BRIEF COMMUNICATIONS

Prospective Study of Mesothelioma Mortality in Turkish Villages With Exposure to Fibrous Zeolite

Y. Izzettin Baris, Philippe Grandjean

Mesothelioma incidence is high in certain villages on the Anatolian plateau in Turkey, where environmental exposure includes erionite, a form of zeolite fibers, from the local volcanic tuff. Previous studies of this exposure were cross-sectional or with a follow-up period of only a few years. A prospective study of residents of two exposed and one nearby control village was initiated in 1979 and continued through December 31, 2003. A total of 891 men and women, aged 20 years or older, were included, 230 of them residing in the village without known exposure to erionite. Mortality data were obtained from hospital records and death certificates. During the 23-year follow-up, 372 deaths occurred; 119 of these were from mesothelioma, which was the cause of 44.5% of all deaths in the exposed villages. Seventeen patients had peritoneal mesothelioma; the rest had pleural mesothelioma. Only two cases of mesothelioma, one of each type, occurred in the control village—both in women born elsewhere. When standardized to the world population, the pleural mesothelioma incidence was approximately 700 and 200 cases per 100 000 people annually in the two exposed villages and about 10 cases per 100 000 people in the control village. When we used Danish data for comparison, the standardized pleural mesothelioma mortality rate was 485 (95% confidence interval = 395 to 590). Our results emphasize the severity of the mesothelioma endemic in erionite-exposed areas of Turkey and call for intensified prevention of mesothelioma by limiting environmental exposures to these fibers. [J Natl Cancer Inst 2006;98:414–7]

An environmentally related cluster of patients with mesothelioma has been described from Cappadocia, Turkey *(1–4)*. This area has had a high mortality rate that was previously attributed to lung cancer and liver cirrhosis, but thorough studies *(1,4)* concluded that this mortality was due instead to malignant mesothelioma of the pleura and the peritoneum and that the affected subjects lived in areas with exposures to a fibrous zeolite called erionite *(5–7)*. This mineral occurs in cavities of the local volcanic tuff. In the past, the local population cut cold-storage rooms into the tuff to store produce and used blocks of tuff as construction material *(4,8,9)*.

The association between erionite exposure and the development of mesothelioma is supported by pathology findings that parallel those of asbestos-exposed populations—i.e., pleural thickening, plaques, calcifications, parenchymal pneumoconiosis, and benign pleural effusion *(1,4)*, as well as ferruginous bodies containing erionite fibers *(10,11)*. Village dust samples and lung tissue from residents contained only traces of tremolite and chrysotile asbestos, whereas most fibers found had the elemental composition of erionite *(2,10)*. Erionite is associated with a higher risk of developing cancer in experimental animals than any other fiber previously tested *(12,13)*.

Initial mortality studies were limited by the duration of follow-up and the lack of data about villagers who had moved away from the area *(1,14)*, and comprehensive follow-up is now reported from three comparable Cappadocian settlements—one village, Karlık, without known erionite exposure, and two exposed villages, Karain and Sarıhıdır. Inhabitants of the last two villages were exposed to erionite in their living quarters, barns, and the surrounding environment *(8,9)*. Karain was one of the first villages identified with a high mesothelioma incidence *(4)*. During recent decades, the population has dwindled, and more than 200 former residents of Karain now live in Sweden *(15)*. Sarıhıdır was founded on the south bank of the Kızılırmak River, where erionite-containing construction materials for residential buildings were obtained from a local quarry *(9)*. A move to the northern bank of this river was initiated in 1958 and was completed in the 1990s, with building materials from the south bank being used only for construction of basements. In the new settlement, fewer and smaller erionite fibers were found in the dust of new houses than in houses in the previous village *(9)*. Karlık is located in the same general area, with similar demographic and occupational characteristics, but it is thought not to be affected by exposure to erionite or other mineral fibers *(9)*.

At the initiation of the study (1979 in Karain and Karlık; early 1980 in Sarıhıdır), villagers aged 20 years or older were interviewed and then given a clinical examination. Oral informed consent was obtained, and resident code number, year of birth, name, and sex were recorded. The 23-year follow-up was continued through December 31, 2003, by Y. I. Baris, who regularly visited the villages, made contact with local informers in each village, and checked death certificates from the village health centers in Karain and Karlık and from the health center in Avanos for residents of Sarıhıdır. Records from the district population office in Ürgüp were also used. The vital status of subjects who had moved was ascertained from the district of their new residence, and the vital status of emigrants was obtained from interviews with relatives and former

Affiliations of authors: Güven Hospital, Ankara, Turkey (YIB); Institute of Public Health, University of Southern Denmark, Odense, Denmark, and Department of Environmental Health, Harvard School of Public Health, Boston, MA (PG).

Correspondence to: Philippe Grandjean, MD, PhD, Department of Environmental Health, Harvard School of Public Health, Landmark Center E3–110, 401 Park Dr., Boston, MA 02215 (e-mail: pgrand@hsph.harvard.edu).

See "Notes" following "References."

DOI: 10.1093/jnci/djj106

Table 1. Vital status of subjects aged 20 years or older who lived in three villages in Cappadocia, Turkey, in 1979

Village	No. alive in 1979	Median age in 1979, y	No. dying before end of 2003	No. alive in 2003 and residing in:			
				Same village	Turkey	Other country	Unknown
Karain	325	46	179	61	68	13	4
Sarıhıdır	336	38	109	163	58	5	1
Karlık	230	49	84	119	24	3	0
Total	891	45	372	343	150	21	5

neighbors. For patients who died suddenly or at home, the cause of death was determined by health center personnel. For some deaths from nonmalignant diseases, the death certificate did not state a cause of death, and so further information was sought from relatives. Lung cancer may have been misdiagnosed in men only, because women are virtually all nonsmokers. By religious tradition, deceased emigrants were buried in sacred soil at their home village, and so the cause of death was obtained from the death certificate issued abroad. The five subjects lost to follow-up during the study were assumed to be alive at the end of the follow-up period.

Age-adjusted mortality rates were calculated by use of world population standardization *(16)*. Comparison data from a nonexposed population are not available from Turkey, and so standardized mortality rates were calculated from incidence data from Denmark, a country without environmental exposure to native mineral fibers and in which 80%–85% of all mesothelioma cases are attributed to industrial asbestos exposure *(17)*. We used the person-years method and Danish cancer mortality data to calculate relative mortality rates standardized according to age, sex, and calendar year.

The 891 adult residents in the three villages alive on January 1, 1979, were born between 1895 and 1959. The median ages in 1979 were 46, 38, and 49 years in Karain, Sarıhıdır, and Karlık, respectively. A total of 420 (47%) of the 891 village residents were men, and 471 (53%) were women. A total of 230 of the 891 people lived in Karlık, the village without erionite exposure. By the end of follow-up in 2003, a total of 372 subjects had died, and a total of 519 were still alive (Table 1). Of the 151 cancer deaths, 119 were attributed to mesotheliomas (Table 2). All but two deaths from mesothelioma occurred in the exposed villages, constituting 44.5% of all deaths in the exposed villages. The two deaths in the control village of Karlık occurred in women born elsewhere in Cappadocia, one of them in Karain. The age at death from malignant pleural and peritoneal mesotheliomas varied from 30 to 80 years and from 46 to 90 years, with medians of 55 and 69 years, respectively. Most mesothelioma deaths (87%) occurred in subjects younger than 70 years, and 23 (19%) occurred in subjects younger than 40 years. The age distribution for mesothelioma deaths was similar in men and women and similar in the two exposed villages. Four Karain women with pleural mesothelioma had been born elsewhere (between 5 and 20 km away) and had moved to this village after marriage to a Karain resident. Their ages at death were 48, 56, 69, and 71 years.

There was only one case of confirmed lung cancer in a male from Sarıhıdır. Other cancer types diagnosed included 13 cancers of the gastrointestinal system, 10 cancers of the genitourinary system, nine other known cancers, and two malignancies of unknown type. Other known causes of death included infectious disease (16 cases, of which were two were tuberculosis and one was hepatitis). Of nine cases of chronic obstructive pulmonary disease, six occurred in Karain (three men and three women), one occurred in men from Sarıhıdır, and two occurred in men from Karlık. There were 14 violent deaths, including two suicides; four deaths had no known cause and were assumed not to be caused by mesothelioma.

When standardized to the world population, the pleural mesothelioma incidence was approximately 700 and 200 cases per 100 000 people annually in the two exposed villages and about 10 cases per 100 000 people annually in the control village (Table 3). The standardized pleural mesothelioma mortality rate for men and women from Karain and Sarıhıdır combined was 485 (95% confidence interval [CI] = 395 to 590). The risk of peritoneal mesothelioma appeared similarly increased, but the smaller number of cases does not allow detailed comparisons to be made.

Initial reports on mortality of Karain and Sarıhıdır residents in the 1970s

Table 2. Major causes of death of subjects residing in three Cappadocian villages in Turkey in 1979, who died before 2003*

Cause of death and age at death	Karain	Sarıhıdır	Karlık	Total
MM, pleura	75 (42)	26 (24)	1 (1)	102 (27)
20–39 y	9	0	0	9
40–59 y	38	16	1	55
≥60 y	28	10	0	38
MM, peritoneum	7 (4)	9 (8)	1 (1)	17 (5)
20–39 y	0	0	0	0
40–59 y	1	2	0	3
≥60 y	6	7	1	14
Other cancers	10 (6)	11 (10)	11 (13)	32 (9)
20–39 y	1	0	1	2
40–59 y	5	2	2	9
≥60 y	4	9	8	21
Other deaths	87 (49)	63 (58)	71 (85)	221 (59)
20–39 y	4	4	0	8
40–59 y	16	17	7	40
≥60 y	67	42	64	173
All causes	179 (100)	109 (100)	84 (100)	372 (100)
20–39 y	14	4	1	19
40–59 y	60	37	10	107
≥60 y	105	68	73	246

*Number (percentage) of subjects. MM = malignant mesothelioma.

Table 3. Age-adjusted mortality (No. of deaths per 100 000 people per year) for each village 1979–2003*

Village	Mortality from pleural mesothelioma (95% CI)			Mortality from peritoneal mesothelioma (95% CI)*
	Men	Women	Both sexes	Both sexes
Karain	775 (491 to 1162)	658 (465 to 902)	697 (531 to 900)	42 (15 to 92)
Sarıhıdır	284 (165 to 455)	124 (57 to 235)	197 (129 to 288)	74 (34 to 140)
Karlık	0 (—)	18 (0.47 to 103)	11 (0.27 to 59)	5.7 (0.15 to 32)

*The world population was used for age adjustment. CI = confidence interval.

suggested that 52% and 36%, respectively, of all deaths were from mesotheliomas *(1,4,14)*. Among villagers who emigrated, substantial numbers of confirmed mesothelioma diagnoses have been reported [e.g., from Belgium *(18)* and Sweden *(19,20)*], some of which were included in this study.

The age at death of mesothelioma patients in this study is slightly higher than in earlier studies. Mesothelioma patients previously diagnosed in Tuzköy were as young as 26 years, with mean ages of about 50 years *(4)*. This study prospectively monitored residents aged 19 years or older and used records on subjects who later moved away from the exposure, thereby possibly including more cases diagnosed at older ages. A previous study had noted that none of the subjects moving to Karain as adults developed mesothelioma *(1)*. The issue of age-related exposure could not be examined in this study, because few of the 1979 residents had not been born there.

Our data were also insufficient to determine whether the mesothelioma mortality rate decreased during the observation period. Most of the Sarıhıdır villagers were born on the southern river bank but later moved across the river to a location with less exposure to erionite. If we assume that the latency period for domestic exposures is approximately 50 years *(5,21)*, this study has insufficient power to detect a decreased risk associated with the move.

Experimental animal studies *(22,23)* indicated that erionite exposure also led to the development of cancers other than malignant mesothelioma. Mortality data from Karain, Sarıhıdır, and Tuzköy before 1994 supported a possible excess of abdominal carcinomas *(14)*. However, we identified only 32 additional cases of cancer that accounted for 9% of all deaths and, therefore, cannot further elucidate this possibility. Although the single case of lung cancer in this study is surprising, more cases may have occurred, e.g., among the nine patients with chronic obstructive pulmonary disease listed as the cause of death. Otherwise, the overall mortality pattern is fairly close to expectation, apart from the dramatic numbers of mesothelioma cases.

Residents of the villages known for a high incidence of cancer may have a limited choice of partners. Family pedigrees from this region show a linkage of six families into one large six-generation extended pedigree with a particularly high risk of disease *(24)*. The cause of the high incidence of malignant mesothelioma has been attributed to hypothetical autosomal dominant inheritance *(25)*; however, the significance of such a genetic predisposition is difficult to judge, because all relatives also shared the hazardous environmental factors since birth. Also, cases of mesothelioma have occurred in subjects, whose parents had apparently died from other causes, and vice versa. The possible impact of heritable disease factors is therefore difficult to determine.

Our results emphasize the severity of the mesothelioma endemic in erionite-exposed areas of Turkey. From the comprehensive evidence available, government authorities have declared the affected villages an emergency area. Because erionite-containing materials were originally used for house construction, new houses are now being erected in two of the affected villages with safe materials. With the likely decrease in mesothelioma rates due to past occupational uses of asbestos *(26)*, the relative impact of environmental exposures to carcinogenic fibers should increase. In the rural part of central Anatolia, Turkey, millions of inhabitants are likely exposed to hazardous amounts of mineral fibers from the environment. Resources should therefore be directed to preventing these environmental exposures and additional study of the association between environmental exposure to nonasbestos fibers and the risk of cancer.

References

(1) Baris YI, Sahin AA, Ozesmi M, Kerse I, Ozen E, Kolacan B, et al. An outbreak of pleural mesothelioma and chronic fibrosing pleurisy in the village of Karain/Urgup in Anatolia. Thorax 1978;33:181–92.

(2) Rohl AN, Langer AM, Moncure G, Selikoff IJ, Fischbein A. Endemic pleural disease associated with exposure to mixed fibrous dust in Turkey. Science 1982;216:518–20.

(3) Simonato L, Baris R, Saracci R, Skidmore J, Winkelmann R. Relation of environmental exposure to erionite fibres to risk of respiratory cancer. IARC Sci Publ 1989;90:398–405.

(4) Baris YI. Fibrous zeolite (erionite)-related diseases in Turkey. Am J Ind Med 1991;19:374–8.

(5) Ross M, Nolan RP, Langer AM, Cooper WC. Health-effects of mineral dusts other than asbestos. Rev Mineral 1993;28:361–407.

(6) Emri S, Demir A, Dogan M, Akay H, Bozkurt B, Carbone M, et al. Lung diseases due to environmental exposures to erionite and asbestos in Turkey. Toxicol Lett 2002;127:251–7.

(7) Dogan U. Mesothelioma in Cappadocian villages. Indoor Built Environ 2003;12:367–76.

(8) Baris YI, Saracci R, Simonato L, Skidmore JW, Artvinli M. Malignant mesothelioma and radiological chest abnormalities in two villages in Central Turkey. An epidemiological and environmental investigation. Lancet 1981;1:984–7.

(9) Baris I, Simonato L, Artvinli M, Pooley F, Saracci R, Skidmore J, et al. Epidemiological and environmental evidence of the health effects of exposure to erionite fibres: a four-year study in the Cappadocian region of Turkey. Int J Cancer 1987;39:10–7.

(10) Sebastien P, Gaudichet A, Bignon J, Baris Yi. Zeolite bodies in human lungs from Turkey. Lab Invest 1981;44:420–5.

(11) Dumortier P, Coplu L, Broucke I, Emri S, Selcuk T, de Maertelaer V, et al. Erionite bodies and fibres in bronchoalveolar lavage fluid (BALF) of residents from Tuzkoy, Cappadocia, Turkey. Occup Environ Med 2001;58:261–6.

(12) Maltoni C, Minardi F, Morisi L. Pleural mesotheliomas in Sprague-Dawley rats by erionite: first experimental evidence. Environ Res 1982;29:238–44.

(13) Wagner JC, Skidmore JW, Hill RJ, Griffiths DM. Erionite exposure and mesotheliomas in rats. Br J Cancer 1985;51:727–30.
(14) Baris B, Demir AU, Shehu V, Karakoca Y, Kisacik G, Baris YI. Environmental fibrous zeolite (erionite) exposure and malignant tumors other than mesothelioma. J Environ Pathol Toxicol Oncol 1996;15:183–9.
(15) Ozesmi M, Hillerdal G, Svane B, Widstrom O. Prospective clinical and radiologic study of zeolite-exposed Turkish immigrants in Sweden. Respiration 1990;57:325–8.
(16) Anderson RN, Rosenberg HM. Age standardization of death rates: implementation of the year 2000 standard. Natl Vital Stat Rep 1998;47:1–16.
(17) Dreyer L, Andersen A, Pukkala E. Occupation. APMIS Suppl 1997;76:68–79.
(18) Dumortier P, Gocmen A, Laurent K, Manco A, De Vuyst P. The role of environmental and occupational exposures in Turkish immigrants with fibre-related disease. Eur Respir J 2001;17:922–7.
(19) Boman G, Schubert V, Svane B, Westerholm P, Bolinder E, Rohl AN, et al. Malignant mesothelioma in Turkish immigrants residing in Sweden. Scand J Work Environ Health 1982;8:108–12.
(20) Metintas M, Hillerdal G, Metintas S. Malignant mesothelioma due to environmental exposure to erionite: follow-up of a Turkish emigrant cohort. Eur Respir J 1999;13:523–6.
(21) Hillerdal G. Mesothelioma: cases associated with non-occupational and low dose exposures. Occup Environ Med 1999;56: 505–13.
(22) International Agency for Research on Cancer. Silica and some silicates. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 42; 1987. p. 225–39.
(23) Ozesmi M, Patiroglu TE, Hillerdal G, Ozesmi C. Peritoneal mesothelioma and malignant lymphoma in mice caused by fibrous zeolite. Br J Ind Med 1985;42:746–9.
(24) Baris YI, Artvinli M, Sahin AA. Environmental mesothelioma in Turkey. Ann N Y Acad Sci 1979;330:423–32.
(25) Roushdy-Hammady I, Siegel J, Emri S, Testa JR, Carbone M. Genetic-susceptibility factor and malignant mesothelioma in the Cappadocian region of Turkey. Lancet 2001; 357:444–5.
(26) Montanaro F, Bray F, Gennaro V, Merler E, Tyczynski JE, Parkin DM, et al. Pleural mesothelioma incidence in Europe: evidence of some deceleration in the increasing trends. Cancer Causes Control 2003;14:791–803.

Notes

Professor Jorgen H. Olsen, MD, and Andrea Bautz, Danish Cancer Society, provided assistance with the mortality calculations.

Funding to pay the Open Access publication charges for this article was provided by the Harvard School of Public Health.

Manuscript received May 25, 2005; revised January 20, 2006; accepted January 26, 2006.