FILE NAME: Household Contact (HC)

DATE: 1993 Apr

DOC#: HC019

DOCUMENT DESCRIPTION: Journal Article - Natural History and Epidemiology of Malignant Mesothelioma

# Natural History and Epidemiology of Malignant Mesothelioma*

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**Asbestos exposure constitutes the primary cause of pleural and peritoneal mesothelioma in humans. Risk relates to the duration and intensity of exposure. Thus, those exposed at younger ages are at higher lifetime risk. Families of asbestos workers exposed to asbestos on hair and clothing as well as to asbestos items brought home from the workplace are also at risk, as are employees working in the same vicinity as asbestos workers. The public health significance of exposure from asbestos in public and private buildings remains controversial. Malignant mesotheliomas is difficult to diagnose and carries a poor prognosis. Chemotherapy with single or multiple agents has thus far been disappointing, but doxorubicin and cisplatin or mitomycin and cisplatin are probably most active with response rates in measurable disease of 25%. Palliative radiotherapy is also problematic since differences between tumor cytotoxicity and pulmonary tolerance are small and radiation pneumonitis may significantly impair quality of life.**

***(Chest 1993; 103:373S-76S)***

## Asbestos: An Overview

The link between asbestos and asbestosis, lung cancer, and mesothelioma is by now well established, although questions remain about the duration and intensity of exposure needed to initiate carcinogenesis. Millions of Americans have been occupationally exposed to asbestos. Although some uses of asbestos have been curtailed, because of the characteristics that make it attractive industrially and its relatively low cost, asbestos is still used widely. Given the wide occupational exposure and the fact that, until 1972, asbestos was sprayed in schools and other public buildings, physicians should be aware of potential public health implications. This article will briefly review asbestos use, mineralogy, and mechanisms of carcinogenicity, and review the diagnosis and management of malignant mesothelioma.

Asbestos is the commercial name for a hydrated magnesium silicate fiber comprising 2 types, the serpentine and the amphiboles. The serpentine chrysotile fibers are curly and pliable, whereas the amphiboles (crocidolite, amosite, anthophyllite, tremolite, and actinolite) are needle-like.[1]

### *Asbestos Use*

Prized industrially for its resistance to heat and combustion, asbestos was used abundantly in ships and other combat material during World War II. When the war ended, industrial and consumer use increased for insulation. Asbestos was also sprayed on the interior structural surfaces of many public and private buildings between 1946 and 1972, including as many as 10% to 15% of the nation's schools. The public health significance of this exposure as well as the cost effectiveness of asbestos removal are controversial.[1]

Asbestos continues to be used extensively in cement, in ceiling and floor tiles, and in automobile, but not airplane, brake linings. Currently, Canadian chrysotile accounts for about 90% of the asbestos used in the United States. More carcinogenic types of asbestos continue to be used, however. Amosite, for example, is used in ships because it resists salt water and some fillers contain anthophyllite.

### *Carcinogenicity*

One of the most inert compounds known, asbestos appears to provoke carcinogenesis through its physical rather than its chemical composition: A 10:1 length-to-width fiber ratio is associated with carcinogenesis; additionally, the fibers must be fairly fine. Indeed, fiberglass and other fibers milled to this standard are also carcinogenic in laboratory animals, although the fiberglass is commonly used in homes.[2]

Amphiboles are about 10 times as carcinogenic as chrysotile. (The fibers with the highest carcinogenic potential are mined in South Africa and other countries, whereas most chrysotile is mined in Canada.) Crocidolite has been associated with a high risk of malignant mesothelioma,[4] whereas amosite appears to carry an intermediate risk. Chrysotile shows the weakest association with malignant mesothelioma.[5] Nonetheless, chrysotile has been shown to cause mesothelioma in laboratory animals.[6] Whether human cases of malignant mesothelioma linked to past chrysotile exposure were caused by the serpentine fiber itself or by amphibole contamination[5,6] remains controversial since such contamination is common.

### *Mechanisms of Carcinogenesis*

Fibers enter the distal airway. About two thirds of the daily dose is eliminated by coughing and swallowing, which may be the mechanism for the development of peritoneal mesotheliomas. As macrophages try to engulf the fibers remaining in the lung, free radicals and lysosomal enzymes are liberated, which probably accounts for the fibrosis that develops.[1]

### *Regulatory Limits*

As the scope of asbestos' effects on health became apparent, attempts to limit permissible exposures grew. By 1970, the Occupational Safety and Health Administration had established 5 fibers per cubic milliliter of air as the standard acceptable exposure, which legally exposed asbestos workers to up to 4 million fibers a day. By 1976, the standard had been reduced to 2 fibers and is currently 0.2 fibers per cubic milliliter of air. Above these limits, respirators, protective clothing, and shower and changing facilities become mandatory. Only exposures to fibers longer than 5 μm are regulated currently, however. Present data do not allow conclusions regarding whether there is a safe threshold

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level for asbestos exposure.

## Asbestos-Related Cancer Risk

Asbestos workers are currently at substantially higher risk for cancer than they are for pulmonary disease. About 8% of asbestos workers will die of asbestosis. While the average American has about an 18% chance of developing and dying of any malignancy, for an asbestos worker this risk is close to 50%, with most of the tumors involving the lung. Currently an estimated 3% of all cancers are asbestos-related, most of which are primary in the lung. The incidence of lung cancer in the United States in nonsmoking, non-asbestos-exposed individuals is about one per million man years, and the expected incidence of lung cancer in the population at large is about 7%. In a cohort of asbestos workers, however, the risk of lung cancer increases to approximately 25%.[10,11]

Asbestos, which is directly cytotoxic, efficiently adsorbs hydrocarbons, which probably accounts for the higher risk of lung cancer in persons who have histories of asbestos exposure and cigarette smoking. (Interestingly, there is no association between cigarette smoking and malignant mesothelioma, and they may even be negatively correlated. This most likely reflects earlier development of and death from lung cancer in smokers, removing them from the risk pool for mesothelioma.) As noted, the risk of lung cancer in the nonsmoking general population with no asbestos exposure is small. This risk increases about 6-fold in nonsmokers who have been exposed to asbestos, still a fairly small risk. However, conservative estimates of the lung cancer risk in smokers with a history of asbestos exposure suggest that their risk for lung cancer increases almost 60-fold (Table 1).[12]

The incidence of gastrointestinal malignancy is also higher in asbestos workers, but whether asbestos is causally related to these tumors is controversial. Anecdotal reports also detail head and neck tumors and B cell malignancies such as myeloma and lymphoma.[10,11]

## Malignant Mesothelioma

Not until 1960, with the publication of a series of patients with mesothelioma by an astute internist in South Africa, was the existence of malignant mesothelioma as a discreet clinical entity and its relation to asbestos exposure, both occupational and bystander risk, established.[13] The annual incidence of malignant mesothelioma in the United States is not known with certainty because cancer mortality in the United States is reported by site of the primary lesion, not the morphology. The incidence is estimated to be approximately 2,200 cases per year or about 12.1 cases per million white men,[14] but in asbestos workers, this risk rises to 8% to 13%. The incidence appears to be increasing,[15] probably reflecting the long latency period from asbestos exposure to clinical disease and the high numbers of workers exposed to asbestos in the decades following World War II.

Table 1—*Age-Standardized Death Rates per $10^5$ Man Years Showing Synergism Between Asbestos Exposure and Smoking for Lung Cancer**

| | No Asbestos | Asbestos |
|---|---|---|
| Nonsmoker | 1 | 6 |
| Smoker | 11 | 59 |

*Data adapted from Hammond et al.[12]

Risk of developing malignant mesothelioma varies, depending on the duration and degree of exposure. Because so many people have been exposed to asbestos, the mathematic risk of developing malignant mesothelioma can actually be calculated and equals a constant (which comprises the intensity and duration of the exposure) multiplied by the time since the first exposure to the third or fourth power. Thus, someone exposed at age 20 years has no higher risk per year for any given exposure, but accumulates a higher lifetime risk than someone who is exposed to asbestos at age 50. In fact, given the latency period, which is 20 to more than 40 years, moderate asbestos exposure would probably carry few medical consequences for asbestos workers 55 years or older. Asbestos workers with heavy exposure have a higher risk of developing peritoneal mesothelioma, whereas those exposed for relatively brief periods are at higher risk of developing pleural primaries.

### *Risks to Workers' Families*

The families of asbestos workers have an approximately 1% risk of malignant mesothelioma. In most cases, this risk arises because of asbestos contamination of work clothes or, less frequently, manufactured articles (*eg*, textiles) workers have brought home. Projections based on the average family size in 1950 suggest that about up to one third of cases of malignant mesotheliomas may develop in family members of asbestos workers.

### *Diagnosis and Management of Malignant Mesothelioma*

*Patient History:* A comprehensive history for patients suspected of having malignant mesothelioma must focus on a period of 20 to 40 years before and should include the occupations of family members living with the patient during this interval. Even the most comprehensive history may fail to establish asbestos exposure in about 30% of cases. For example, a cluster of cases of malignant mesothelioma with no stated history of asbestos exposure was explained when 2 patients being treated at the Dana-Farber Cancer Institute realized they knew each other. Both had worked at a factory manufacturing asbestos paper filters for cigarettes. When epidemiologists traced the histories of the approximately 50 people who had worked in that plant, they found that most had already died of malignancies, either lung cancers or mesotheliomas.[16]

Malignant mesothelioma is difficult to diagnose. Most patients come to medical attention when they develop dyspnea, chest pain, or both symptoms. Examination will usually reveal a large, unilateral effusion; only about 5% of patients have bilateral disease at diagnosis.

*X-Ray Findings:* Only about 20% of patients with pleural mesothelioma demonstrate characteristic signs of asbestosis—a low diaphragm, interstitial fibrosis, or even pleural plaques on chest films. Since the development of both malignant peritoneal mesothelioma and asbestosis requires longer asbestos exposures, about 50% of patients with primary peritoneal tumors will demonstrate x-ray evidence of asbestosis and pleural calcifications. Other than being markers for prior asbestos exposure, the calcifications are of no medical significance.

Patients with late-stage disease often develop a character-

istic scoliosis toward the side of the lesion as the lung is encompassed by tumor and cannot be fully expanded, pulling the mediastinum to the ipsilateral side. Other primary tumors almost always displace the mediastinum to the contralateral side with increased tumor volume.

Computed tomography is helpful in determining disease extent and, in about 50% of patients, will also reveal pleural calcifications not large enough to be visible on the chest x-ray.

*Pathologic Verification:* Malignant mesothelioma remains a diagnostic challenge. An adequate biopsy specimen must be obtained. When pleural mesothelioma is suspected, part of the sample should be placed in glutaraldehyde preservative. Pathologists may have difficulty differentiating mesothelioma from adenocarcinoma. With a PAS (periodic acid-Schiff) stain, both histologies stain pink. However, the distinction can be made after diastase digestion. Adenocarcinomas remain positive, but mesotheliomas become negative. By electron microscopy, mesotheliomas characteristically have long, lush microvilli that are helpful in diagnosis.

*Prognostic Variables and Causes of Mortality:* Because malignant pleural mesothelioma is generally locally invasive, extensive work-up of other sites is usually unnecessary. Fever of unknown origin and clotting abnormalities, including an elevated platelet count, are common and indicate a poor prognosis. Patients generally die of local extension and respiratory failure. Occasionally, tumor extension below the diaphragm may result in death from small bowel obstruction. In a series of patients at Dana-Farber,[17] about 10% had tumor invasion of the pericardium or cardium and died of arrhythmias or heart failure, while 5% died of stroke.

Two early series of 69 patients from Mount Sinai[18] and 40 patients from Dana-Farber[17] suggested that women survived longer than men, but a larger series of 180 patients at Dana-Farber was unable to confirm this finding.[19] Similarly, the Mount Sinai series identified stage I disease as an independent independent variable, but the Dana-Farber series could not confirm this.[18,19] The presence of symptoms for more than 6 months before diagnosis (indolent disease) suggests slower disease progression. Epithelial histology has been an independent variable in both series, as have younger age and better performance status.

In the Dana-Farber experience, recent patients with malignant peritoneal mesothelioma have had a better prognosis than those with pleural primaries, which probably reflects the technical ease of administering intraperitoneal chemotherapy as well as the fact that multiple resections of a peritoneal mass are possible. Four of a cohort of six carefully selected patients with malignant peritoneal mesothelioma treated in a phase I Dana-Farber trial 10 years ago are currently disease-free. About one third of the 25 patients treated in a subsequent phase II series are disease-free at from 2 to 3 years.[20,21] Pleuropneumonectomy and chemotherapy were independent predictors of longer survival in both series.

The response rate to single-agent chemotherapy is generally 0% to 20%, with the highest single agent response rate for doxorubicin. Mitomycin and cisplatin may be active in combination.

Only a few randomized trials have been conducted. The Eastern Cooperative Oncology Group assessed radiotherapy with or without doxorubicin, but results have not yet been published. When the Southwest Oncology Group tested doxorubicin and cyclophosphamide with or with dacarbazine, no benefit was found for the addition of dacarbazine. The Cancer and Leukemia Group B assessed cisplatin combined with either doxorubicin or mitomycin, but no difference was evident in the response rates (25%) of patients with measurable disease. However, patients treated with cisplatin and doxorubicin lived somewhat longer.

Palliative radiotherapy with attempted delivery to the whole pleural surface is technically daunting and associated with a significant incidence of radiation pneumonitis. Symptomatic improvement is documented in only a minority of patients.

Because surgery or radiotherapy alone have resulted in only a few anecdotal long-term survivors among mesothelioma patients, intensive combined-modality approaches have been studied at a few institutions.[20,22,23] Updated results will be covered in other papers in this issue.

Thus the etiology and natural history of malignant pleural mesothelioma has been well documented in the past 2 decades, and initial trials are under way with some encouraging preliminary data in selected subsets of patients.

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