

## Asbestos-Induced Gastrointestinal Cancer: An Update

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### Abstract

Asbestos-related diseases, such as malignancies and asbestosis, remain a significant occupational and public health concern. Asbestos is still widely used in many developing countries despite being a recognized carcinogen that has been banned over 50 countries. The prevalence and mortality from asbestos-related diseases continue to pose challenges worldwide. Many countries are now experiencing an epidemic of asbestos-related disease that is the legacy of occupational exposure during the 20th century because of the long latency period (up to 40 years) between initial asbestos exposure and exhibition of disease. However, the gastrointestinal (GI) cancers resulting from asbestos exposure are not as clearly defined. In this review, we summarize some of the recent epidemiology of asbestos-related diseases and then focus on the evidence implicating asbestos in causing GI malignancies. We also briefly review the important new pathogenic information that has emerged over the past several years that may account for asbestos-related gastrointestinal cancers. All types of asbestos fibers have been implicated in the mortality and morbidity from GI malignancies but the collective evidence to date is mixed. Although the molecular basis of GI cancers arising from asbestos exposure is unclear, there have been significant advances in our understanding of mesothelioma and asbestosis that may contribute to the pathophysiology underlying asbestos-induced GI cancers. The emerging new evidence into the pathogenesis of asbestos toxicity is providing insights into the molecular basis for developing novel therapeutic strategies for asbestos-related diseases in future management.

**Keywords:** Asbestos; Gastric cancer

### Introduction

Asbestos, which is a naturally occurring hydrated silicate fiber, is ideal for a variety of construction and insulation purposes. In industry, utilization of asbestos began in the 1850s, but its harmful risks for causing pulmonary malignancies (pleural mesothelioma and bronchogenic carcinoma) and other nonmalignant disease (pleural plaques, asbestosis) as well as other type of cancers were increased by the middle of the 20<sup>th</sup> century [1,2]. The first cases of asbestos associated pulmonary fibrosis were evident in the early 1900s, and Cooke coined the term “asbestosis” in 1927 [3]. Bronchogenic carcinoma caused by asbestos exposure was established by the mid-1950s. The relationship between asbestos exposure and mesothelioma as well as with gastrointestinal (GI) cancers was recognized by the 1960s. In the early 1970s, the United States placed a moratorium on asbestos use, and over 50 countries have banned or severely restricted asbestos use [4]. Although asbestos mainly causes pulmonary diseases resulting from inhalation of dusts containing asbestos fibers, there are accumulating studies suggesting that GI malignancies can also result, possibly by oral ingestion of asbestos fibers. The purpose of this review is to summarize the important epidemiological, *in vivo*, and *in vitro* information that has increased our understanding of asbestos-related GI cancers as well as emerging novel molecular targets.

### Asbestos Fiber Types

Asbestos is a term applied to naturally occurring fibrous silicate minerals that have high tensile strength, the ability to be woven, and resistance to heat and most chemicals [5]. Asbestos fibers are still being used in developing countries in part because they can provide thermal insulation and have great tensile strength, because of their withstanding ability from fire, heat, and acid [6-9]. The World Health Organization (WHO), the National Institute for Occupational Safety and Health (NIOSH), and the Occupational Safety and Health Administration (OSHA) define the regulated form of asbestos as fibers whose length is greater than 5 µm and whose length:width ratio is 3:1 [8]. Asbestos is derived from two types of minerals, serpentine and amphiboles. Chrysotile (white) asbestos, the only serpentine fiber, accounts for nearly 95% of the asbestos used for industrial purposes around the world and is still commercially used [8]. Chrysotile asbestos has characters likely as curled, wavy, flexible, easily breakable, and soluble in tissues.

Amphibole asbestos fibers (e.g. amosite, crocidolite, tremolite, anthophyllite, and actinolite, etc) are rigid, sharp, highly resistant to chemical and biological degradation, and, not surprisingly, have a longer biological persistence compared with chrysotile fibers [8-10]. Amphibole asbestos consists of double-chain silicates that are also characterized by hydrated silicate units similar to chrysotile. The most common commercially important amphiboles are amosite (brown asbestos) and crocidolite (blue asbestos); with an iron content of (~27-30%) as compared to chrysotile's iron content primarily as a surface contaminant (6-8%).

### Exposures to Asbestos

#### Occupational exposures to asbestos

Diseases related with asbestos exposure are a common clinical problem and a major health concern worldwide. Epidemiologic studies have established that exposure to asbestos fibers causes pulmonary fibrosis, pleural abnormalities, and malignancies such as bronchogenic carcinoma and mesothelioma, including peritoneal mesothelioma [6,8,11-13]. Many workers worldwide, including North America, Western Europe, Scandinavia, and Australia, had sustained asbestos exposure through the 20<sup>th</sup> century that peaked in the 1970s when asbestos-related diseases were well established and regulatory measures invoked [4,8,13]. An estimated 20% to 40% of adult men who worked past occupations may have exposed with asbestos in France over the past century [14]. In the most highly affected age groups of occupationally-exposed asbestos workers, mesothelioma of the pleura

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and peritoneum accounts for over 1% of all deaths [15]. Additionally, 5% to 7% of all lung cancers are potentially related with occupational exposures to asbestos [13]. In 11 industrialized countries that had used the most asbestos 2.0 to 5.5 kg/capita/year over 25 years had the highest incidence of mesothelioma [16]. The annual number of asbestos-related cancer deaths in worldwide-workers is estimated to be 100,000 to 140,000 [17]. There are an estimated 20,000 new cases of lung cancer and 10,000 cases of mesothelioma attributable to asbestos exposure every year in Western Europe, North America, Japan, and Australia [18]. Recently, Britain has reported the highest mesothelioma death rate in the world; with 1740 deaths in men (1 in 40 of all male cancer deaths below age 80) and 316 in women in 2006 [15]. In Australia, the incidence of mesothelioma is predicted to reach 18,000 by 2020, with 11,000 cases yet to appear [19]. In America, NIOSH confirmed a strong exposure-response relation between chrysotile asbestos exposure and mortality from lung cancer, and estimates that current occupational exposures to asbestos even at OSHA's permissible exposure limit will cause 5 deaths from lung cancer and 2 deaths from asbestosis in every 1,000 workers exposed for a working lifetime [20]. Similar findings were reported in Chinese chrysotile miners and, notably, they detected an increased risk of GI cancers [21].

### Environmental exposures to asbestos

Non-occupational and/or environmental exposure to asbestos remaining construction materials in homes, schools, and commercial buildings is also a serious and often neglected problem in developed countries throughout the world [17]. Also, the causal relationship between asbestos exposure and GI cancers is unclear [22]. As compared to crocidolite, there is more evidence linking non-occupational and environmental chrysotile asbestos exposure to GI cancers possibly resulting from contaminated drinking water as the most likely route of GI entry [22]. In developing countries, large quantities of asbestos

have accumulated in thousands of buildings and the potential for asbestos contamination of drinking-water supplies by asbestos-cement water pipes [17]. In Norway, over 90% of the water pipes contain asbestos [17,23]. Despite continued and repeated warnings about the toxicity and carcinogenicity of asbestos-containing materials, large numbers of people of all ages, including young children, are potentially exposed to asbestos [23,24]. Women residing in Canadian asbestos mining communities have an increased mortality rate from several cancers including those of the respiratory and GI tract [24]. The environmental exposures to asbestos following in-home dust from the windowsill in communities near mines, on the surfaces of roads and yards in a contaminated community, and widespread environmental contamination can result in malignant mesothelioma [15,25,26]. Although the GI tract has a large ability of transporting and eliminating the fibers rapidly from the GI tract, the relation between transport and retention of asbestos fibers in the development of GI cancers is an important consideration that has not been well investigated [22].

## Epidemiological Evidence: Gastrointestinal Cancers with Asbestos

### Asbestos exposure sources and gastrointestinal cancers

Several types of cancer have been linked to asbestos exposure. The association between asbestos and cancers, such as lung cancer and mesotheliomas of the pleura and peritoneum, is well established [13,27,28]. Asbestos exposure has been consistently linked with outcomes of GI tract-related cancers such as the stomach [23,29], colon [23,30] and esophagus [31]. The association of GI cancers with asbestos was first shown by Selikoff et al. [28]. Since then over 50 publications have been examined the relationship between asbestos exposure and cancers of the GI tract, colon/colorectal cancer and stomach cancer. These studies are summarized in Table 1. All asbestos fiber types have

End point	Fiber Type	Occupational Exposure	Ingested/Water	Animal Studies	Non-Occupational/ Environmental Exposure
GI Cancer (general)	Amosite/Termolite Chrysotile	3(+) <sup>b</sup> 6(-) <sup>c</sup>	1(-) <sup>d</sup>	2(-) <sup>a</sup> 1(+) <sup>e</sup>	
	Crocidolite	1(-) <sup>f</sup>			1(+) <sup>g</sup>
	Unknown	2(-) <sup>b</sup> 6(+)	3(-) <sup>f</sup>		
Colon/colorectal Cancer	Amosite/Termolite Chrysotile	1(-) <sup>k</sup> 1(-) <sup>k</sup> 1(-) <sup>j</sup>		3(+) <sup>m</sup>	
	Crocidolite				1(-) <sup>n</sup>
	Unknown	1(-) <sup>p</sup> 6(+) <sup>q</sup>	1(+) <sup>r</sup>	1(+) <sup>o</sup>	
Stomach cancer	Amosite/Termolite Chrysotile	1(-) <sup>k</sup> 1(-) <sup>k</sup>	2(+) <sup>s</sup>		
	Crocidolite	1(-) <sup>i</sup> 3(+) <sup>u</sup>			
	Unknown	6(+) <sup>v</sup>	2(+) <sup>w</sup>		

**Note:** The number indicates how many articles were found with a positive (+) or negative (-) association between asbestos and disease. Modified from Bunderson-Schelvan M [22].

"Unknown" exposures indicate the data came from occupational exposure matrices, including textiles, insulation, or cement workers.

### Sources

<sup>a</sup>McConnell et al. (1983) [75,76]; <sup>b</sup>Finkelstein (1984) [86]; Wang et al. (2013) [21]; Weiss (1977) [87]; <sup>c</sup>Albin et al. (1990) [88]; Berry et al. (1983) [89]; Finkelstein (1989) [90]; Gardner et al. (1986) [91]; Pira et al. (2009) [92]; Thomas et al. (1982) [93]; <sup>d</sup>Toft and Meek (1983) [51]; <sup>e</sup>Jacobs et al. (1978) [73]; <sup>f</sup>Reid et al. (2004) [94]. <sup>g</sup>Weiss (1995) [66]. <sup>h</sup>Hodgson and Jones (1986) [50]; Tsai et al. (1996) [95]. <sup>i</sup>Kang et al. (1997) [31]; Lacquet et al. (1980) [96]; Lumley (1976) [52]; Newhouse et al. (1985) [97]; Santibañez et al. (2008) [98]; Selikoff et al. (1974) [99]; <sup>j</sup>Browne et al. (2005) [49]; Harrington et al. (1978) [47]; Levy et al. (1976) [48]; <sup>k</sup>Strand et al. (2010) [100]; <sup>l</sup>Clin et al. (2011) [56]; <sup>m</sup>Amacher et al. (1974) [69]; Corpet et al. (1993) [72]; Donham et al. (1980) [101]; <sup>n</sup>Reid et al. (2004) [94]; <sup>o</sup>Reid et al. (1987) [102]; Raffin et al. (1989) [34]. <sup>p</sup>Corpet et al. (1993) [72]; <sup>q</sup>Garabrant et al. (1992) [61]. <sup>r</sup>Albin et al. (1990) [88]; Aliyu et al. (2005) [44]; Fang et al. (2011) [41]; Gerhardsson de Verdier et al. (1992) [60]; Germani et al. (1999) [30]; Szeszenia-Dabrowska et al. (1998) [35]; <sup>s</sup>Kjaerheim et al. (2005) [23]; <sup>t</sup>Kanarek et al. (1980) [45]; Polissar et al. (1983) [46]. <sup>u</sup>de Klerk et al. (1989) [103]; <sup>v</sup>Armstrong et al. (1988) [54]; Botha et al. (1986) [104]; Newhouse et al. (1988) [53]. <sup>w</sup>Enterline et al. (1987) [55]; Lumley (1976) [52]; Raffin et al. (1989) [34]; Rushton et al. (2012) [105]; Santibañez et al. (2012) [106]; Sun et al. (2008) [33]. <sup>x</sup>Anderson et al. (1993) [29]; Kjaerheim et al. (2005) [23].

**Table 1:** Publications on asbestos-induced gastrointestinal disease.

been implicated in possibly mediating GI cancers based upon studies involving occupational epidemiologic assessments, ingested water epidemiologic studies, animal *in vivo* studies, as well as some non-occupational asbestos exposure studies. Some indications were found in a study among Norwegian lighthouse keepers [23]. Recently, the evidence for causal associations between asbestos exposure and selected cancers was reviewed by a multidisciplinary committee appointed by the Institute of Medicine, U.S. National Academy of Sciences. Sufficient evidence was found for laryngeal cancer, while only suggestive evidence was found for pharyngeal, stomach, and colorectal cancers [32]. The most likely route of exposure for GI disorders due to asbestos is in contaminated drinking water. However, the evidence linking occupational asbestos exposure to stomach cancer is more convincing than exposure through the drinking water [33-35]. The drinking water contaminated with asbestos fibers diffused through asbestos-containing water pipes or natural contamination has been noted [36,37]. Millette et al. [38] reported that asbestos fibers of <1 million fibers/L, which the majority of water consumers are in fact exposed to, is not be a harmful dose. However, people in some areas are exposed to concentrations of over 1 billion fibers/L of asbestos with various size (less than 5  $\mu\text{m}$  in length), a dose that may account for GI cancers [37]. Asbestos fiber from cement pipelines results in an average of 1  $\mu\text{m}$  fiber pieces due to natural erosion [38]. Furthermore, diet supplies (food, beverages, and orally administered drugs) contaminated by asbestos in water or airborne must also be considered as a possible source to GI cancer [39].

### Gastrointestinal tumor with asbestos

As summarized in Table 1, many studies have shown an association between asbestos exposure GI cancers involving the esophagus, stomach, intestines, and colorectal regions. Ehrlich et al. reported that the presence of asbestos bodies and fibers in the colon mesentery from adenocarcinoma by asbestosis in colon increased interest [40]. In 2011, one article showed that a number of occupations and industries, particularly those with low physical activity and those involving exposure to asbestos and other pollutant was observed to excess colon cancer risks in occupational histories collected from 15,463 incident cancer cases [41]. In addition, recent study has shown that inhaled asbestos fibers can be translocated from the lung to extra pulmonary tissues or other organs including brain, liver and kidney, though they have been demonstrated only in the pleura and peritoneum [42,43]. The presence of asbestos-induced pleural plaques and risk of colorectal cancer risk increased with based on years of asbestos exposure among men occupationally exposed to asbestos, especially those with evidence of nonmalignant asbestos-associated radiographic changes [44]. Stomach malignancies caused by asbestos exposure have been well documented [22,23,29,45,46], and associations between asbestos exposure and colon and esophageal cancer have been noted [23,30,31]. In contrast, several reports showed that environmental asbestos exposure via the drinking water may not increase GI-related cancers, including stomach cancer [47-51]. The discrepant results among these studies might be attributed to varying amounts of the asbestos released from water pipelines at various times, the asbestos composition in the water, and methodologic differences [22]. Despite these differences in environmental exposure, asbestos-related stomach cancer following occupational exposure is the best validated to date [10,33-35,52-55]. Recently, asbestos exposure is linked with colorectal cancer in 285 cases of cancers while confirming the established relationship between asbestos exposure and pleuropulmonary and peritoneal cancers [56]. Some studies have concluded that a positive association may exist between asbestos exposure and GI cancer [41,44,56-61]. Among chrysotile miners, an increased risk related with gastrointestinal cancer

was also detected [21]. Of note, others have failed to demonstrate a clear association between asbestos exposure and GI cancers as noted in Table 1 [59,62]. Furthermore reviews and meta-analyses have not clarified the relationship between exposure to asbestos and the risk of GI cancer [63-68].

### Mechanism Study of GI Cancer by Asbestos

As shown above, the carcinogenic potential of asbestos fibers (chrysotile and amphiboles) were found in samples of city drinking water or some diet supplies from several countries. Possible sources of such contamination include asbestos-cement conduits, widely used in city water mains, and asbestos filters, used in the clarification of beverages. The earliest finding is that neoplastic transformation can down-regulate the cancer cell proliferation caused by reducing DNA synthesis [69]. They suggested that the ingested asbestos (chrysotile) can attack the gastrointestinal mucosa and influences regulation of steady-state DNA synthesis in the gastrointestinal tract [69]. Increased DNA synthesis was detected in the small intestine and colon of rats following ingestion of UICC standard chrysotile A (5 mg/kg for 2 wk) [69]. In addition, augmented DNA metabolism detected by the incorporation of [3H] thymidine into DNA in tissues lining the GI tract following ingestion of asbestos (50 mg/day, short or long term) was observed [70]. In cellular immunity, patients exposed to asbestos dust evaluated showed significantly lower values of phytohaemagglutinin-induced proliferative and cytotoxicity [71]. Furthermore, induction of aberrant crypt foci indicating colon carcinogenesis using the aberrant crypt focus assay was shown both crocidolite- and chrysotile (3 treatments of 33 mg/kg each) -induced in the colon of rats [72]. Additional studies indicated changes in the mucosal lining cells of the ileum, rectum, and colon along which were consistent with a mineral-induced cytotoxicity after ingestion of 50 mg/day chrysotile asbestos detected by cellular debris and Alcian blue staining [73]. *In vivo* intestinal permeability studies with long term ingested chrysotile in the drinking water (0.5 g/L), absorptional ability of non-metabolizable sugars was decreased in GIT [74]. But, McConnell group showed that toxic or neoplastic lesions are not observed in gastrointestinal tract and mesothelium in Fischer 344 rat and in Syrian golden hamsters given the diet with amosite (at a concentration of 1% of pelleted diet) for their lifetime even though increasing C-cell carcinomas of the thyroid and monocyte significantly [75,76].

It is well established in pulmonary fibrosis caused by asbestos that some of the important molecular mechanisms are related with asbestos-induced ROS productions inducing a fail of mitochondrial dysfunctions, such as protection of mtDNA integrity and protection of intrinsic apoptosis in patients with pulmonary fibrosis have increased oxidative stress as measured by various [5,77-79]. Although mechanistic studies related with GI cancer or GI disorder by asbestos at the cellular level are lacking using epithelial cells of them, expose with asbestos result in change a surface charge, crystallization, morphologic and biochemical changes of epithelium that resemble effects of classical tumor promoters on target cells in both the pulmonary and GIT systems [80]. Also, ingested asbestos gastrointestinal system can go through the lungs using a lymphohematological route and inducing to mesothelial cell proliferation, which may lead to malignancies [81]. But, the mechanical studies for cancer of the gastrointestinal tract caused by ingested asbestos are still needed. Ingested asbestos has not been shown to cause cancer in animal studies [82], but there is experimental evidence of increasing DNA strand breaks in intestinal cells from rats gavaged with aqueous solutions of asbestos fibers [83]. Recent studies addressed that orally ingested and exposed asbestos can effect on GI and other tissue such as liver and the lungs and pleura [81,84].



Asbestos-exposed pulmonary and gastrointestinal tract increase the levels of 8-oxo-7,8-dihydroguanine causing oxidative-damaged DNA in the lung and internal organs [84].

## Conclusions

The accumulating evidence implicate that all forms of asbestos exposure appear to minimally increase the risk of stomach cancer as well as possibly other GI cancers involving the larynx, esophagus, intestines and colorectal regions. As compared to the pulmonary effects, however, these effects appear much less robust and not all studies demonstrate a positive association suggesting that the risk is small. The strongest association between asbestos exposure and GI cancers is with stomach cancer, but even there are discordant studies. Further, the International Agency for Research on Cancer (IARC) concluded that the overall evidence linking asbestos to stomach cancer is limited [22,85]. The route of asbestos exposure via the respiratory tract (most common source of asbestos exposure overall) as compared to asbestos-contaminated drinking water requires further epidemiologic investigations using well-defined cohorts as well as animal *in vivo* studies. The molecular basis of GI cancers arising from asbestos exposure also awaits further study. There have been significant advances in our understanding of mesothelioma and asbestosis that may advance our knowledge of the pathophysiology underlying asbestos-induced cancers, including GI cancers. The emerging new data are informing the pathogenesis of asbestos toxicity and providing novel insights into the molecular basis for developing unique therapeutic targets for possibly diagnosing and managing asbestos-related diseases.

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