Environmental asbestos exposure and mesothelioma

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Epidemiologic studies of mesothelioma have focused primarily on occupational exposures to asbestos. Nonoccupational exposure to asbestos can be grouped into three main categories: paraoccupational (familial), neighborhood, and true environmental exposures. Elevated mesothelioma rates not attributable to occupational exposures have been observed in asbestos mining and manufacturing areas. Asbestos is one of the most dangerous environmental carcinogens because of the small dose known to cause mesothelioma and the rapid lethality of the disease once it develops. Further research is needed to characterize the contribution and risk profile for environmental asbestos and mesothelioma, and for the development of public health policy. Curr Opin Pulm Med 2000, 6:371–377
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Mesothelioma

Mesothelioma is a rare cancer that primarily affects the pleura and peritoneum—the linings of the lungs and abdominal cavity, respectively. In the United States, 2000 to 3000 new cases of mesothelioma are reported each year [1]. Although mesothelioma is rare, the social impact of this disease is devastating because there is no satisfactory clinical treatment, and the survival time after diagnosis is typically less than 18 months [2–4].

Mesothelioma occurs in the substantial majority of cases as a result of asbestos exposure in occupational and environmental settings, although mesotheliomas from other exposures have been recognized [5,6]. Inhaled fibers that pass through the alveoli migrate to the pleura of the lungs, where they affect the mesothelial cells, thereby producing mesothelioma. Mesothelioma may also occur in the peritoneum of the abdomen, or even more rarely, the pericardium of the heart. Risk is strongly related to the intensity of asbestos exposure and to latency, so a very short period of exposure may be followed decades later by the sudden onset of malignancy and death. The latency period has a wide range, from a minimum of about 5 years [7] to a maximum of 72 years, so those exposed are at risk all their lives [8]. Children appear to be especially susceptible to even short periods of asbestos exposure and typically develop the disease at ages 45 to 50, whereas those exposed after age 20 most often develop the disease at age 60 to 70. Exposed women have been reported to develop pleural mesothelioma at rates at least as high as men with the same exposures, although their overall numbers are much lower since fewer women have occupational exposures [9]. Of greatest concern with regard to environmental asbestos exposure is the recognition that smaller, nonfibrogenic doses of asbestos are adequate to cause mesothelioma.

Asbestos

Asbestos is the name given collectively to the fibrous forms of several naturally occurring silicate minerals that form under high pressure in the earth's crust and are commonly found around earthquake faults. Geologists divide asbestos into two categories, which differ in both structure and chemical composition: (1) serpentine, of which chrysotile is the only asbestiform type, and (2) amphiboles, which includes crocidolite, amosite, anthophyllite, and the fibrous forms of actinolite and tremolite.

Although most investigators agree that amphibole asbestos is more potent in causing mesothelioma, there is still debate as to whether all mesotheliomas are caused by amphiboles (by themselves or as contamination of chrysotile asbestos), or whether chrysotile alone can cause mesothelioma. The amphibole hypothesis suggests that mesothelioma is caused primarily by the amphibole species of asbestos. This is supported by lung burden studies, which have demonstrated that amphiboles accumulate to a much greater degree in lung tissue, including cases of malignancy, despite the fact that chrysotile is the predominating type of asbestos [3,10–12]. McDonald *et al.* [13] have found that amphibole fibers, including tremolite, are also more likely than chrysotile fibers to cause fibrogenic changes in the lung. Stanton *et al.* [14] postulated that fibers with large aspect ratios (the ratio of length to width) are most responsible for the carcinogenic effects of asbestos. Given larger aspect ratios for amphibole species, this theory lends credence to the idea that amphibole asbestos is the most toxic.

Other researchers have concluded that chrysotile is an equally potent carcinogen with regard to mesothelioma [15–17]. Lung burden studies that analyzed asbestos content in the pleura (as opposed to lung tissue) have yielded greater amounts of chrysotile in mesothelioma cases. Because mesothelioma is a cancer of the lung pleura, this would seem to support this view. Chrysotile fibers are cleared more rapidly from the body than asbestos fibers, and it is conceivable that they may "hit-and-run," initiating disease before they are cleared [18].

Although the matter remains unresolved, most natural chrysotile deposits are contaminated with amphiboles, clouding the issue for exposed populations.

Occupational and environmental asbestos exposure

The association between asbestos exposure and mesothelioma was first demonstrated in 1960 by Wagner *et al.* [19]. Mesotheliomas of the pleura were observed in people living or working in a crocidolite mining region in South Africa. Ten of the 33 patients with mesothelioma were born in the vicinity of the mines and had no occupational asbestos exposure. Many patients had reported exposure to asbestos dust as a child. Although occupational exposures constituted the majority of the cases, the report suggests that childhood exposure to asbestos was a cause of several cases. It is not possible to definitively separate occupational from familial or environmental asbestos exposure in this case series.

Current rates of mesothelioma worldwide mirror raw asbestos consumption, and there is general agreement that occupational asbestos exposure accounts for the majority of mesothelioma cases. The incidence of mesothelioma has been on the rise [2,20] and is expected to reach its peak in 2000 in the United States [1] and around 2020 in Europe [21,22••] (Table 1). This trend reflects the average 25- to 40-year latency period between asbestos exposure and disease presentation while taking into account the slow decline of asbestos usage after World War II [1,23].

Exact estimates of mesothelioma attributable to asbestos exposure vary from 60 to 88% of all cases [20,24,25]. Identifying prior asbestos exposure in mesothelioma cases may be particularly difficult because small amounts of asbestos exposure many decades before the disease onset can result in malignancy. The estimated prevalence of prior asbestos exposure may in part vary with how intensively such a history is sought. However, there is no question that the substantial majority of cases are attributable to prior asbestos exposure.

Few studies have delved deeply into the question of whether naturally occurring environmental asbestos poses any significant threat to the health of those living near such deposits. Epidemiologic studies of mesothelioma have focused primarily on occupational exposures to asbestos (*eg*, asbestos miners, railway and construction workers, brake mechanics, building maintenance workers) [26–28]. Although these studies have yielded a great deal of important information, there are many ways in which environmental exposures are likely to differ from occupational exposures, and little is known about the occurrence and risk factors for mesothelioma from environmental asbestos exposure. Occupational exposure to asbestos is generally much greater in concentration and occurs at different ages than environmental exposure. Environmental exposures

Table 1. Incidence of mortality of mesothelioma in various countries and areas over time (per million inhabitants per year)

Country or area	Year	Male	Female
United States	1968–81	2.1	0.8
North America	1972	2.8	0.7
Nantes-Saint-Nazare, France	1956–74	5.2	0.2
Texas	1976–80	5.8	2.1
Selected cities, United States	1970s	4.4–11.1	1.2–3.8
United States	1986	7.0–13.0	1.0–2.0
Barcelona, Spain	1983–90	8.3	4.7
Great Britain	1968–71	8.4	2.3
Finland	1990–94	10.0	2.9
Great Britain	1972–76	12.6	2.8
Nantes-Saint-Nazare, France	1975–84	17.2	0.8
United Kingdom	1998	17.5	3.2
Denmark	1978–80	14.7	7.0
Nantes-Saint-Nazare	1985–92	19.4	4.0
Great Britain	1968–71	20.7	4.3
Australia	1982–88	28.3	3.3
Great Britain	1982–86	30.5	4.9
Great Britain	1987–91	44.0	6.4
Australia	1994	49.9	4.8

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may begin at a younger age and continue for a longer duration than the normal working lifetime. Nonoccupational exposure to asbestos can be grouped into three main categories: paraoccupational (familial), neighborhood, and true environmental exposures.

Paraoccupational (familial) exposure

In close association with occupational exposures are those of spouses and children of exposed workers. These family members breathe asbestos dust brought home on the worker's clothing. These have been called "familial" or "domestic" exposures, and have been classified as both environmental and occupational exposures [29,30]. Although there is disagreement on the issue of definition, there is agreement that the dose associated with increased mesothelioma risk in these cases is lower than that resulting from usual workplace exposures.

Neighborhood exposures

The most ubiquitous environmental asbestos source is from asbestos mining, which produces so-called "neighborhood" exposures. Studies of mining areas in Australia, South Africa, and Canada have documented elevated rates of mesothelioma among residents who never worked for the mines. Other studies have examined neighborhood rates of mesothelioma around factories producing asbestos-based goods and found elevated mesothelioma risk (Table 2). Attributing mesotheliomas to environmental exposure is difficult in some of these studies because of their ecologic nature, and it can be difficult to prove an absence of occupational exposure to asbestos in some cases.

Rees *et al.* [31] conducted a large, multicenter, case-control study of mesothelioma in South Africa. Since patients were enrolled as they were diagnosed, exposure information was obtained from live subjects—an exception with this rapidly fatal disease. Twenty-two cases (17.9%) had exclusively environmental exposure. The odds ratio for those environmentally exposed in the northwest Cape region (where asbestos is primarily crocidolite) was 32.7 (95% CI [confidence interval], 8.1–131); for the northeast Transvaal region (crocidolite plus amosite asbestos), it was 12.7 (95% CI, 1.9–84.7).

A large retrospective cohort study was conducted in Wittenoom, Western Australia, the site of a large crocidolite mine and mill [32]. Mesothelioma was tracked

Table 2. Studies of mesothelioma and neighborhood asbestos exposure

Location	Year	Type of asbestos	Source of asbestos	Type of study	Study population	Environmental mesotheliomas (*n*)	Mesothelioma risk	Comments	Reference
Northwest Italy	1980–91	Chrysotile, crocidolite (≤10%)	Industrial	Retrospective case series	Hospital admissions from local area	64	Men: 4.2–7.4 cases per 100,000 person-years Women: 2.3–7.1 cases per 100,000 person-years		Magnani *et al.* [35]
New Jersey, USA	1979–90	–	Industrial	Retrospective case series	State cancer registry records	–	Males: SIR = 10.1 (95% CO, 5.8–16.4) Females: SIR = 22.4 (95% CI, 9.7–44.2)		Berry [36]
Western Australia	Roving between 1943–1993	Crocidolite	Mining, industrial	Retrospective cohort	4659 residents who never worked for mining company	27	26 cases per 100,000 person-years	24/27 cases had domestic (familial) exposure	Hansen *et al.* [32]
South Africa	1988–90	Crocidolite, amosite, chrysotile	Naturally occurring, mining, industrial	Case-control	Patients in all hospitals in six major South African centers	22	OR-32.7 (95% CI, 8.1–131) for those environmentally exposed in NW Cape region; OR012.7 (1.9–84.7) in NE Transvaal.		Rees *et al.* [31]
Quebec	1970–89	Chrysotile	Mining	Case-control	Population-based mortality survey	7	SMR=7.63 (95% CI, 3.06–15.03)	Some cases may have occupational exposure to amphiboles	Camus *et al.* [33]

through a mandatory tumor registry, so case ascertainment was likely complete. The 4659 people who had lived in Wittenoom for less then 1 month between 1943 and 1993, and who never worked for the mining company, were enrolled. Twenty-seven cases of mesothelioma were found, yielding an age-standardized incidence rate of 26 in 100,000 person-years for residents aged 15 years or more. The rate was similar for males and females. This study did not exclude patients with "familial" exposures, which could have accounted for 24 out of 27 cases. One case occurred in an individual who went to Wittenoom after the mining operations ceased.

A recent study from Quebec designed to test an Environmental Protection Agency dose-response model for asbestos among women in a chrysotile mining community found a high standardized mortality ratio for mesothelioma (7.63; 95% CI, 3.06–15.03) [33]. However, the study was designed to specifically address lung cancer, and mesotheliomas were based on a historical death certificate review, which may be inaccurate. Seventy percent of the women in the study had lived in the house of an asbestos worker, suggesting that familial exposures accounted for some of the cases. The study has also been criticized because high levels of amosite and crocidolite fibers were found in the lungs of some patients, indicating occupational exposure to asbestos in other industry [34].

Magnani *et al.* [35] surveyed pleural mesothelioma in health authority records of a town in northwest Italy where a large asbestos cement factory was located. Eighty-eight cases of histologically confirmed mesothelioma were identified in the area from 1980 to 1989, with no occupational or paraoccupational exposure to asbestos. Mesothelioma mortality rates in men were 4.2 to 8.2 per 100,000 person-years; in women rates were 2.3 to 5.1 per 100,000 person-years. These rates compared to national rates based on Italian cancer registry of 1.8 and 0.6 per 100,000 for men and women, respectively.

Mesothelioma incidence rates were analyzed in New Jersey, in the area of the largest asbestos plant in North America. Berry [36] found standardized incidence ratios among residents in the town with the factory to be 10.1 for men (95% CI, 5.8–16.4) and 22.4 for women (95% CI, 9.7–44.2) compared with New Jersey rates. Standardized incidence ratios for the rest of the county (minus the town) were 1.9 and 2.0 for men and women, respectively. No personal interviews were conducted and some occupational exposures may have been missed.

Naturally occurring asbestos

There have been few epidemiologic studies looking specifically at exposure to naturally occurring asbestos. Naturally occurring asbestos (particularly amphibole) is common in several populated areas of the world, and exposure to environmental sources of asbestos is thus an important public health concern. Human activities that perturb asbestos-containing rock are particularly of concern due to the high potential for asbestos dust to be released and inhaled. Construction, grading, quarrying, or cars travelling on unpaved roads are examples of activities that may generate asbestos dust. Also, natural weathering and erosion may release asbestos fibers into the air.

Exposure to naturally occurring amphibole asbestos and related fibers is thought to be a cause of malignant mesothelioma in several areas of the world (Table 3) Most of these studies have focused on areas of the world in which asbestos deposits have been used by the local population for domestic purposes, such as grinding asbestos by hand to make whitewash, insulation, or plaster. This practice has been almost entirely abandoned, and the extremely high rates of mesothelioma seen in these studies resulted from high levels of exposure 30 to 40 years ago. The high rates are not necessarily representative of rates in these locations in the future, or in parts of the world in which asbestos is not used for such purposes.

Naturally occurring tremolite asbestos is abundant in the Metsovo area of Greece. In a retrospective review of hospital cases from 1981 to 1985, seven cases of malignant mesothelioma were found in a population of approximately 5000, corresponding to 28 cases per 100,000 person-years [37]. In a follow-up study, the mesothelioma rate had decreased to 14 in 100,000 person-years for 1985 to 1994 [38]. This drop paralleled the decrease in domestic use of asbestos, which had fallen from 92% of households in 1950 to 18% by 1980, and which disappeared altogether by 1985. However, the numbers of cases were small (7 and 6, respectively), so a statistical overlap of these rates is possible. Additionally, the follow-up was not age-standardized, preventing a direct comparison between them. It is likely that the median age of the population shifted upward, which would make the earlier figure relatively undervalued, and the difference in age-standardized rates larger than the unstandardized figures.

Several studies have investigated environmental exposure to tremolite deposits in Turkey. Yazicioglu *et al.* [39] document a series of mesotheliomas in southeast Turkey. In 1977–78, 22 of 23 patients admitted to the regional hospital with pleural mesotheliomas came from asbestos districts, which contained only 51% of the population. The mesothelioma rate for these districts averaged 9.7 per 100,000 person-years. However, rates were between 14.6 and 19.1 per 100,000 person-years in the three districts in which asbestos outcrops were most

Table 3. Studies of mesothelioma and environmental exposure to naturally occurring asbestos

Location	Year	Type of asbestos	Type of study	Study population	# of environ. mesotheliomas	Mesothelioma risk	Comments	Reference
Southeast Turkey	1977–78	Tremolite some chrysotile	Retrospective case series	Hospital admissions from local area	23	9.7 cases per 100,000 person-years	Most highly contaminated villages have rates up to 17 per 100,000 person-years	Yazicioglu et al. [39]
Central Turkey	1980–87	Tremolite, some chrysotile	Retrospective case series/cohort	Health center records	2	59 cases per 100,000 person-years		Baris et al. [40]
Central Turkey	1981–1990	Tremolite some chrysotile	Case series	Hospital admissions from local area	77	Cannot be calculated		Selcuk et al. [41]
Central Turkey	1989–1997	Tremolite some chrysotile	Prospective case series	Patients from one clinic	97	86% of presenting mesothelioma patients had nonoccupational exposures.		Metintas et al. [42]
Northwest Greece	1981–85	Tremolite	Retrospective case series	Hospital admissions from local area	7	28 cases per 100,000 person-year		Constantopoulos et al. [37]
Northwest Greece	1985–1994	Tremolite	Cohort	Hospital admissions from local area	6	14 per 100,000 person-years	Domestic use of asbestos whitewash dropped from 92% in 1950 to 18% by 1980.	Sakellariou et al. [38]
Central Cyprus	?–1986	Chrysotile, some tremolite	Retrospective case series	Unspecified	4	4 of 12 patients had apparent occupational or paraoccupational exposure	Mining also located in area	McConnochie et al. [46]
New Caledonia	1978–87	Tremolite	Retrospective case series	Unspecified	12/9 (see comments)	8.3/6.2 cases per 100,000 person-years	12 cases of pleural cancer, of which 3 were "probable" mesothelioma	Goldberg et al. [47]
Northeast Corsica	1973–91	Chrysotile, tremolite	Retrospective case series	Hospital admissions from local area	14	10 cases per 100,000 person-years		Rey et al. [48]

frequent. Baris [40] reports two mesothelioma cases in a population of 425 people in central Turkey over a period of 7 years (59/100,000 person-years). However, the number of cases and population in this report are both small and statistically unstable. Additionally, occupational or other possible exposures to asbestos were not explored, although the argument for overwhelming environmental exposure is convincing.

Selcuk et al. [41] reported 77 nonoccupational, nonindustrial mesothelioma cases from 30 asbestos villages in central Turkey. Metintas et al. [42] found that 86% of patients diagnosed with mesothelioma in their clinic came from villages with large natural asbestos deposits. Incidence rates cannot be calculated for either of these studies, as the contributing population is not recorded.

Erionite is a nonasbestos fiber morphologically similar to amphibole asbestos. It has been implicated in causing mesothelioma in people environmentally exposed. The Cappadocia region of Turkey is rich in naturally occurring erionite and has been found to have exceedingly high rates of mesothelioma in both present and former residents. Mesothelioma is thought to account for 51% of deaths among villagers living in the area [41,43] and up to 78% of former residents who had emigrated to Sweden [44]. If these figures are accurate, they suggest that erionite is more carcinogenic than even crocidolite asbestos.

An interesting study in Cyprus by McConnochie et al. [45] reported on 14 cases of mesothelioma over an unspecified number of years. Asbestos deposits in Cyprus contain mostly chrysotile, but there is some tremolite contamination. The area is rich with natural deposits, but also has an asbestos mine in the central mountains. These investigators used environmental dust sampling and fiber analysis of human lung tissue to confirm the presence of asbestos in the air. Uniquely, they also used sheep as "mobile air samplers" and further confirmed the presence of both

tremolite and chrysotile in the lung. The researchers suggested that the impact of environmental exposure was high because the number of occupational exposures among cases was low (5 of 12; 3 more had familial exposures, two had neighborhood exposures, and two had no apparent asbestos exposure). However, the article does not indicate the source of the cases, so the representativeness of the sample is unknown.

Studies on exposure to naturally occurring asbestos also have been conducted in New Caledonia and Corsica. Goldberg *et al.* [47] recorded all cases of pleural cancer between 1978 and 1987 in New Caledonia. There were nine definite mesotheliomas and a further three that were classified as "probable." Of the 12 patients, 3 had worked in the nickel industry, which can disturb natural asbestos fibers in the soil. Mesothelioma rates were compared to five reference registries (from France (2), Britain, New York, and Australia). Standardized incidence ratios ranged from 201 to 517. An earlier study by this group (1978–1981) had detected a relationship between pleural cancers and zones of residence within New Caledonia; however, the later study did not establish an association with particular areas of the country, or with nickel mining sites.

Rey *et al.* [48] collected mesothelioma cases in Corsica, in an area where both chrysotile and tremolite can be found, and which is remote from asbestos mines. They found 14 cases in the population, with an incidence rate of 10 per 100,000 person-years. It was ascertained that asbestos-related industries were not the usual occupation of the patients. However, other asbestos-using or -producing industries were not excluded.

Taken together, these findings confirm the ability of natural asbestos deposits to cause mesothelioma in nonoccupationally exposed populations. However, further characterization of the routes of exposure, latency, and risk are needed.

Conclusions

Asbestos is one of the most dangerous environmental carcinogens because of the small dose known to cause mesothelioma and the rapid lethality of the disease once it develops. However, many questions remain unanswered about the contribution of environmental asbestos exposure to the development of mesothelioma. These include the extent and nature of asbestos exposure in nonoccupational environments, the proportion of mesothelioma cases with purely environmental exposure, and the relative risk of chrysotile and amphibole asbestos. These issues have direct public health relevance for many areas in the world where development is occurring in areas with naturally occurring asbestos.

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