposure in women, compared to other studies claiming, contrary to pleural mesothelioma, a lesser relationship between asbestos exposure and peritoneal mesothelioma in women than in men.[55] In our study, the predominant employment of women in the textile industry, involving mixed asbestos exposure (amphiboles associated with chrysotile), could offer a partial explanation for the varying incidence between women and men.

In men, significantly elevated incidence of oesophageal cancer was also noted for CEIs above

80 fibres/mL × years. A clear male preponderance in oesophageal cancer and increased incidence with age are both firmly established. However, we avoided age-related bias as all of our calculations were standardized for age and for each gender in our reference population, which was local and perfectly comparable to our study population. In a case-control study in 1987, Magnani[6] evidenced a significantly high relative risk of oesophageal cancer among naval construction labourers having been subjected to asbestos exposure [RR = 2.3 (1.0; 5.1)]. Similarly, in a mortality study conducted by Selikoff,[3] based on a cohort of 17 800 pipe insulators, the number of observed cases of oesophageal cancer was above the number of expected cases (17 cases observed for 6.35 expected). In this study, Selikoff reported that, among pipe insulators, there was a 3-fold increased risk of gastro-intestinal cancers.

Finally, a recent mortality study,[56] conducted on a cohort of 3072 asbestos exposed workers in South Carolina, demonstrated a significant excess in mortality by oesophageal cancer in the study population (SMR = 1.87 [1.09; 2.99]).

Over-incidence of cancer of the small intestine was also observed among men with CEIs in excess of 80 fibres/mL × years, with mean exposure durations in excess of 25 years and exposure levels above 4 fibres/mL. For this type of digestive cancer, to our knowledge, no other study has concluded in favour of an association with asbestos exposure.

For colorectal cancer, our study revealed no significantly elevated incidence, even if it had the best statistical power for this anatomic site, the expected result being 26.48 cases. This result is compatible with currently available epidemiological data, which cannot confirm the existence of a causal relationship between occupational exposure to asbestos and the onset of colorectal cancer, and also concords with conclusions by the collective INSERM expert's report published in 1997.[36] Furthermore, a more recent review of the literature, published in 2007 by Gamble[18] and focusing on the relationship between asbestos exposure (by either inhalation or ingestion) and the onset of gastro-intestinal cancers, reached the same conclusions : by reconsidering 22 epidemiological studies in cohorts of occupationally asbestos exposed workers, published up to 2003, this recent review revealed a standardized mortality ratio (SMR) <1 in 13 studies and a standardized mortality ratio above 1 in 9 studies. However, this ratio was statistically significant in only three studies, with a relatively limited force of association, the highest SMR being only 2.12 (1.06–3.8) for Selikoff 1980,[57] 1.85 (1.16–2.79) for Seidman 1986[34] and 1.38 (1.05–1.82) for Selikoff 1979.[3] The particular relevance of this review lies in the fact that it attempted to document a potential dose-effect relationship by comparing the risk of colorectal and/or colon cancer observed in the different cohorts published, based on the risk, recorded in the same cohorts, of bronchopulmonary cancer, mesothelioma in particular. The risk of colorectal cancer would tend to increase in cohorts for whom the SMR is above 4 for bronchopulmonary cancer; however, no significant difference is observed based on reported mesothelioma risk. Two studies focusing on the incidence of digestive cancers in communities affected by asbestos contamination of drinking water were published in 2005. The first, involving inhabitants of the town of Woodstock in the United States, was negative[22] and the second, conducted on Norwegian lighthouse keepers[23], revealed a slight over-incidence of colon cancer, only becoming significant after over 20 years' follow-up. Overall, currently available epidemiological data do not enable a causal relationship to be established between occupational exposure to asbestos and the onset of colorectal cancer; however, they incite further study on the subject.

The results of our study raise the question of the medico-legal compensation for small intestine and oesophageal cancer sufferers having been exposed to asbestos during their professional activity. Indeed, whereas peritoneal mesothelioma may be subject to compensation when occupational exposure to asbestos is established, no other digestive cancer currently falls within the scope of such medico-legal compensation according to applicable French laws and regulations. If our results are to be confirmed, the tables and/or lists of occupational cancers eligible for compensation would require to be revised. Moreover, the medical follow-up of subjects having been exposed to asbestos could being extended beyond the currently recommended pleuropulmonary system to include the digestive system.

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