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Exposure to asbestos and the risk of gastrointestinal cancer: a reassessment

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ABSTRACT In 1964 it was first reported that asbestos workers had a higher risk of gastrointestinal cancer. This notion has persisted despite several studies that have found no increased risk. The risks of gastrointestinal cancer to workers exposed to asbestos were reassessed, based on the results of published studies on 32 independent cohorts of asbestos workers. Not all studies provided risk estimates (SMRs) for all gastrointestinal sites (ICD codes 150–159). No consistent evidence was found to indicate that exposure to asbestos increases the risk of gastrointestinal cancer. Generally, the higher SMRs came from studies conducted in the United States or Canada and might reflect factors not related to exposure to asbestos. In studies in which asbestos exposed and non-asbestos exposed workers were evaluated the SMRs were not consistently higher for the group exposed to asbestos. There was no apparent dose response relation between accumulated asbestos dose and the risk of gastrointestinal cancer. It is concluded that there is no dose response relation between exposure to asbestos and risk of gastrointestinal cancer, and asbestos workers are not at an increased risk of gastrointestinal cancer.

In 1964 Selikoff and coworkers reported on the mortality experience of 632 asbestos insulation workers in the New York metropolitan area.[1] The study showed that these workers had an apparent excess of gastrointestinal cancers; there were 12 deaths from gastric cancer compared with 4·3 expected (standardised mortality ratio (SMR) = 2·79) and 17 deaths from cancer of the colon or rectum compared with 5·2 expected (SMR = 3·27). Both SMRs were significantly greater than 1 ($p < 0·05$), indicating an increased risk compared with all United States white men. In the 24 years since the publication of this paper the notion of an increased risk of gastrointestinal cancer to asbestos workers has persisted even though several other papers have failed to substantiate it.

In 1978 Miller reviewed reports relating to exposure to asbestos and the risk of gastrointestinal cancer and concluded that they were causally related.[2] Another review was published in 1985 by Morgan *et al* who found some raised risks of cancer to some parts of the gastrointestinal tract but believed that these rises were not related to exposure to asbestos.[3] The present paper provides a more detailed review of the risks of gastrointestinal cancer to asbestos workers and is based on data from published studies. Studies that evaluated risks of gastrointestinal cancer from "bystander" exposure including exposures from asbestos contaminated drinking water were not included.

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Study methods

Thirty two cohorts of asbestos exposed workers were identified that provided data on their risks of gastrointestinal cancer[4–35]; table 1 summarises the types of

Table 1 *Occupational exposures to asbestos of cohorts evaluated*

Industry occupational exposure	*No of cohorts*
Asbestos cement	4
Insulation work	1
Manufacturing:	
Gas masks	2
Paper, millboard, friction products, etc	9
Textiles	2
Mining and milling	5
Nitric acid production plant	1
Railroad	1
Shipyard dockyard	3
Workers reported to registries, pneumoconiosis panels, or applying for workman's compensation	4

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Table 3 *Summary of SMRs given in table 2*

ICD	Studies	Median SMR	Range of SMRs	SMRs < 1 ($p < 0.05$)	SMRs > 1 ($p < 0.05$)
150	6	1·13	0·64–2·62	0	1
151	9	1·00	0·17–2·04	1	0
150–151	8	1·22	0·91–1·82	0	2
153	4	1·49	0·36–2·27	1	0
154	3	1·09	0·77–1·24	0	0
153–154	10	1·18	0·74–2·46	2	2
150–154	10	1·08	0·74–2·46	1	2
157	7	0·99	0·00–2·97	0	1
150–159	11	1·06	0·47–1·52	2	2
Gastrointestinal	6	1·05	0·49–1·55	2	0

smoking habits of the asbestos workers differ from those of the populations with whom the asbestos workers are compared.

The figure shows no consistent dose response relation for gastrointestinal cancers. Although the data from some studies suggest dose response relations, they are most probably an artifact of the way in which accumulated dose was measured. For example, McDonald *et al* in their study of miners and millers show that the SMR for colon and rectal cancer increases with accumulated asbestos dose.[24] They also show that the same relation exists for deaths from respiratory tuberculosis and cerebrovascular disease. In another study of miners and millers death rates from lung cancer, gastrointestinal cancer (ICD 151–159), tuberculosis of the lung, and cardiovascular disease increased with increasing accumulated dose of asbestos.[31] Since diseases such as cardiovascular disease and respiratory tuberculosis have not been associated with asbestos exposure, it appears that the reported "dose response" relation are in fact a measure of other factors unrelated to accumulated asbestos dose.

Discussion

In evaluating the risks of gastrointestinal cancer to workers exposed to asbestos several problems were encountered.

(1) The studies reviewed made no attempt to evaluate gastrointestinal tract death rates in terms of any of the known risk factors.

(2) Some studies identified the site of the gastrointestinal cancer by an ICD code, others did not. The different ways in which the ICD codes were combined precluded comparisons of cancer risks among the 32 cohorts.

Table 4 *Comparison of SMRs for gastrointestinal cancers from studies that included a group of workers not exposed to asbestos*

Reference	Occupational group	Cancer site	Asbestos workers	Other workers
6	Shipyard workers†	Oesophagus, stomach, colon, rectum	45/47 = 0·96¶	18/25·6 = 0·70
12	Insulation board manufacturing	Stomach	7/ 7·5 = 0·94	4/ 2·5 = 1·59
		Colon	6/ 4·4 = 1·37	2/ 1·4 = 1·42
		Rectum	4/ 3·2 = 1·24	0/ 1·1 = 0·00
15	Asbestos cement factory	GI (ICD 150–154)	9/ 3·65 = 2·46*	1/ 1·64 = 0·61
28	Shipyard workers‡	Oesophagus	1/ 1·41 = 0·71	1/ 5·55 = 0·18
		Stomach	7/ 6·67 = 1·05	31/21·34 = 1·45
		Colon	7/ 4·34 = 1·61	19/10·49 = 1·81*
		Rectum	3/ 2·74 = 1·09	5/ 7·32 = 0·68
		Pancreas	0/ 1·38 = 0·00	3/ 4·23 = 0·71
34	Anthophyllite miners§	GI (ICD 150–159)	7/14·9 = 0·47*	9/14·9 = 0·60
35	Asbestos production (building products, friction materials, textile products)‖	GI (ICD 150–159)	83/78·2 = 1·06	22/22·8 = 0·96

GI = Gastrointestinal.
*$p < 0.05$.
†Non-exposed workers included workers who had no or at most minimal likelihood of asbestos exposure.
‡Separation into asbestos exposed and non-exposed was made on the basis of descriptions of occupations and whether they brought the workers into contact with asbestos.
§Non-exposed group consisted of subjects selected from an agricultural area with no mines or other industrial plants. This group was matched to the asbestos workers by age and sex, and for date of death for those workers who had died.
‖Non-exposed group consisted of workers from cotton textile plants.
¶For the exposed group the SMRs were similar for different latency intervals (0–19, 20–29, ≥30 years from first employment) and durations of exposure (<15, ≥15 years). For the non-exposed group the SMRs were similar for different latency intervals.

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1/ 5·55	= 0·18
1/21·34	= 1·45
9/10·49	= 1·81*
5/ 7·32	= 0·68
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9/14·9	= 0·60
2/22·8	= 0·96

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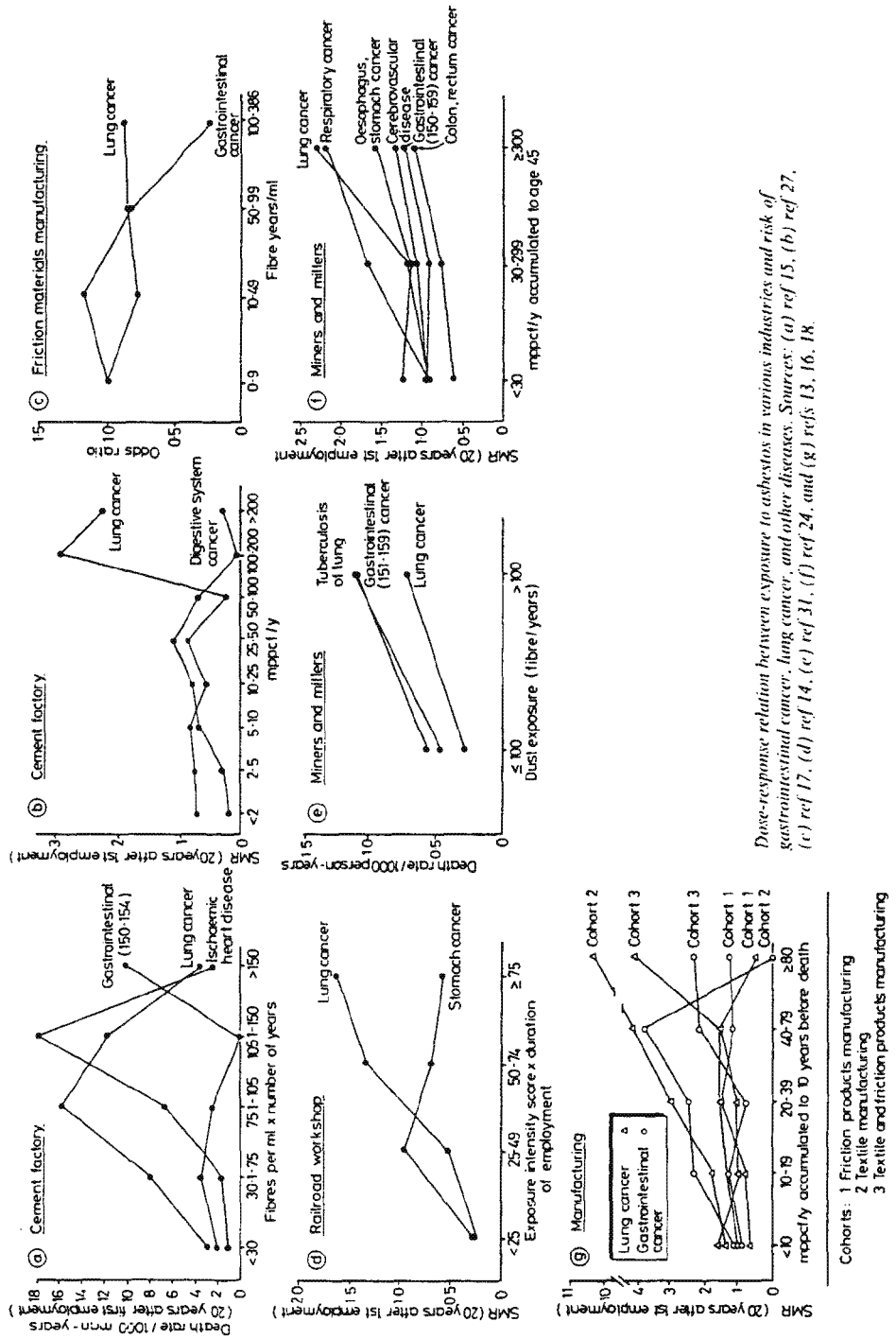

Dose-response relation between exposure to asbestos in various industries and risk of gastrointestinal cancer, lung cancer, and other diseases. Sources: (a) ref 15, (b) ref 27, (c) ref 17, (d) ref 14, (e) ref 31, (f) ref 24, and (g) refs 13, 16, 18.

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(3) Although mesotheliomas were identified in most studies, in some it was not clear whether these cancers were included or excluded from the group of gastrointestinal cancers, including the group of cancers under GI and ICD codes 150–159.

(4) Since there is a high likelihood of misdiagnosing mesotheliomas as gastrointestinal cancers and since some studies may have included mesotheliomas among the gastrointestinal cancers, the reported SMRs may overestimate the true SMRs for gastrointestinal cancers.

Numerous articles have identified factors that might place an individual at an increased risk of cancer to any gastrointestinal site (ICD codes 150–159). These risk factors include smoking; diet including alcohol, beer, and beef; familial/inheritance factors—for example, adenomatosis; history of ulcerative colitis; and place of residence.

Small but significantly increased relative risks (relative risks less than 2, for example) may occur because of spurious associations or failure to account for the effects of other risk factors, such as diet or smoking, that might affect the relative risk. For relative risks that lie between 1 and 2 it is extremely difficult to disentangle the various contributions of biased information, confounding of two or more factors, and cause and effect. Doll and Peto note that the simplest and most likely explanation of the excess mortality of gastrointestinal cancer reported for asbestos workers in some studies is from the misdiagnosis of cancer of the lung and mesothelioma of the pleura or peritoneum.[38] In studies that seek out moderate risks considerable care must be taken both in the analytical methods used and in the interpretation of the results, since the biases inherent in poorly controlled and designed epidemiological studies may exceed the magnitude of the effects that could be observed.

Doll and Peto noted that unless local death specific rates are used, ratios (SMRs) under 1·5 may be largely or wholly artifactual.[38] The importance of using local death rates is illustrated by the study of brewery workers reported by Dean *et al*.[39] These investigators found a higher SMR for colonic cancer based on all Ireland death rates (1·65, $p < 0·05$) than the SMR based on death rates in Dublin county borough (1·18, $p > 0·10$).

One major difficulty with the dose response data provided in most studies is that the accumulated asbestos dose (either in terms of the quantity of dust or asbestos fibres) is computed for workers in terms of their average exposure in different jobs multiplied by the duration of exposure. This procedure does not differentiate between workers with high exposures of short duration or low exposures of long duration. In addition, if there are no major differences in level of exposure between workers in different job categories the procedure will result in people with longer durations of exposure being placed in the higher exposure groups. These higher exposure groups will tend to include the older workers who are at an increased risk of death, regardless of their exposure to asbestos. One approach to the evaluation of dose response relations that would not suffer from the above deficiency would be to compute mortality risks (SMRs, mortality rates, odds ratios) for cohorts of workers who experienced relatively constant doses of asbestos over time.

The data in the figure show no consistent dose response relation between accumulated asbestos dose and lung cancer. This certainly raised questions concerning the validity of this reported dose response relation. One problem with the lung cancer dose response data is that the lifetime smoking habits of the asbestos workers were not taken into consideration. Even if the smoking habits of the asbestos workers were known similar information was not available on the comparison populations. Since rates of lung cancer generally increase with the duration of smoking, one may expect to find higher SMRs for higher accumulated asbestos doses, especially if the accumulated asbestos dose is computed as a product of the average concentration of asbestos and duration of employment. Since in most of the studies the accumulated asbestos dose was a function of the duration of employment, the dose response relation between lung cancer and accumulated asbestos dose might more correctly reflect a dose response relation between lung cancer and duration of smoking.

If asbestos has a carcinogenic effect on the gastrointestinal tract it should be possible to show this effect through lifetime ingestion studies in laboratory animals. Selikoff and Lee noted that "attempts to induce carcinoma in the intestinal epithelium or mesothelioma in the peritoneum by feeding asbestos have been uniformly disappointing . . . ."[40] In a later review of published studies of asbestos administered by mouth Condie concluded, "the bulk of the experimental evidence indicates that the long-term, high-level ingestion exposure to various types of asbestos fibres failed to produce any definite, reproducible, organ-specific carcinogenic effect."[41] Condie cited the evidence from 12 studies that had evaluated the carcinogenic effects of ingesting asbestos. In two subsequent life time studies of asbestos ingestion by F344 rats and Syrian golden hamsters McConnell *et al* reported no increase in the incidence of gastrointestinal cancers[42,43] and reaffirmed the conclusions of Condie.[41] Ward *et al* evaluated the effects of intragastically administered asbestos in F344 rats.[44] Some groups of rats also received subcutaneous injections of azoxymethane (AOM), a known gastrointestinal carcinogen. The proportions of rats that developed intestinal tumours were 66·7%, 77·1%, and

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32·6% in the AOM (48 rats), AOM plus amosite asbestos (48 rats), and amosite asbestos (49 rats) treated groups, respectively. The authors noted that F344 rats at the same laboratory "rarely develop intestinal tumours." Several investigators have suggested that the feed of the rats who received amosite might have been contaminated by AOM, thus giving an erroneously high rate of intestinal tumours.[41–43]

The criteria that should be met to establish cause and effect relation have been stated in many different ways by numerous investigators. These criteria as restated by Selikoff and Lee[40] are that:

(1) a statistically significant association be established between exposures of subjects to the agent (asbestos) and the subsequent development of the syndrome;

(2) some degree of dose response relation should be demonstrable;

(3) in the event that the agent or its metabolic product can be shown in tissue, the concentration in exposed subjects should be greater than in unexposed subjects;

(4) the demonstration of pathological changes in animals after exposure to the agent, similar to those seen in man, would strengthen the evidence for causation, but the failure to obtain such changes would not negate other evidence supporting a causative relation; and

(5) the role of numerous attendant circumstances capable of influencing the appearance of manifestations of the disease initiated by the agent should be evaluated.

The present evaluation found no consistent statistical association between exposure to asbestos and gastrointestinal cancer, a dose response relation was not apparent, and results of ingestion studies in laboratory animals were negative. In terms of these criteria the findings of the present evaluation do not support a cause and effect relation between exposure to asbestos and gastrointestinal cancer. The third criterion was not evaluated since studies have not been conducted to evaluate the concentration of asbestos fibres or bodies in the gastrointestinal tissues of asbestos exposed and non-exposed subjects. Although various factors associated with an increased risk of gastrointestinal cancer have been identified, none of the 32 studies made any adjustments to the risk estimates for gastrointestinal cancer for any of these factors. Based on the epidemiological, clinical, and experimental studies evaluated, there is no evidence to support a cause and effect relation between exposure to asbestos and cancer of any gastrointestinal site.

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