



## Asbestos and Colon Cancer: A Weight-of-the-Evidence Review

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In 1964, Selikoff et al. (1) found a three-fold excess risk of cancer of the stomach, colon, and rectum among insulation workers exposed for 20 or more years. Since that time there has been a number of other studies of asbestos workers and reviews on the relationship of asbestos exposure and gastrointestinal (GI) cancer. The hypothesis of an increased risk of GI cancer among asbestos workers originated from the 1964 study of 632 asbestos insulation workers. The notion has persisted, although results of subsequent studies are not consistent. Reviewers of the asbestos-GI cancer hypothesis have reached a variety of conclusions, such as:

•“Exposure to asbestos is associated with the subsequent development of gastro-intestinal malignancies. In the absence of an explanation to the contrary, this exposure must be regarded as causal,” and only those causes identified after 20 or more years latency should be accepted. (2: 23)

•“No simplistic cause-effect relationship can be ascribed to asbestos at the present time and the answer to the question,

‘Does asbestos exposure cause gastrointestinal cancer?’ must await the results of additional studies.” (3: 1189)

•“The simplest explanation of the excess mortality of gastro-intestinal cancer . . . and in our opinion the most likely, is that it results largely or wholly from misdiagnosis of cancer of the lung and mesothelioma of the pleura or peritoneum. We cannot, of course, rule out the possibility that asbestos may cause a small number of cancers in many different organs, even though there is no strong evidence that it does.” (4: 90)

•“Asbestos exposure is the best defined occupational risk factor for colorectal cancer.” (5: 123)

•“No consistent evidence was found to indicate that exposure to asbestos increases the risk of gastrointestinal cancer.” (6: 75)

•“. . . significant asbestos exposure, as indicated by a lung cancer standardized mortality-ratio (SMR) of at least 200, is associated with an elevated gastro-intestinal cancer SMR.” (7: 79)

The various views expressed above relate to gastrointestinal cancer, and there-

What is the evidence that exposure to asbestos causes colon cancer? This weight-of-evidence review considers epidemiologic evidence from cohort studies of asbestos-exposed workers, case-control studies of colon cancer, animal bioassays, and other corroborative evidence. The major evidence for a causal association at high exposure is a combined colorectal standardized mortality ratio (SMR) of 1.5 for asbestos cohorts where the lung cancer SMR was greater than twofold. However, misdiagnosis may spuriously elevate the SMR. The strongest evidence against a causal association between colon cancer and asbestos exposure is the lack of an exposure-response gradient in asbestos cohorts where trends for lung cancer are observed. Population-based case-control studies of colon cancer do not show any consistent risk associated with asbestos exposure. Long-term ingestion studies show no evidence of an increased incidence of colon cancer in animals by this route of exposure and do not provide biological plausibility for a causal association between asbestos exposure and colon cancer. *Key words:* asbestos, colon cancer, colorectal cancer, gastrointestinal cancer, weight-of-evidence review. *Environ Health Perspect* 102:1038-1050 (1994)

fore, include such sites as the esophagus, stomach, small intestine, colon, rectum, and pancreas. This review will narrow the question to colorectal cancer, and where possible, to colon cancer. Before arriving at a conclusion, the following issues need to be considered: What are some of the known risk factors for colon cancer? Can they bias the results of epidemiologic studies? Is misdiagnosis likely to bias the estimates of risk in asbestos-exposed population? What is the experimental evidence from animal studies regarding the risk of colon cancer from ingested asbestos?

The epidemiologic data are reviewed for strength of association, temporality (is there sufficient latency after first exposure?), exposure response, and consistency. Results from studies of asbestos workers (or workers exposed to asbestos such as maintenance workers) are summarized when colon or colorectal cancer (CRC) risks are provided. Exposure-response data are also evaluated. The determination of whether asbestos causes colon cancer depends in part on these factors. Given there is no bias or confounding, strong evi-

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Table 1. Overweight as a risk factor for colon cancer<sup>a</sup>

Study design and reference	RR by level of overweight				Comments
	Lower weight	Higher weight	Higher weight	Higher weight	
Cohort (10)	1.0	1.26	1.23	1.53*	Incidence of colorectal cancer in males significant when ≥130% overweight
Cohort (11)	1.0	0.86	1.6	1.78	Increased incidence in males when ≥60th percentile at age ≥55
Case-control (12)	Third tertile: 1.14				Males
Cohort (13)					
Males	1.0	2.8*	2.4*		Retired subjects; increased incidence in upper two-thirds of distribution of Quetlet's index
Females	1.0	0.95	1.19		
Cohort (14)	1.04 per 0.1 unit in Quetlet index				Incidence among males and females; significant association
Cohort (15)	No apparent association				14-year follow-up of Swedish twin registry; overweight at 25, 40, or both 25 and 40 years of age
Case-control (16)	OR for highest compared to low category of body mass index = 2.0				Males and females

Abbreviations: RR, risk ratio; OR, odds ratio.

<sup>a</sup>Overweight was usually measured as body mass index.

\*p<0.05.

**Table 2.** Physical activity as a risk factor for colon cancer

Study design and reference	RR by level of activity				Comments
	High	Low			
Proportional incidence (17)	1.0	1.3	1.6		Proportional incidence ratios; rated by job
Case-control (18)	1.0	1.53*	1.58*	2.10*	Proportion of work-years in sedentary job
Cohort (19)	1.0	1.3			Physically active job vs. sedentary job at time of Swedish census, 19-year follow-up
Cohort (13)					
Males	1.0	1.12	2.5		Time/day spent in physical activity in retirement
Females	1.0	1.39	1.12		
Twin registry cohort (15)	1.0		3.6* total		Similar risk of 1.6 for males and females for recreational and occupational activity
	1.0		1.6		
Case-control (16)					
Males	1.0	0.84	1.14	1.43	Total activity; when compared to intense activity, RR for low activity is 3.4 (2.1) for males (females)
Females	1.0	1.03	1.10	2.08	
Case-control (20)					
Males	1.0	1.0	1.22*		Protective effect in descending and sigmoid colon but not in appendix, cecum, and ascending colon
Females	1.0	1.05	1.47*		
Cohort (21)					
Total	1.0	1.79*	1.41*		Physical activity index from questionnaire; Japanese males in Hawaii
Home	1.0	1.5* (mostly sitting)			
Work	1.0	1.39* (mostly sitting)			
Case-control (22)	1.0	1.1	1.4*		Males; occupational physical activity
Case-control (23)	1.0	2.0*	2.0*		Males; occupational activity; recreational activity less important than activity at work

RR, risk ratio.  
\* $p < 0.05$ .

**Table 3.** Alcohol consumption as a risk factor for colon cancer

Study design and reference	RR by level of consumption				Comments
	Low	High			
Case-control (24)					
Males	1.0	1.38	1.54*		Ounces/year, controlling for smoking, age, and race; among males, OR for highest wine, beer, and hard liquor exposure levels = 2.14*, 1.68*, 1.61*.
Females	1.0	1.19	1.44		
Cohort (25)	1.0	0.57	1.05	0.88	Japanese males in Hawaii; ounces/month at beginning of 14-year follow-up
Case-control (26)					
Males	1.0	0.6	0.4	0.8	Total alcohol intake, higher risk for spirits
Female	1.0	1.4	1.2	2.0	
Cohort (13)					
Male	1.0	2.24*	2.42*		Colorectal cancer, but similar findings for colon; retirement community
Females	1.0	1.13	1.45		
Cohort (14)					
Males	1.0	0.89	1.15	1.16	OR for ex-drinkers = 0.81, males; 0.74, females
Females	1.0	1.29	1.80	2.56	
Case-control (27)		No apparent association			Stratified by coffee consumption and $\pm 4$ drinks/day

Abbreviations: RR, risk ratio; OR, odds ratio.  
\* $p < 0.05$

dence for a causal association includes a consistent increased risk of colon cancer occurring 15–20 years or more after first exposure, with the risk increasing with exposure.

Another criterion useful in evaluating causality is plausibility. Are animals exposed to asbestos at increased risk of colon cancer? What are the mechanisms of action for asbestos, and are they relevant to the human colon? These are the criteria that will be used to evaluate the weight-of-evidence in determining whether asbestos causes colon cancer (8,9).

**Some Risk Factors for Colon Cancer**

Overweight has been shown in a number of studies to increase the risk of colon cancer. All but one of the studies reviewed showed an increased risk when overweight. The risk for someone 20–30% overweight is estimated at about twofold (Table 1).

There is a consistent body of evidence suggesting increased physical activity decreases the risk of colon cancer. Such an association is biologically plausible, as physical activity stimulates peristalsis, thereby reducing stool transit time and contact time between carcinogens in the fecal material and the lining of the colon (21). The inverse association is observed when activity is estimated by job title and by more direct evaluation of activity. The risk of low activity/sedentary jobs ranges from about 1.4 to 3.7 (Table 2).

Overweight and increased physical activity are not considered significant confounders in the studies reviewed, as the risk is modest. If confounding is occurring (say if higher-exposed workers are more active and have a lower proportion of overweight), the effect will be to decrease their perceived risk. However, it is in those studies with exposure–response trends that confounding is considered least likely.

The possible role of alcohol consumption as a risk factor for colon cancer is not obvious. At least one study has shown an association among women but not among men (14). Three studies show about a 1.6–2.2 increased risk for those drinking daily (13,14,26). At least two studies suggest no association (25,27). The reason for the differences is not known (Table 3).

The 1964 Surgeon General’s report on Smoking and Health (28) reports observed and expected deaths from seven prospective studies for cancer of the small intestine and colon for cigarette smokers only. The overall mortality ratio was 0.93 (95% CI, 0.84, 1.03). Three of the seven studies were positive (SMRs ranging from 1.1 to 1.4), and four were negative (SMRs from 0.4 to 0.9). Perhaps because of the apparent lack of excess mortality, there are relatively few analytic studies investigating the

**Table 4.** Cigarette smoking as a risk factor for colon cancer

Study design and reference	RR by level of smoking				Comments
	Never	Increasing pack-years			
Case-control (24)					
Males	1.0	0.65*	0.73	0.79	Pack-years smoked; controlled for age and race; no apparent association
Females	1.0	1.18	0.94	0.66	
Retired cohort (13)	Never	<20 years, EXS	>20 years, EXS	Current	
Males	1.0	1.71	2.63*	1.8	
Females	1.0	1.61	0.71	1.35	
Cohort (14)	NS	EXS	<1 pack/day	>1 pack/day	
	1.0	1.03	0.76	1.35	Male and female
Case-control (16)	NS	Ever			
Males	1.0	0.60			Ever vs. never; unadjusted and calculated from number of cases and controls
Females	1.0	1.20			
Case-control (27)	No association				By smoking category for all strata of coffee consumption
Case-control (20)	NS	Smoker + EXS			
	1.0	1.0			Males and females

Abbreviations: RR, risk ratio; NS, nonsmoker; EXS, ex-smoker. \**p*<0.05.

**Table 5.** Comparison of standardized mortality ratios (SMRs) for colon and colorectal cancers in studies of asbestos workers where causes of death are available

Lung cancer SMR	Observed/expected = SMR (95% CI)		Reference
	Colon cancer	Colorectal cancer	
≥ 20-year latency			
1.36	5/15.4 = 0.33 (0.10, 0.68)	14/27.4 = 0.51 (0.27, 0.82)	(32)
1.71	7/13.4 = 0.52 (0.21, 1.08)	23/24.8 = 0.93 (0.58, 1.35)	(33)
2.71	14/14.24 = 0.98 (0.53, 1.58)	23/19.9 = 1.16 (0.72, 1.69)	(34)
Total	26/43.04 = 0.60 (0.39, 0.87)	60/72.1 = 0.83 (0.63, 1.06)	
No latency			
0.99	56/50.6 = 1.11 (0.94, 1.44)	91/83.3 = 1.09 (0.88, 1.33)	(35)
1.15	12/5.73 = 2.09 (1.08, 3.66)	16/9.44 = 1.69 (0.95, 2.65)	(36)
1.69	8/17.9 = 0.45 (0.2, 0.89)	24/30.2 = 0.79 (0.50, 1.15)	(33)
1.8	32/30.16 = 1.06 (0.73, 1.5)	67/57.93 = 1.16 (0.89, 1.46)	(37)
2.1	6/4.4 = 1.37 (0.48, 2.70)	10/7.6 = 1.32 (0.62, 2.28)	(38)
Total	114/108.8 = 1.05 (0.86, 1.25)	208/188.5 = 1.10 (0.96, 1.26)	

association of colon cancer and smoking. Table 4 summarizes six more recent studies. None of these studies shows a statistically significant colon cancer risk associated with smoking; two of the six show a risk ratio greater than one for smokers. These results are not dissimilar from the 1964 report and suggest that if there is a risk of colon cancer from smoking, it is small.

Neither alcohol nor smoking can be significant confounders, as the association with colon cancer is negligible.

**Colorectal Cancer: Diagnosis and Grouping**

Doll and Peto (4) report that in asbestos cohorts, 17–20% of the excess mortality from lung cancer is attributed to GI and other cancers. They argue that this excess has one of two explanations. Either asbestos exposure causes cancer in practically every organ, or some of the lung cancers and mesothelioma deaths are misclassified as GI cancers. The latter is considered more likely.

The former is considered more likely.

Lung cancer may clinically mimic other diseases, and its common occurrence was not generally realized at least until the 1960s (1964 was the date of the Surgeon General's report on smoking that raised consciousness concerning the relationship of smoking and lung cancer). Mesothelioma misclassification is even more likely. Pleural mesothelioma was not recognized as a specific cancer until 1960, and peritoneal mesothelioma did not achieve some recognition until 1964.

Misclassification of GI cancers during this time period and before is supported by Newhouse and Wagner (29). They compared gastrointestinal cancer deaths determined from the death certificate with causes of death (COD) determined by additional necropsy and histological material. The number of GI tumors was reduced from 14 to 7, lung cancer increased from

39 to 42 (8 added and 5 removed), and mesotheliomas increased from 5 to 20. Seven of the deaths reclassified as mesotheliomas were from gastrointestinal cancers, 3 from other tumors, and 5 from lung cancers.

Doll and Peto (4) suggest the data presented by Selikoff et al. (30) regarding misclassification cannot be interpreted because the extent of "best evidence" is not known. It seemed to Doll and Peto unlikely that there were no transfers out of asbestos-related cancers, while 37% of the transfers into asbestos-related categories were not thought to be asbestos related. Selikoff later concluded that about one-half (23/49) of the pancreatic cancers were misclassified. These are the data on which the asbestos/GI cancer hypothesis is based.

Doll and Peto (4) considered classification of death from death certificates at present to be somewhat better than previously. This seems to be supported by Percy et al. (31). They compared causes of death on death certificates with hospital diagnoses. Colon cancer had a high detection rate (89%), but only 79% of the deaths were confirmed by the hospital diagnosis. For rectal cancers the rates were 56% and 86%. Thus, colon cancer was overreported, and rectal cancer was underreported. Colorectal cancer had both high detection and high confirmation rates (93 and 95%, respectively). Detection and confirmation rates for stomach and pancreatic cancers showed good agreement (~90%) as did lung cancer (~95%).

The effect of overreporting colon cancer is to spuriously inflate the number of deaths ascribed to it. To bias the SMRs,

the diagnoses would have to be increased more among asbestos workers than nonasbestos workers, and the asbestos-related respiratory cancers would have to be misdiagnosed as GI cancers. Misclassification appeared to be a significant problem before the 1980s in asbestos cohorts based on best evidence. The problem should be greatest where asbestos exposure is highest because the proportion of asbestos-related cancers will be higher than in less-exposed workers. The effect of misclassification is to spuriously reduce SMRs for respiratory cancers and spuriously inflate SMRs for colon cancer, particularly in high-exposed workers. The effect in low-exposed groups is not considered significant.

Percy et al. (31) do not provide any information as to the "correct" diagnosis and whether it might be mesothelioma. Whether a person exposed to asbestos is more likely to be misdiagnosed for colon cancer compared to a person not exposed to asbestos is unknown, but "diagnostic suspicion bias" does occur.

In the asbestos studies being reviewed, there are eight cohorts reporting colon cancer and rectum cancer separately; three cohorts stratify by  $\geq 20$  years latency, and five cohorts do not consider latency. The SMRs for colon and colorectal cancers are similar where latency is not considered. Where latency is considered, the SMR for CRC is 0.83, whereas the SMR for colon cancer in these same studies is 0.60, about 30% less (Table 5). That is, when latency was considered, the SMR for CRC was always greater than that for colon cancer alone. Thus the SMR for CRC used in the analysis of asbestos cohorts may overestimate the true risk ratio for colon cancer.

An important reason for stratifying by latency is that both CRC and lung cancer are generally considered to take about 20 years or so to develop after exposure to an etiologic agent. Thus a restriction to  $>20$ -year latency should exclude at least some of the nonoccupational cases.

### Colorectal Cancer in Asbestos Workers: Cohort Studies

The validity of the hypothesis that asbestos causes colon cancer is tested here among asbestos workers where a major portion of the cohort is presumed to be exposed. Because asbestos is a known lung carcinogen and lung cancer shows a linear relationship to asbestos exposure (39), the risk of lung cancer provides a surrogate estimate of asbestos exposure. In the analysis presented below, the risk of CRC is stratified into cohorts with high asbestos exposure (risk of lung cancer greater than twofold) and cohorts with lower asbestos exposure (risk of lung cancer less than twofold).

The SMR for lung cancer in asbestos-exposed workers is only a surrogate measure of exposure because there is no control for smoking, a major cause of lung cancer. Smoking and asbestos exposure together multiply the risk of lung cancer, but smoking does not appear to increase the risk of colon cancer. The SMR for lung cancer includes the effect of exposure to both asbestos and cigarette smoke. The lower SMRs for lung cancer could in part be due to less smoking and/or less asbestos exposure. The justification for using lung cancer SMRs as a surrogate for asbestos exposure is based on the demonstrated relationship between asbestos exposure and lung cancer. Two assumptions are made that support the idea that increased lung cancer SMRs indicate asbestos exposure more than they indicate prevalence of smoking: 1) smoking prevalence is similar in the asbestos cohorts, 2) smoking alone is unlikely to increase the lung cancer SMRs much above twofold, even with a high incidence of smoking.

Results are combined within each category by summing observed and expected deaths for an overall observed/expected risk ratio, thereby crudely evaluating risk of CRC at low and high exposures using risk of lung cancer as a surrogate of exposure. Results are presented for cohorts in which only workers with 10 or more years since date of hire (and by implication date of first exposure) are included.

Asbestos exposure has been specifically identified with mesothelioma, so the proportion of mesotheliomas can also serve as a surrogate measure of asbestos exposure. Mesothelioma is affected more by type of asbestos than by exposure, however, as a clear exposure-response relationship has not been demonstrated. With some exceptions, the classification of asbestos exposure by lung cancer SMRs and percent mesotheliomas is consistent. The mean percent mesotheliomas for cohorts with lung SMRs  $<2$  is 0.8%, compared to 4.9% for studies where lung cancer SMRs are  $>2$ . Six of the ten studies with lung cancer SMRs  $<2$  have  $<1\%$  mesotheliomas, five of six of the studies with lung cancer SMRs  $>2$  have  $\geq 1\%$  mesotheliomas. Somewhat less credence is given to these exposure-response trends than to the trends evaluated within individual studies where exposure is more quantitative.

Cohort studies are useful for evaluating the risk of disease associated with work in a particular industry and/or exposure to specific substances. This is because the cohort is defined by exposure status, or more correctly, by employment status within an industry. The results of such a study may not be conclusive for a variety of reasons: 1) dilution of exposed workers by less

exposed/nonexposed workers, 2) lack of information on confounding exposures and nonoccupational risk factors, or 3) lack of information on magnitude of exposure.

In 1964, Selikoff et al. (1) reported a threefold excess of cancers of the stomach, colon, and rectum among 632 asbestos insulation workers (29 observed/9.4 expected). There was a 6.8-fold excess of cancer of the lung and pleura.

There are at least 19 cohort studies since then that have reported SMRs for lung cancer and colorectal cancers among asbestos workers (or workers exposed to asbestos) with 10–20 or more years of latency. These are listed in Table 6 and graphically displayed in Figure 1. The original cohort of insulation workers was followed up by Selikoff et al. (30) and is included in Figure 1. These data are not included in the meta-analysis because they should not be part of the data used to test the hypothesis of whether asbestos causes CRC. That is, an initial study that generates a hypothesis should not be used to test that same hypothesis. Studies are included that have reasonably complete follow-up ( $\geq 90\%$ ) and either colon cancer or CRC deaths are listed. Only the last update of a study was included if more than one report had been published.

In the high lung cancer exposure group (SMRs  $\geq 2$ ), there are seven eligible cohorts. All but two have SMRs for CRC  $>1$ ; the overall SMR for CRC is 1.48 (1.21, 1.78). In the low lung cancer exposure group (SMRs  $<2$ ), there are 12 eligible cohorts; 5 studies have SMRs for CRC  $>1$  (1 is significant), and 7 have CRC SMRs  $<1$  (2 are significant). The overall SMR for CRC for this exposure group is 0.95 (0.84, 1.05).

The low-exposure cohort with the highest and only statistically significant SMR for CRC (2.3) comprises production and maintenance workers at a calcium carbide plant in Norway where there was exposure to polyaromatic hydrocarbons, volatile coal-tar-pitch products, and cadmium as well as asbestos (36). Asbestos had been used regularly in past years for insulating material around furnaces with some use in the mechanic shop. Because there was no definite excess of lung cancer (SMR = 1.15), the authors were reluctant to suggest asbestos as a possible causal agent for CRC. They also suggest some statistically significant associations could be chance given the large number of comparisons.

The Swedish study of asbestos cement workers (45) had a statistically nonsignificant SMR of 1.5 for CRC. Exposure was mainly to chrysotile, with smaller amounts of crocidolite and amosite. There was a significant excess of pleural mesothelioma (13

**Table 6.** Summary of standardized mortality ratios (SMRs) for lung cancer, colon cancer, and colorectal cancer among asbestos-exposed cohorts (latency ≥20 years unless noted otherwise)

Lung cancer <sup>a</sup>	Observed/expected = SMR (95% CI)		Reference	Exposure (type of asbestos)
	Colon cancer	Colorectal cancer		
<b>SMR ≤2.0</b>				
0.99 (NR)		52/44.5 = 1.17 (0.87, 1.52)	(35)	Maintenance; ferroalloy industry; PAH; SiO <sub>2</sub> ; asbestos (≥15 years L)
1.05 (0.5%)		15/20.9 = 0.72 (0.39, 1.14)	(40)	Swedish railroad shopworkers (Am, Cr, Ch)
1.15 (NR)		12/5.2 = 2.31 (1.17, 3.8)	(36)	Calcium carbide plant; maintenance workers; PAH, Cd (≥15 years L)
1.17 (0.2%)		10/8.3 = 1.20 (0.56, 2.09)	(41)	Asbestos cement (Am, Cr)
1.25 (0.2%)		79/101.3 = 0.78 (0.61, 0.97)	(42)	Chrysotile mining
1.36 (4.1%)	5/15.4 = 0.33 (0.10, 0.68)	14/27.4 = 0.51 (0.27, 0.82)	(32)	UK asbestos workers (≥10 years L)
1.44 (1.4%)		13/16.7 = 0.78 (0.41, 1.27)	(43)	UK textiles (Ch, Cr)
1.44 (0.8%)		11/15 = 0.73 (0.36, 1.24)	(41)	Asbestos cement (Ch, Cr)
1.44 (3.2%)		5/6.34 = 0.79 (0.24, 1.65)	(44)	German asbestos workers, ≥3 years before 1977
1.71 (0.3%)	7/13.4 = 0.52 (0.21, 1.08)	23/24.8 = 0.93 (0.58, 1.35)	(33)	Norwegian shipyard (Ch) (≥10 years L)
1.8 (2.2%)		26/17.3 = 1.5 (0.7, 3)	(45)	Swedish asbestos cement (Ch, Cr, Am)
1.83 (0.8%)	32/30.16 = 1.06 (0.73, 1.5)	67/57.9 = 1.16 (0.89, 1.46)	(37)	Danish asbestos cement (Ch, Am, Cr) (≥15 years L)
Total (0.8%)	44/58.96 = 0.75 (0.54, 0.99)	327/345.64 = 0.95 (0.84, 1.05)		
<b>SMR ≥2.0</b>				
2.41 (1.5%)		2/1.46 = 1.37 (0.17, 4.9)	(38)	Insulation board UK (Am), approximate to exposures in Selikoff (1) (≥15 years L)
2.71 (0.8%)	14/14.24 = 0.98 (0.53, 1.58)	23/19.9 = 1.16 (0.72, 1.69)	(34)	Retired asbestos workers, USA
3.47 (4.2%)		3/1.39 = 2.15 (0.39, 5.4)	(44)	German asbestos workers working prior to 1972
3.88 (all causes NR)		3/3 = 1.0 (0.18, 2.5)	(46)	Production and maintenance workers, HNO <sub>3</sub> plant in Norway
4.0 (7.1%)		1/1.3 = 0.77 (0, 3.1)	(47)	Swedish maintenance workers ferrochromium plant (Cro, Cr <sup>3+</sup> , asbestos)
4.2 (5.2%)		54/34 = 1.59 (1.29, 2.05)	(30)	USA, Canada insulation workers (Cr, Am)
4.97 (1.0%)		22/11.9 = 1.85 (1.14, 2.7)	(48)	NJ amosite factory making insulation for navy (5–40 years L)
Total (4.9%)		108/72.95 = 1.48 (1.21, 1.78)		

Abbreviations: Cr, crocidolite; Am, amosite; Ch, chrysotile; NR, not reported; L, latency.  
<sup>a</sup>Percent mesotheliomas (number mesotheliomas/total deaths) are in parentheses.

cases of 592 deaths and an SMR of 7.2) and nonmalignant respiratory disease (56 cases and an SMR of 2.6). The SMR for lung cancer was 1.8 but was not statistically significant. There was “no overall risk” from cancer in the upper or lower gastrointestinal tract, although there was an exposure–response relationship between CRC and cumulative fiber exposure, but not

between CRC and tenure. The authors suggest the “overrisk of colorectal cancer in highly exposed workers might be due to cement exposure” (45). This speculation is based on an excess of rectal cancer in a cohort of cement workers and an overrepresentation of cement workers in an unpublished study of CRC. Jakobsson et al. (49) found an odds ratio of 3.2 for blue-color

cement workers with ≥25 years tenure, a finding supporting a cement rather than asbestos etiology. Thus, no studies of asbestos-exposed workers with lung SMRs <2 were found that showed an appreciable or convincing increased risk of CRC that could not also be attributed to chance or confounding exposures.

Hill (8) and others argue that an exposure–response relationship in an observational study gives support to a causal explanation for a disease–exposure association. Exposure–response relationships have been observed for lung cancer. On the basis of nine published studies of asbestos workers where individual exposure was estimated, Browne (50) suggested that there is a threshold of increased risk of lung cancer in the range of 25–100 fibers/cm<sup>2</sup>-years. The larger database on CRC suggests that if the lung SMR is <2, there is probably no increased risk of CRC. In the exposure group where lung SMRs are >2, only two of seven studies clearly show a large increased risk of CRC.

One can further evaluate exposure–response relationships within the same study and between studies where workers are stratified by some measure of exposure. The exposure measures available in asbestos cohorts for both lung cancer and CRC are million particles per cubic foot (mppcf)-years (41,42), length of exposure (32,41,43), and fiber-years/ml (45) (Table 7). Hughes et al. (41) found no apparent exposure–response association for either lung cancer or CRC. Albin et al. (45) found no apparent exposure–response association for lung cancer. For CRC there was an apparent association, with an SMR of 3.4 in the ≥40 fibers-years/ml category, but no increased SMR in the lower exposure categories. The remaining four cohorts show an exposure–response trend for lung cancer, but no trend for CRC.

Figures 2–5 display the SMRs for lung cancer and CRC by exposure category. Lung cancer SMRs are significantly above the no-effect level for ≥15 years tenure and ≥150 mppcf-years. CRC SMR point estimates are at or below the no-effect level over the same range of exposures, although the confidence intervals are generally quite wide, and only one is statistically significant.

A trend is also observed if the SMRs for lung cancer and CRC are combined for the low-, medium-, and high-exposure categories for all six studies in Table 7 [mppcf-years used for plant 2 (41)]. The Albin et al. (45) study was not included because observed and expected deaths were not provided. These exposure–response trends from Table 7 are combined in Table 8.

The advantage of these analyses is that the exposure–response association for lung

cancer and asbestos exposure is less likely to be confounded by cigarette smoking, and there is less likelihood of exposure misclassification. These data indicate an exposure-response relationship for lung cancer but not CRC and indicate that mortality from lung cancer is elevated at higher exposure levels, but mortality from CRC in the same cohorts and at similar exposure levels is not elevated.

**Colon Cancer and Occupation: Case-Control Studies**

A nested case-control study (colon cancer cases/controls from a cohort of asbestos workers) is potentially the most appropriate and efficient study design for determining causality, but none was found.

Several population-based case-control studies are summarized in Table 9. A weakness of this study design is that a number of occupational exposures are evaluated in one study. It is difficult to obtain good occupational histories, and the prevalence of exposure is often low (52). Several results can occur, including too few exposed subjects to analyze, and a negative result that may or may not be reported. The lack of an observed association may be due to exposure misclassification, confounding, too low an exposure, and/or no true association. A false positive association is possible, for example, because of confounding occupational and/or nonoccupational exposure and sampling variability.

Hardell (51) reported a 1.9-fold excess

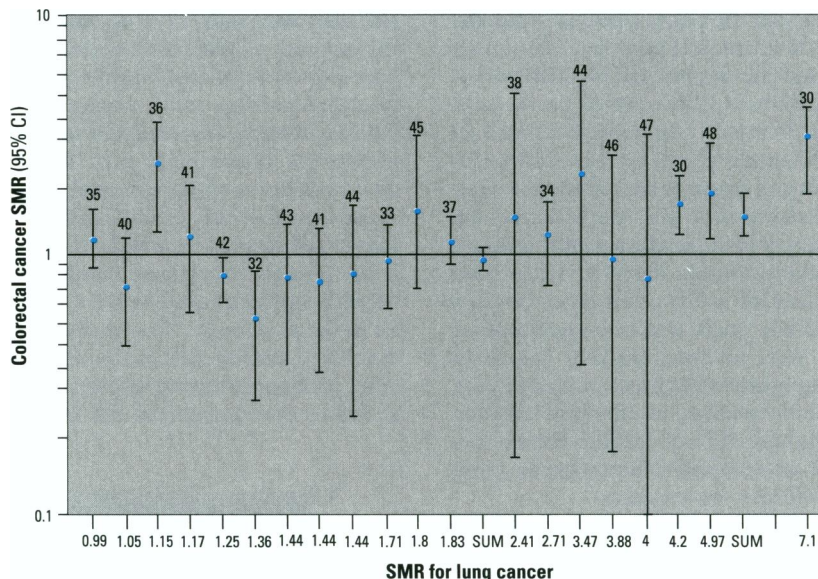


Figure 1. Risk of colorectal cancer in asbestos workers with >20 years of latency.

odds ratio (OR) among Swedish men exposed to asbestos. Other than matching on age and place of residence, there was no control for potential confounders nor consideration of degree of exposure. Spiegelman and Wegman (12) used data from the Third National Cancer Survey to generate hypotheses about colon cancer and occupational exposure. Using the NIOSH Hazard Survey, they calculated a cumulative exposure probability score (probability of expo-

sure and years worked) for each case and control. They found no apparent excess when comparing medium-high exposure versus low asbestos exposure scores for males and low-medium versus high exposure for females and controlling for potential confounders. Fredriksson et al. (20) reported a twofold excess risk for Swedish males and females exposed to high-grade asbestos and no apparent risk when exposure was to low-grade asbestos. High and low grade were not

Table 7. Exposure response for colorectal cancer and lung cancer by exposure among asbestos cohorts

Cumulative exposure	Observed/expected = SMR (95% CI)		Exposure and reference
	Lung cancer	Colorectal cancer	
<30 mppcf-years	91/97.8 = 0.93 (0.75, 1.14)	34/54.84 = 0.62 (0.43, 0.85)	Chrysotile mining (42)
30-300 mppcf-years	81/68.6 = 1.18 (0.93, 1.46)	28/36.36 = 0.77 (0.51, 1.09)	
≥300 mppcf-years	70/31.1 = 2.25 (1.74, 2.82)	18/16.2 = 1.11 (0.65, 1.70)	
<10 years	53/45.4 = 1.17 (0.87, 1.51)	8/11.8 = 0.68 (0.28, 1.24)	Textiles (43)
>10 years	40/19.1 = 2.09 (1.48, 2.81)	5/4.86 = 1.03 (0.31, 2.15)	
<1 year	32/24 = 1.33 (0.90, 1.85)	4/4.6 = 0.87 (0.22, 1.96)	Plant 1, asbestos cement (41)
1-5 years	6/8 = 0.75 (0.26, 1.49)	4/1.7 = 2.38 (0.59, 5.29)	
5-15 years	4/3.5 = 1.15 (0.29, 2.57)	1/0.8 = 1.2 (0, 5)	
≥15 years	6/5.7 = 1.05 (0.37, 2.09)	1/1.2 = 0.81 (0, 3.3)	Plant 2, asbestos cement (41)
<1 year	55/45.5 = 1.21 (0.90, 1.56)	5/9.3 = 0.54 (0.16, 1.13)	
1-5 years	20/14.4 = 1.39 (0.84, 2.08)	1/2.8 = 0.36 (0, 1.42)	
5-15 years	8/3.6 = 2.24 (0.93, 4.07)	0/0.7 = -(0, 1.43)	
≥15 years	24/10.9 = 2.2 (1.39, 3.19)	3/2.1 = 1.4 (0.26, 3.55)	
<6 mppcf-years	20/18.9 = 1.06 (0.64, 1.58)	2/3.9 = 0.51 (0.04, 1.49)	Plant 2, asbestos cement (41)
6-24 mppcf-years	19/14.5 = 1.31 (0.78, 1.98)	1/2.8 = 0.36 (0, 1.43)	
25-49 mppcf-years	12/6 = 2.0 (1.01, 3.32)	0/1.2 = -(0, 0.83)	
50-99 mppcf-years	10/5/5 = 1.81 (0.85, 3.15)	3/1.1 = 2.73 (0.49, 6.79)	
≥100 mppcf-years	12/5.2 = 2.31 (1.17, 3.83)	0/1 = 0 (0, 1)	Asbestos, cement (45)
<15 fibers-years/ml	1.8 (0.8, 3.9)	1.3 (0.5, 2.9)	
15-39 fibers-years/ml	1.9 (0.7, 5.3)	1.1 (0.3, 3.9)	
≥40 fibers-years/ml	1.9 (0.5, 7.1)	3.4 (1.2, 9.5)	UK asbestos workers (32)
<10 years <sup>a</sup>	40/43.3 = 0.92 (0.65, 1.24)	1/2.5 = 0.40 (0, 1.60)	
≥10 years <sup>a</sup>	145/102.8 = 1.41 (1.19, 1.65)	2/5.5 = 0.36 (0.03, 1.06)	
≥20 years <sup>a</sup>		3/5.6 = 0.35 (0.10, 1.33)	

mppcf-years, million particles per cubic foot-years.  
<sup>a</sup>Years before 1969.

defined, and the OR is based on a dichotomous classification of exposure. Adjustments were made for age, sex, and physical activity.

Siemiatycki (52) reported on the association between 183 substances and 11 types of cancer at two exposure levels classified as any exposure and substantial exposure. Subjects were from the Montreal area with cancer controls and a smaller group of population controls. Potential confounders controlled for in the colon cancer analyses were ethnic origin and beer consumption. There were no apparent ORs associated with exposure to inorganic insulation dust, amphibole asbestos, or chrysotile asbestos. The authors did not include the association of asbestos and colon cancer as priorities for further investigation.

Gerhardsson de Verdier et al. (53) reported on a population-based case-control study in Stockholm. Elevated risks were observed among males exposed to asbestos, and there was little difference between adjusted and unadjusted ORs. About one-third of the asbestos-exposed cases were also petrol/auto-repair workers, a group also showing elevated ORs. Because of the small numbers of exposed subjects and high correlation between risk exposures, the authors could not separate out the effects of single exposures. They suggest the potential for simultaneous exposure to several occupational risk factors should be considered in other investigations.

Garabrant et al. (54) found no association between asbestos exposure and colon cancer in Los Angeles County, California. They found a weak association in a univariate analysis, but when adjusted for confounding factors, the association disappeared, reducing the overall OR 15–20%. Exposure-response was evaluated by several measures, including frequency of exposure, duration of exposure, and cumulative exposure, with none showing any trend. The authors concluded that in this population asbestos is not a risk factor for colon cancer, and it is important to control for nonoccupational risk factors before interpreting an observed association as causal.

These case-control studies do not provide much support for a causal association between asbestos exposure and colon cancer. The two studies with nearly twofold excess risk have either not controlled for potential confounders (51) or have other correlated occupational risk factors (53). The other studies show no apparent association at all. One reason for the lack of an association could be an exposure that is too low to have a measurable effect. It seems unlikely that cases in the high-exposure group in the study by Garabrant et al. (54) have exposures of the magnitude producing twofold or higher excess lung cancer deaths seen in asbestos cohorts. For exam-

ple, there were only 11 of 66 cases reporting exposure to asbestos who were likely to have exposures of this magnitude (i.e., 6 insulation workers and 5 workers in shipbuilding/repair). The results of these studies are not inconsistent with studies of asbestos cohorts, which indicated at most a slight increased risk of CRC when exposure to asbestos was very high. However, it is not possible to compare exposure levels between studies or even between individuals in the same study. Two studies (53,54) show how uncontrolled confounding from other jobs not involving asbestos exposure as well as nonoccupational risk factors can

spuriously elevate risk ratios and make causal inferences more difficult.

### Biological Plausibility

Is it plausible that asbestos causes colon cancer? Are there increased colon tumors in animals exposed to asbestos?

Condie (55) reviewed 11 animal studies of orally administered asbestos. At least 4 were not lifetime studies, and in 9 of 11 studies the rat was the experimental animal. In only two of the studies (56,57) were there any colon cancers. Rats were fed 10% chrysotile in the diet *ad libitum* for 32 months. The incidence of colon tumors

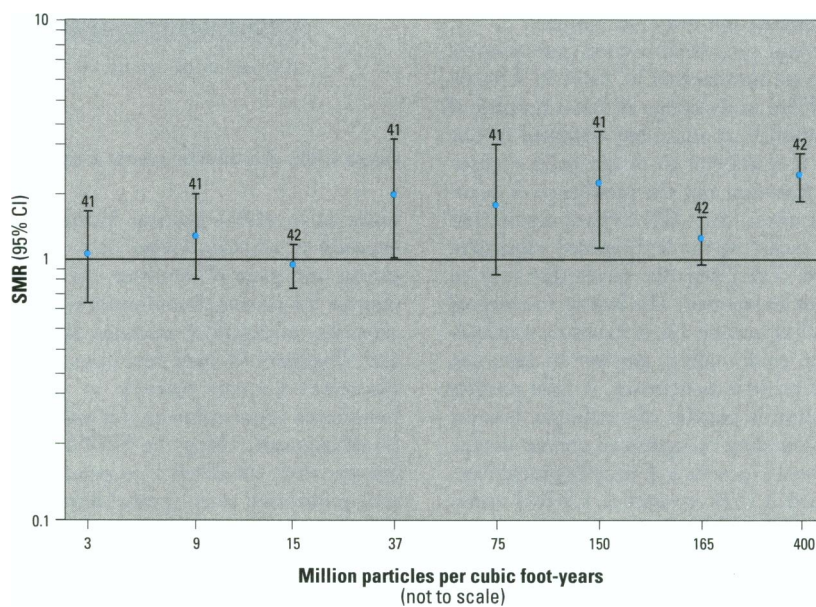


Figure 2. Exposure-response for lung cancer among asbestos cohorts by million particles per cubic foot-years.

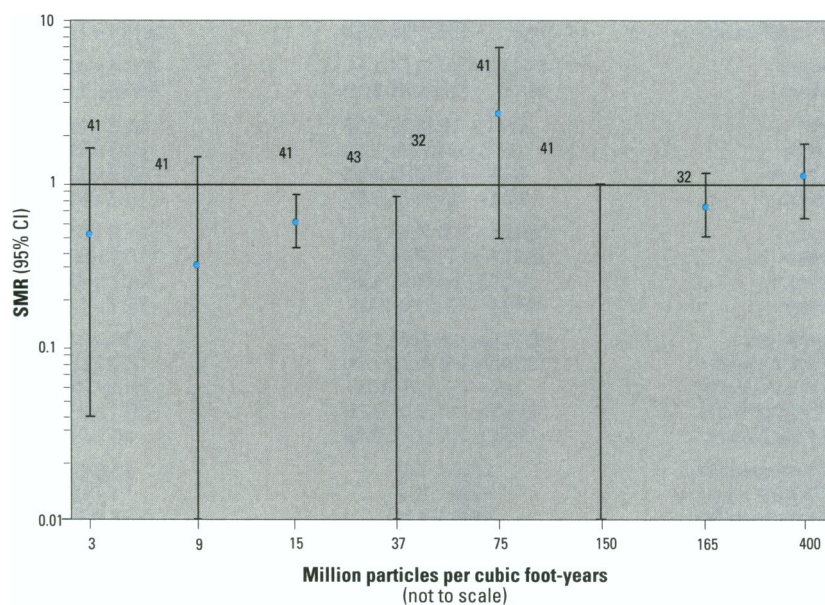


Figure 3. Exposure response for colorectal cancer among asbestos cohorts by million particles per cubic foot-years.

was 1.6%. The incidence in the group fed 10% cellulose fiber was 1% and incidence in the control group was 2.6%. Thus the number of colon tumors from asbestos ingestion was not increased compared to controls (56).

In the other experiment, rats were exposed to azoxymethane and/or asbestos for 10 weeks and followed for 34 weeks or a lifetime in two separate experiments (57). In the shorter experiment, exposure to amosite and chrysotile produced no tumors. In the lifetime study the incidence of colon tumors was 56% when exposed to azoxymethane, 60% when exposed to azoxymethane plus amosite, and 33% when exposed to saline plus amosite. There was no control group, and the incidence of

**Table 8.** Exposure–response trends from low, medium, and high exposure categories from Table 7

	Low	Medium	High
<b>Lung cancer</b>			
Observed: SMR	236:1.03	132:1.24	273:1.67
(95% CI)	(0.90, 1.17)	(1.04, 1.47)	(1.47, 1.87)
<b>Colorectal cancer</b>			
Observed: SMR	49:0.63	37:0.84	29:0.84
(95% CI)	(0.46, 0.82)	(0.59, 1.14)	(0.56, 1.19)

SMR, standardized mortality ratio.

zymbal gland tumors was 14% in the amosite lifetime exposure group. Zymbal gland tumors are rare (-0.3%), and both intestinal carcinomas and zymbal gland tumors are induced by a single dose of azoxymethane. An inadvertent exposure to

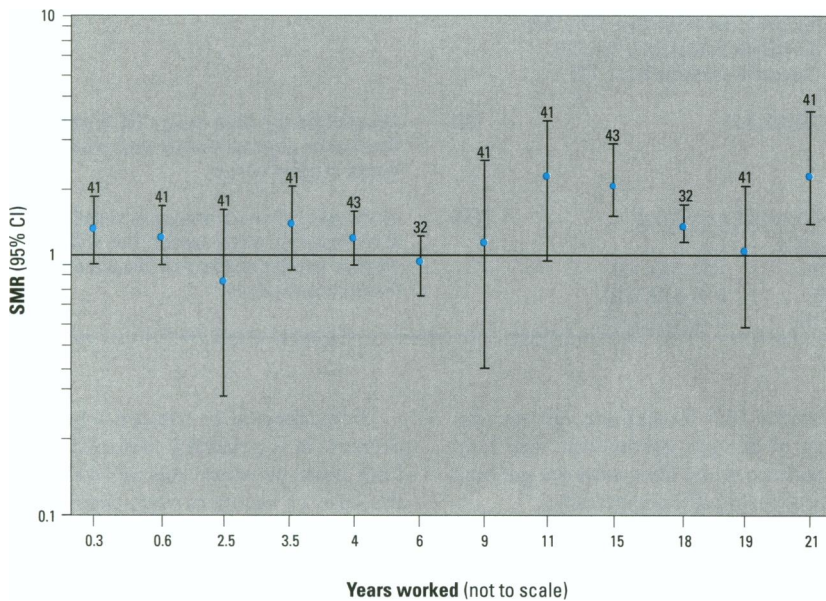
azoxymethane may have caused the increase in the amosite–exposed group.

From his review, Condie (55) concludes that “long-term, high level ingestion exposure to various types of asbestos fibers failed to produce any definite reproducible, organ-specific carcinogenic effect,” and in particular no effect specific to the colon. Ingestion is considered relevant to humans because exposure may occur by swallowing fibers cleared from the lung.

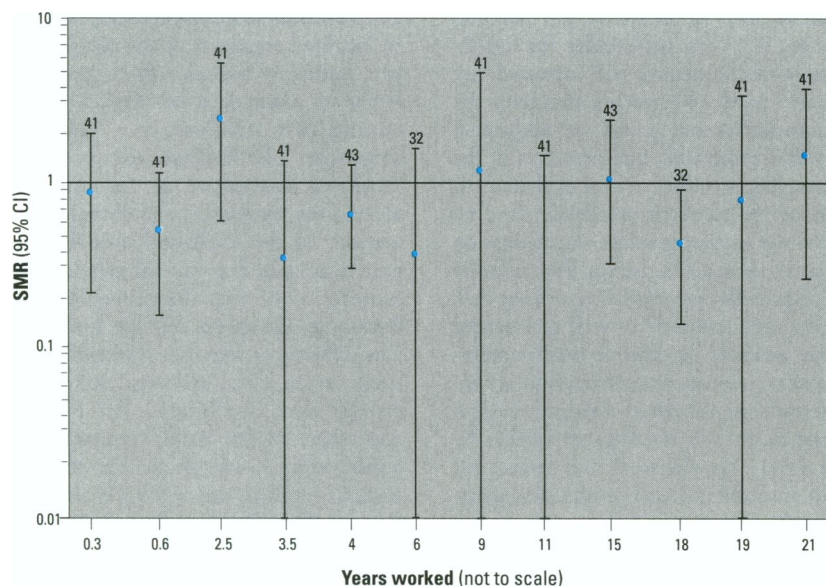
There have been at least three long-term ingestion studies since the review by Condie. McConnell et al. (58) reported on a study that overcomes the criticisms regarding asbestos ingestion studies with respect to the small number of animals and the less-than-lifetime length of the study. Groups of 250 male and 250 female F344 rats were fed 1% amosite over their entire lifetime and compared to control groups of over 100 animals each. There was some increase of thyroid cancer and monocytic leukemia in the male rats. These effects were discounted by the authors, who questioned the biological significance of the cancers. No toxic or neoplastic lesions were observed in the gastrointestinal tract or in the mesothelium.

McConnell et al. (59) also reported on a similar lifetime study of hamsters fed 1% amosite, short-range chrysotile, or intermediate range chrysotile in the diet. The results were statistically the same in the exposed and control groups. There were no adverse effects on body weight gain, survival was enhanced, and there was no increase in number of tumors. There were increases in adrenal tumors in male and female hamsters exposed to intermediate-range chrysotile asbestos, but the biological significance was questioned.

Truhaut and Chouroulinkov (60) fed male and female rats daily doses of 10, 60, and 360 mg of a mixture of chrysotile/crocidolite in palm oil for two years. Observation continued for an additional 6 months. There was no sign of toxicity and no adverse effect on survival or body weight. There were no statistically detectable differences in tumor incidence between exposed and controls, no exposure–response relationships, and no gastrointestinal tumors.



**Figure 4.** Exposure response for lung cancer among asbestos cohorts by years worked.



**Figure 5.** Exposure response for colorectal cancer among asbestos cohorts by years worked.



**Table 9.** Summary of population-based case-control studies of asbestos and colon cancer

Source of cases/controls	No. of cases/controls	OR (95% CI)	Reference	Comments
Swedish Cancer Registry (1978–1979)/population in same region	16/137	1.9 (1.0, 3.6)	(51)	No information on latency, duration, intensity of exposure; no apparent control of nonoccupational risk factors
Third National Cancer Survey (cancer controls)	Males 850 total Females 1406 total	1.22 ( $p = 0.33$ ) 1.09 ( $p = 0.64$ )	(12)	Exposure based on job title and classification from NIOSH hazard survey of dichotomous (high vs. low) exposure analysis; control for confounders (including diet and weight)
Cases from Swedish Cancer Registry (1984–1986); controls from population registry; both residents of Umea	329/658 (male and female)	High-grade asbestos: 2.1 (0.8, 5.8); low-grade asbestos: 1.2 (0.6, 2.4)	(20)	Stratified by age, sex, and physical activity index score in analysis
Montreal metropolitan area		Any	(52)	90% CI
	54 <sup>a</sup>	Inorganic insulation dust 1.2 (0.9, 1.5)		
	34	Amphibole asbestos 1.2 (0.8, 1.7)		
	78	Chrysotile asbestos 1.0 (0.8, 1.3)		
		Substantial		
	20 <sup>a</sup>	Inorganic insulation dust 1.6 (1, 2.5)		
	4	Amphibole asbestos 1.0 (0.4, 2.1)		
	18	Chrysotile asbestos 1.6 (1, 2.5)		
Stockholm residents, 1986–1988; males	22/20	1.9 (0.9, 4.2)	(53)	Adjusted for age, total energy, fat, protein, and fiber intake, physical activity, body mass, family history of colon cancer
Los Angeles tumor registry and neighborhood controls		Cumulative exposure (freq × duration)	(54)	Males with ≥15 years latency; adjusted for family history of colon cancer, diet, weight, and physical activity; unadjusted ORs were higher than adjusted values
		Never (343/361)	1.0	
		1–30 (36/31)	1.07 (0.63, 1.8)	
		31–60 (10/8)	0.94 (0.33, 2.65)	
		≥61 (11/11)	0.55 (0.21, 1.47)	

OR, odds ratio.

<sup>a</sup>Number of exposed cases.

Bolton et al. (61), in addition to finding no colon tumors in a lifetime study of rats ingesting amosite, crocidolite, or chrysotile, found “no evidence of widespread penetration of, or damage to, the gastrointestinal mucosae.” They used the scanning electron microscope and could detect fibers >0.1 μm in diameter. Of particular note was the absence of fibers in the mesenteric lymph nodes, where concentration of fibers would be expected if fibers penetrated the mucosae. No evidence of either intestinal damage or changes in cellular proliferation was observed.

A number of investigators have examined the penetration of asbestos into cells and tissues, assuming that a large number of fibers must penetrate the gastrointestinal mucosa to lead to carcinogenesis. Cell membranes appear to be resistant to penetration by sharp mineral fibers, and most fibers seen in cells are enclosed in phagocytic vacuoles or phagosomes (62). Rarely are fibers seen in cells other than phagocytes, and free fibers in nonphagocytes may be an artifact of the preparation (61). Penetration of the surface membrane of the gut may be particularly difficult because of the closely packed brush border, the longitudinal bundles projecting from the base of the brush border to form the “terminal web,” and the close apposition of gut epithelial membrane attached by

desmosomes (62). In addition, the mucous coating of the gut epithelium may help limit contact of the fiber with the gut wall and therefore inhibit penetration.

Cook (63) reviewed available studies investigating fiber accumulation in tissues and body fluids after ingestion of asbestos fibers. Cook does not conclude that asbestos fibers do not cross the intestinal barrier, but suggests the data indicate that only a small fraction of fibers penetrate the gut wall and that there is a “low probability for significant tissue accumulation and increased risk of cancer.” Meek (64) reaches essentially the same conclusion and points out additional factors that complicate interpretation of the evidence. These include a lack of characterization of the analytic methods used to examine the tissues; possible contamination from external sources; use of thin samples rather than bulk tissue residues, thereby limiting the area searched as well as creating possible artifacts by thin section preparation; and no conclusive confirmation of biological response associated with penetration. The last factor was investigated further by Meek (64). He showed that injecting amosite into the gut wall produced a short-term tissue response including granulomas characterized by dense masses of macrophages. However, 5 days after administration of amosite for 5 days there was no evidence of a macrophage response.

For asbestos to induce a neoplastic process, it is generally assumed that the fiber must penetrate the cell wall, and in the case of colon cancer, penetrate the mucosa of the colon. Donham et al. (56) tried to answer two questions: 1) is some minimum fiber penetration necessary to cause cancer, and 2) if fiber penetration does occur, do fibers act as direct carcinogens, tumor promoters, or cocarcinogens? To answer these questions, they X-irradiated localized segments of the colon, divided two strains of rats into three groups, and fed them a standard lab diet, a diet containing 10% cellulose, or a diet of 10% chrysotile. The X-irradiation produced a localized disruption of the colon with ulcerations, dysplasia, and chronic inflammation. At the irradiated sites there were four tumors in the rats fed cellulose, three tumors in the rats fed asbestos, and no tumors in the group fed the normal diet. The differences were not statistically significant, even if the asbestos and cellulose groups were combined. The histologic appearance of the tumors resembled those produced by X-rays alone. The number of animals studied was small (47 Holtzman rats and 90 Fisher rats), and further studies were recommended. These authors conclude that studies to date “indicate ingested asbestos may have only a weak effect, if any, with respect to development of

epithelial cancers of the large bowel” and that asbestos “does not seem to be co-carcinogenic or a tumor promoter in combination with disruption of mucus coating and localized X-irradiation.” There was also no difference between treatment groups in colon lesions including dysplasia, ulceration, chronic inflammation, and proliferative hyperplasia.

Patel-Mandlik and Millette (65) report data that appear somewhat contradictory. They used transmission electron microscopy (TEM) to assess the accumulation of asbestos fibers in the kidney cortex of four groups of rats gavaged twice weekly with 50 mg/kg of intermediate-range chrysotile asbestos. There was increased fiber recovery in 17 of the 20 exposed rats, a finding consistent with the passage of chrysotile across the gut wall. The length distribution of the recovered particles was highly skewed, with 97% being <3.1 µm long. Thus there were very few particles longer than 5 µm, the federal criteria used to count asbestos. Diameter of the particles was not measured, but small fibers were detectable as TEM was used and fibrils as well as bundles and clusters were counted. The biological significance of these very small particles is not

clear. Other evidence (such as implantation) show that these size particles do not produce tumors and may not be toxic (66).

A possible early indicator of neoplastic transformation is increased cell proliferation, which can be measured as an increase in DNA synthesis. Amacher et al. (67) administered chrysotile to rats by gavage and observed increased DNA synthesis in the stomach, small intestine, and colon, but not in the liver. The increases occurred at different time intervals: 1 day after dosing in the stomach, 7 days in the small intestine, and 28 and 63 days after dosing in the colon. However, these results do not appear to correlate with tumor incidence in lifetime studies, as no increased tumors are seen in these organs.

In summary, the lifetime exposure of animals to asbestos in the diet shows a consistent lack of colon (or even GI) tumors, even when the colon wall is damaged. Table 10 summarizes the experimental data on bioassays regarding the biological plausibility of asbestos causing colon cancer. The one observation supporting the hypothesis is increased cell proliferation as measured by DNA synthesis.

Ehrlich et al. (68) examined the

asbestos burden of 44 asbestos workers with colon cancer. Asbestos fibers and/or bodies were not present in 30 of 44 (68%) of the colon tumors and were present in 32%. Normal colon tissue was also examined in 9 of 14 cases, and asbestos bodies and/or fibers were found in 2 of the 9. These data indicate asbestos does enter and reside in the colon wall of a minority of asbestos-exposed workers with colon cancer and may be associated with the tumor tissue. However, fibers appear to be associated equally with normal tissue and tumors. Tissues of asbestos-exposed workers without colon cancer were not examined.

Corroborative evidence relevant to ascertaining a human colon cancer risk is generally either not available or does not show the effects observed in the lung (Table 11). Both genotoxic and nongenotoxic mechanisms are applicable to humans, and in the lung both may be operative. It is not clear that either occur in the GI tract. In the colon there are no data adequate to show long-term cell proliferation. Some genotoxic effects of asbestos have been shown in some cell types *in vitro* but to less of an extent than chemical carcinogens. None were found for cells from the gut epithelium.

**Table 10.** Bioassay observations relevant to ascertaining human colon cancer risk<sup>a</sup>

Supportive	Nonsupportive
Same route of administration as in humans is important for drawing inferences about human hazard.	<i>Humans are exposed via inhalation, with subsequent clearance and swallowing. Animals are exposed via ingestion. Exposure via inhalation results in fewer long fibers in gut. Adsorption of surfactant reduces hemolytic activity of asbestos. Toxicity is reduced for shorter fibers.</i>
Activity in several species makes it more likely a similar response will be present in humans.	<i>Ingestion studies have not consistently shown activity in rat or hamster.</i>
Tumor-site correspondence across species increases confidence that an effect is not species specific and unrelated to humans.	<i>Inhalation of asbestos produces fibrosis, bronchial carcinomas, and mesothelioma (mainly in rats), but not gastrointestinal cancers.</i>
Activity at several sites increases likelihood humans will show a similar response.	<i>Lifetime exposure via diet of large numbers of animals showed adrenal cortical tumors in male hamsters and thyroid tumors and leukemia in male rats. Neither was considered significant. Inhalation exposures that produce lung cancer, mesothelioma and fibrosis do not induce GI tumors.</i>
Target sites common to humans. Tumors in nonhuman organs are unlikely to be predictive.	<i>14% incidence of zymbal gland tumors in rats exposed to amosite, probably due to exposure to azoxymethane.</i>
1% asbestos in diet during entire lifetime of rats and hamsters produced no clinical signs of toxicity, decreased survival, or tumors. Tumors observed when there is no other toxic effect are considered more likely to occur in humans.	Tumors appearing under conditions causing toxicity are considered less likely to predict a human response. The offspring of mothers fed 1% asbestos in diet were smaller at weaning and later, but no clinical effects or tumors.
Genotoxic carcinogens generally induce tumors early; often they progress rapidly and cause death.	<i>There appear to be no increased tumors, and mortality is unaffected by asbestos ingestion.</i>
Increased tumors at several exposure levels implies a greater probability of hazard to humans.	<i>As much as 5% asbestos in the diet has not produced any increased tumor incidence.</i>
Background rate of colon cancer in animals is low.	<i>Cell proliferation is at a high rate, so inherent mechanisms must exist to repair genetic damage or eliminate altered cells before cancer progression can occur.</i>
Induced cell proliferation may promote development of tumors from initiated cells. A dose of 100 mg/kg chrysotile increased cell proliferation as measured by DNA synthesis 1.5 times or less from 28 to 63 days after exposure, and is suggestive of the potential for nongenotoxic mechanism.	No hyperplasia was observed in a lifetime ingestion study and is not supportive of a nongenotoxic mechanism.

<sup>a</sup>Regular type indicates the criteria being assessed. Italic type indicates that the weight of the evidence favors that criteria. If both column entries are in regular type, it indicates that the evidence is contradictory as to whether those criteria are supportive of the hypothesis.

**Table 11.** Nonbioassay corroborative observations relevant to ascertaining human colon cancer hazard<sup>a</sup>

Supportive	Not supportive
<i>The mechanism of action at the cellular level is applicable to humans.</i>	Mechanism not relevant to humans.
Agent causes mutations.	<i>Asbestos does not appear to cause mutations in most cell types.</i>
<i>Asbestos induces chromosomal changes which may activate a gene that transforms a cell into an immortal neoplastic condition or inactivate tumor-suppressor genes that suppress cell proliferation in vivo.</i>	<i>Genotoxic effects specific to certain cell types and evidence not clear as to occurrence in epithelial cells of colon.</i>
Asbestos induces lung cancer and mesothelioma, but a difference in surface charge and longer residence time than in the GI tract.	<i>Exposure to acid in stomach changes surface charge, may leach out ions that are required for fiber toxicity; clearance is shorter and not dependent on phagocytic macrophages.</i>
Hyperplasia in the target organ before tumor development suggests <i>tion</i> , a nongenotoxic mechanism of carcinogenesis.	<i>No increased non-neoplastic diseases of the GI tract (enteritis, ulceration-inflammation) and no hyperplasia have been noted in long-term studies.</i>

<sup>a</sup>Regular type indicates the criteria being assessed. Italic type indicates the weight of the evidence favors that criteria. If both column entries are in italic type, it indicates the observed effects are contradictory and are both supportive and not supportive.

**Table 12.** Effect of epidemiologic and experimental data on the hypothesis that asbestos causes colon cancer<sup>a</sup>

Criterion	Support	Detract	Indeterminate
Time order: >10–20 years latency Compatible			+
Strength of association			
Lung cancer SMR <2—no association		+	
Lung cancer SMR >2—weak association (possible positive bias from misdiagnosis)			+
Presence of biological gradient			
Exposure–response trend for lung cancer but not colorectal cancer (exposure = mppcf/years)		++	
Slight increase in SMRs when lung cancer SMRs >2 (possible positive bias from misdiagnosis)			+
Consistency			
No or weak association		+	
Biological gradient (all studies)		+	
Biological plausibility			
Lung cancer, yes	++		
Colon cancer, no		++	

mppcf-years, million particles per cubic foot-years.

<sup>a</sup>Overall conclusion for colon cancer: Low asbestos exposure: evidence of noncarcinogenicity in both humans and animals. High asbestos exposure: possible colon cancer carcinogen based on limited evidence in humans using surrogate measure of exposure, but probable disease misclassification bias. No evidence of carcinogenicity in animals and lack of exposure response within studies considered strongest evidence against colon carcinogenicity.

Genotoxic effects may be less likely to occur in the gut compared to the lung because of the preponderance of shorter fibers, shorter residence time, greater protective features, and shorter exposure time.

**Summary**

Table 12 summarizes the evidence evaluating the hypothesis that asbestos causes colon cancer, using well-known criteria for determining whether an association is causal.

The potential confounding effect of four nonoccupational risk factors was not considered to significantly bias the results of the epidemiologic studies. The risk from alcohol consumption and smoking is negligible, and so these factors cannot bias the results. Obesity modestly increases risk, and physical activity is somewhat protective. However, the potential confounding effect

is considered minimal. Misdiagnosis is likely to bias the risk estimates so the SMRs for colon cancer are spuriously elevated. Use of the combined colon and rectal cancer instead of just colon cancer also appears to overestimate risk.

The evaluation of human risk was largely confined to studies where the risk of colon or colorectal cancer was determined among workers for whom 10–20 or more years had elapsed since date of hire, a surrogate measure of date of first exposure. It is thought likely that among this group there is sufficient time to ascertain the occurrence of disease caused by exposure, as the occurrence of disease earlier than 20 years since first exposure is likely due to some other causes.

Among asbestos workers with lower exposures, as measured by the risk ratio for

lung cancer, there is no apparent increased risk of colorectal cancer. Among asbestos workers with higher exposure (lung cancer SMR >2), there is about a 50% increase in colorectal cancer. The consistent lack of an association at lower exposures detracts from the hypothesis. The weak association at higher exposures is considered to be indeterminate because of the possibility that misdiagnosis was the reason for the increased colorectal cancers. The reduction in SMRs for colon cancer compared to colorectal cancer observed in five studies where both were presented further weakens the case for a casual relationship for colon cancer.

The overall evidence from within individual studies suggests there is no biological gradient. Although there are few studies assessing exposure response and the estimates of exposure are poor, there is a consistent finding of an exposure–response trend for lung cancer (five of seven studies), and an equally consistent finding of no apparent exposure–response trend (six of seven studies) for CRC. The lack of any consistent findings showing clear exposure–response relationships detracts from the hypothesis.

None of these cohorts have information on colon cancer risk factors such as diet, obesity, or physical activity, so possible confounding cannot be assessed directly. Most of the occupations do not appear to be sedentary. Whether these factors have reduced the SMRs is not known, but because the association is not strong, the potential confounding effect is considered minimal.

The animal studies are consistently negative in showing no increase in colon tumors and no increase in mortality or morbidity in at least two species. The finding of increased cell proliferation in the colon after asbestos dosing suggests several possible interpretations including a possible nongenotoxic mechanism, cytotoxic dose, and/or mechanisms to repair damage. Based on animal studies, it is not biologi-

cally plausible that asbestos exposure would cause colon cancer in humans exposed via inhalation and at much lower concentration levels. These data detract from the causal hypothesis.

Corroborative evidence suggests that asbestos can be weakly genotoxic and/or act as a tumor promoter. The data are relevant to the respiratory system and to some but not all cell types. The relevance of these data for the colon is not clear.

There are no animal or human data supporting an increased risk of colon cancer at lower levels of asbestos exposure. High exposure to asbestos does not produce colon cancer in animal studies. A slight increase in risk was observed in human populations when lung cancer SMRs were the surrogate measures of exposure, but there was no exposure response for colon when quantitative estimates of exposure were available. In these same studies an exposure-response relationship was observed for lung cancer. These results are among the strongest epidemiological evidence detracting from the argument for a causal association. In conclusion, asbestos exposure does not appear to increase the risk of colon cancer.

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Abstract deadline is February 1, 1995.

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