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Muzaffer Metintas MD [a], Gunnar Hillerdal MD, PhD [b], Selma Metintas MD, PhD [c] & Pascal Dumortier PhD [d]

[a] Department of Chest Diseases, Eskisehir Osmangazi University, Medical Faculty, Eskisehir, Turkey

[b] Department of Chest Diseases, Karolinska Hospital, Stockholm, Sweden

[c] Department of Public Health, Eskisehir Osmangazi University, Medical Faculty

[d] Mineralogy Laboratory of the Chest Department, Erasme Hospital in Brussels, Belgium

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Endemic Malignant Mesothelioma: Exposure to Erionite Is More Important Than Genetic Factors

Muzaffer Metintas, MD; Gunnar Hillerdal, MD, PhD; Selma Metintas, MD, PhD; Pascal Dumortier, PhD

ABSTRACT. The village of Karain, Turkey, has the world's highest prevalence rate of malignant mesothelioma (MM). Environmental exposure to erionite is thought to cause the disease. However, it has also been suggested that the disease is mainly genetic. Residents in Karain village were traced from 1990to 2006. Mineral samples were obtained from stones used in construction of their houses and any fibers present were identified. All women who had moved to the village as brides were traced and their cause of death determined. MM was the cause of death in 52 of 322 villagers, representing 50.5% of all deaths. Only 2 of 8 types of stones used in construction contained erionite, and these stones had been used almost exclusively in the mid-sections of the village, where MM was common. In houses not containing erionite, no cases of MM were observed. Sixty-four women came as brides to Karain from villages where erionite or asbestos is not found. Of the 16 women who have died, 11 (69%) died from MM. The extreme risk of MM in Karain is due to indoor exposure to erionite. The effect of genetic factors on mesothelioma development cannot be evaluated in this study, but is likely to be minor.

KEYWORDS: cancer, epidemiology, etiology, genetic, mesothelioma

Endemic malignant mesotheliomas (MMs) have been reported in many places around the world. Generally, locally occurring asbestos has been used for various purposes, such as white-washing of houses. In 1978, 11 cases of MM were reported over 2 years among 575 inhabitants of the small village of Karain in Cappadocia, Turkey.[1] No asbestos deposits were found in the area, and further investigations indicated that a zeolite fiber, erionite, was the cause of the disease.[2,3] In 2 other Turkish villages, Tuzköy and Sarihidir, erionite exposure and MMs were also found. Experiments confirmed this mineral to be extremely active in causing MM.[4–6] Furthermore, erionite bodies and fibers in the lungs, bronchoalveolar lavage, and sputum of mesothelioma victims were also found.[7–10]

In immigrants from Karain living in Stockholm, Sweden, the mesothelioma standardized incidence ratio was 135 times higher in men and 1,336 times higher in women than in the society in which they lived.[11] Because the occurrence of the disease seems more often in certain families living in Karain village,[12] the question of a genetic factor was raised early. Analysis of a 6-generation extended pedigree of 526 individuals from the village suggested a genetic transmission, probably in an autosomal dominant way.[13,14] Furthermore, erionite is also found in a neighboring village, Karlik, situated 4 km from Karain, where only 2 mesotheliomas are known to have occurred,[10] and analysis showed that the type of erionite was identical to the one in Karain.[3,14]

Muzaffer Metintas *is with the Department of Chest Diseases at Eskisehir Osmangazi University, Medical Faculty, in Eskisehir, Turkey.* **Gunnar Hillerdal** *is with the Department of Chest Diseases at Karolinska Hospital in Stockholm, Sweden.* **Selma Metintas** *is with the Department of Public Health at Eskisehir Osmangazi University, Medical Faculty.* **Pascal Dumortier** *is with the Mineralogy Laboratory of the Chest Department at Erasme Hospital in Brussels, Belgium.*

A genetic factor, if there were, in MM etiology would be of importance for prevention.[12,14] However, much of the familial incidence could be explained by families living in the same houses.[2,10] In addition, there were reports of young women moving into the village as brides who 20 to 30 years later developed MM.[10] The present study was therefore planned.

The goals were thus to relate the risk of MM to duration of stay in the village and to gender; and among those who have emigrated from or immigrated to the village, to identify the stone and soil types utilized in construction of houses in Karain; and to relate households with and without MM to their respective houses and their building stones.

METHODS

Demographics

The study was focused on those who resided in Karain village at any time from 1990 to 2006. The village was visited repeatedly by 2 of us (M.M. and S.M.) during 2004 to 2006. All households in the village were visited together with the elected headman of the village (mukhtar), 2 old villagers who knew the inhabitants and their history, and stonemasons who had worked to build old houses. Questions included which individuals had migrated to and from the village and the causes of any deaths. Information on the inhabitants of now-ruined and abandoned houses was obtained from the neighbors and the muhktar. Names of immigrants and emigrants and causes of deaths or disease were carefully collected and cross-checked. The official book of records of the mukhtar was compared with these data. The village cemetery was visited and dates and names on tombstones recorded. Karain villagers in Urgup (a nearby city to which many villagers had moved) and in Stockholm, Sweden, were also visited by the researchers.

Death certificates were obtained from the village muhktar. Village clinics records and records from the large nearby hospitals were also consulted. Death causes was identified on death certificates. For subjects without hospital records, information from relatives and the muhktar was used to make the diagnosis ("verbal autopsy").[15] If symptoms and other available information were compatible with MM, it was recorded as such.

All women who had ever moved to Karain village were also analyzed. Registers were found dating back to the year 1930.

Statistics

The number of years living in the village was calculated for those who died between 1990 and 2006. A year that contained an immigration, emigration, mesothelioma diagnosis, or death was counted as half a year. For individuals living in Urgup, 3 months were added for every single year after the migration, since they regularly visited Karain.

The mesothelioma incidence rate was standardized for the World Population and 95% confidence intervals calculated.[16] For the standard mortality ratio (SMR), reference values were obtained from the Turkish Cancer Registry (KIDEM).[17,18] The expected value was then calculated by utilizing the indirect standardization method. Cox regression analysis was modeled separately and in combination in order to analyze the effect of age, gender, duration of stay in the village, and the age at the first year living in the village. Statistical software was used for analysis (SPSS 13.0).

Investigations of houses and minerals

The streets of the village were toured together with the headman and 2 of the oldest villagers, specifying whether mesothelioma had occurred among former inhabitants of the houses. The types of stone used in construction and the location of each of these houses were registered. The source of each type of stone was established by contacting older stonemasons. The mid-section of the village is today mostly in ruins, but the stones used could be identified.

Samples were obtained from every stone and soil in 3 sets. One was subjected to x-ray diffraction (XRD) at the Ceramic Institute of Anadolu University to determine the main mineral phases. Fibrous minerals were searched for in the 2 other sets sent on different dates to Erasme Hospital, Brussels, Belgium. After macroscopic examination, fragments of samples were crushed under acetone. After drying, the resulting dust was suspended in carbon tetrachloride, dispersed by ultrasonication and collected on 0.45-μm porosity cellulose ester membrane filters. The filters were fixed on glass slides and clarified by exposure to acetone vapours. For examination under light microscopy, slides were covered with immersion oil (refractive index: 1.518). Light microscopic examination was performed at 100× to 400× magnification with natural and polarized light, and under phase contrast. For electron microscopic examination, sections of filters were carbon coated and transferred to Cu-supporting grids. Fibers were searched for using transmission electron microscopy (TEM) at magnifications ranging from 2800× to 28000×. Chemical composition of the fibers was determined by energy dispersive x-ray spectrometry (EDS) and compared to a set of reference spectra, including Oregon erionite and UICC asbestos reference samples.[7]

The persons who conducted the analyses did not have any information on the locations of the stone samples and whether these samples had any connection with persons with disease.

RESULTS

Demographic characteristics and prevalence of mesothelioma

The cohort comprised 322 individuals who resided in Karain village any time between the years 1990–2006, and for whom data in the registers could be studied (Table 1).

Table 1.—Characteristics of Karain Village Cohort.

Characteristics	Number,%
Karain cohort, number	322
Male	154 (47.8%)
Female	168 (52.2%)
Mean age of the cohort, year (range)	53.3 ± 18.5 (22–95)
Male*	52.3 ± 18.2 (22–88)
Female*	54.3 ± 18.6 (22–95)
Status, number	
Living	220 (68.0%)
Dead	103 (32.0%)
Migration characteristics, number	
Not migrated	187 (58.1%)
Emigrated	71 (22.0%)
Immigrated	42 (13.0%)
Emigrated, then came back	22 (6.8%)

*$t = 0.946$; $p = .345$ between the ages of the male and female.

Of the 103 deaths, 52 were due to MM (22 men and 30 women), representing about half (50.5%) of all deaths. In 32 cases (62%), the results from the "verbal autopsies" were confirmed by hospital diagnoses.

There were 3851.0 person-years in the cohort, 1851.0 for males and 2000.0 for females. The annual MM incidence rate (AMIR) for males was significantly lower than that for women (Table 2).

Those who died from MM were significantly younger at death than the 51 persons who died from other causes (59.9 ± 13.6 and 68.6 ± 17.1 years, respectively) ($t = 2.873$; $p = .005$). The men who died from MM tended to be older than the women who died from it (63.5 and 56.4 years, respectively), but this was not statistically significant ($p = .09$).

The age of diagnosis of the patient was assumed to be the latent period of the disease, since exposure starts with birth.

Years spent in Karain

Years spent in Karain were 53.8 ± 15.8 years (range: 27–79 years) for MM cases; 56.0 years for men, 52.1 years for women ($p = .381$). No MM victim had lived less than 20 years in the village (Table 3), and the 3 with the shortest stay in Karain had spent 27, 29, and 29 years, respectively, there. Among individuals living in the village for 20–29, 30–39, 40–49, or over 50 years, the prevalences of mesothelioma were 5%, 24%, 28%, and 20%, respectively.

According to the findings in Table 3, the lowest mesothelioma incidence was found in villagers who lived 20 to 29 years there, and the highest rate was observed in those with 30 to 49 years of stay. Mesothelioma death rates in those who had lived more than 50 years in the village appeared to decrease (Figure 1).

The multivariate analysis results of independent factors affecting mesothelioma development are shown in Table 4; only years living in the village was found to be significant.

Migrations

MM developed in 11 (11.8%) of 93 persons who left Karain between the years 1990 and 2006. The average age at MM diagnosis in this group was 60.1 ± 10.6 years, and the mean time living in the village was 39.3 ± 12.2 years, which is similar to those who stayed in the village. The mean age of the 82 persons who did not develop MM was 41.2 ± 13.6 (23–86) years, and their mean stay in the village was 26.0 ± 14.4 (4–84) years.

Six of the individuals who immigrated to Karain were males who married Karain women, and no mesothelioma was observed among them. Their mean age was 45.3 ± 11.1 (32–59) years, their age at moving to Karain was 21.7 ± 11.7 (7–34) years, and the time spent there was 24.2 ± 4.8 (16–30) years.

Forty-one women, all unrelated to the villagers, came from other villages where neither asbestos nor erionite occurs. Three of the 5 who died during the period studied succumbed to MM. The mean age of the 38 women without MM was 44.7 ± 17.5 years, and they had lived in Karain for an average 20.1 ± 17.1 years. The 3 MM victims were aged 53, 69, and 89 years, and their stay in Karain was 29, 44, and 51 years, respectively.

From 1930 to 2006, 64 women are known to have moved to Karain for marriage. They came from 9 different villages, in none of which has erionite or asbestos have been found. Sixteen of them died, and 11 of the deaths (69%) were due to MM (Table 5). Thus, MM developed in 9 (38%) of the 24 brides who had lived in the village for 30 years or more, and in 2 (5%) of the 40 brides with less than 30 years' stay there.

Table 2.—Average Annual Mesothelioma Incidence Rates (AMIR) per 100,000 in the Karain Cohort and Observed/Expected Rate (O/E).

Gender	Observed cases	AMIR (100,000)	(O/E)
Men	22	639 (597.5–681.1)	687.5 (447.6–1032.5)
Women	30	1,267 (1231.08–1302.7)	1,666.7 (1134.1–2319.7)

Note. 95% confidence intervals (CIs) are given in parentheses.

Table 3.—Mesothelioma Incidence Rates Based on Duration of Stay and Gender.

Living in Karain, years	Male		Female	
	Death	Death rate (95% CI)	Death	Death rate (95% CI)
1–19	0	0	0	0
20–29	1	295.9 (99.9–491.9)	2	646.2 (507.6–784.8)
30–39	5	1623.4 (1535.7–1711.0)	6	2580.6 (2500.6–2660.7)
40–49	3	1463.4 (1350.3–2868.3)	5	3367.0 (3279.4–3454.7)
≥50	13	1416.1 (1361.8–1470.4)	17	1685.7 (1638.1–1733.2)

Note. CI = confidence interval.

Table 4.—Multivariate Analysis Results of Independent Variables that Affected Mesothelioma Development in the Karain Village Cohort.

Variable	RR	95% CI	*p*
Born in village	0.700	0.332–1.476	.349
Years spent in village	1.628	1.070–2.474	.023
Gender	1.441	0.822–2.528	.202

Stones used for Karain village houses and MM

A total of 8 stone types and 1 kind of soil (for coating purposes) have been used in construction from the 1900s until recent years (Table 6, Figures 2 and 3). Erionite was detected only in Akkusak stone and water stone. Both types of stones have been used almost exclusively in homes in the mid-sections of the old Karain village, and less commonly on the north side of the village. MM was prevalent in families living in nearly all the houses in this part of the village. MM was not detected in those who had lived in houses constructed mostly from Keyrek and Urgup stones, predominantly located on the west side of the village. No MM cases were seen in families living in homes located near the east entranceway of the village that were constructed from Akkoy and Urgup stones. No cases were observed in residents of houses closer to the caves on the north side of the village, which were built by carving out rocks from the caves.

Stones and minerals in Karlik

Akkusak stone does not exist in the village of Karlik. In some parts of the village, however, there were stones on the ground resembling the water stone and containing erionite. They were never used for construction purposes.

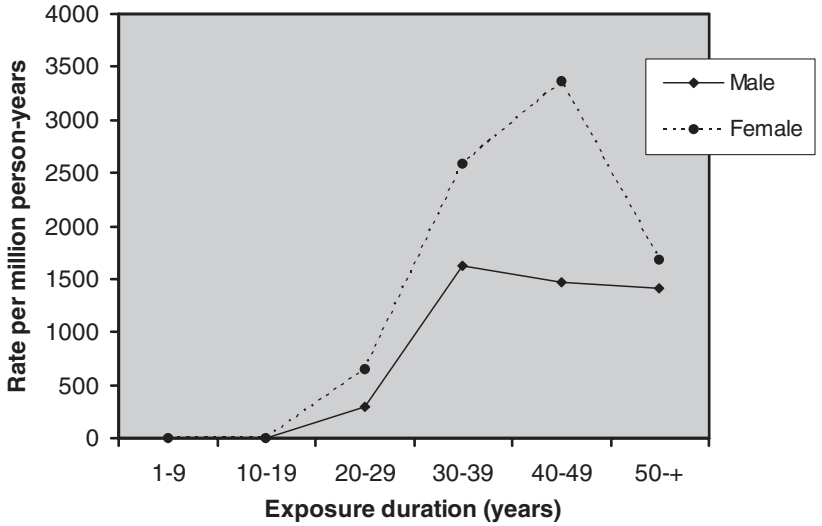

Fig. 1. Relation between the risk of mesothelioma and the years of staying in Karain based on gender.

Table 5.—Characteristics of Women Who Immigrated as Brides to Karain Since 1930.

Characteristics	Died of mesothelioma ($N = 11$)	Died from other causes ($N = 5$)	Living ($N = 48$)	p value
Age of death, year, $M \pm SD$	60.1 ± 13.8 (50.8–69.4)	70.0 ± 15.51 (45.3–94.7)	—	
Mean age of the living, (range)	—	—	48.4 ± 15.6 (21–96)	
Age of moving to Karain, year, $M \pm SD$	24.6 ± 8.7 (14–44)	20.6 ± 6.8 (12–30)	20.6 ± 6.6 (12–47)	$F = 1.525$; $p = .226$
Years of living in Karain, $M \pm SD$All	38.7 ± 9.1 (20–51)	47.0 ± 16.8 (25–71)	22.06 ± 16.97 (0–67)	$F = 9.216$; $p = .000$
0–9	—	—	10 (20.8)	
10–19	—	—	13 (27.1)	
20–29	2 (18.2)	1 (20.0)	14 (29.2)	
30–39	4 (36.4)	0	5 (10.4)	
40–49	4 (36.4)	2 (40.0)	1 (2.1)	
50 and above	1 (9.1)	2 (40.0)	5 (10.4)	

COMMENT

Because practically all those who have emigrated from Karain continue their connections with the village, reliable information was available for these individuals as well as those who stayed. MM is the most well-known disease in the village for the last 30 years, and hospital records, when available, confirmed the "verbal" diagnosis.

More than half of deaths were due to MM. The average annual mesothelioma incidence per 100,000 was 639 for men and 1,266 for women, the world's highest values. The women in the village have a higher risk for mesothelioma than the men, confirming findings from native Karainers living in Stockholm.[11] In a study from Turkish villages with high asbestos exposure, women also had a higher risk than men, with an O/E rate of 53 and 144, respectively (19).

Some authors have shown a higher risk for women.[20,21] In our study, the upper value of the confidence interval of males for AMIR is much lower than the low value of the confidence interval of females (Table 2). This may indicate that females in the Karain cohort have a higher risk of MM than the males. As an explanation, a difference between male and female respiratory physiology has been suggested.[21] For villagers exposed to environmental asbestos or erionite, more time spent in houses by women and heavier exposure due to sweeping and house cleaning could be another explanation.[22] In fact, the mean cumulative exposure to erionite for women was more than that for men, despite fewer years spent in Karain. In addition, the multivariate analysis of independent factors affecting mesothelioma development, including gender, revealed that only the years living in the village was significant (Table 4). In bronchoalveolar lavage of 65 Turkish villagers with environmental asbestos exposure, the levels of asbestos bodies and fibers in women were not higher than in men.[23] In Wittenoom, Western Australia, an area with considerable environmental pollution from an asbestos mine,

Table 6.—Stone Types Used in Karain Village Houses.

Stone name	Quarry site and some characteristics of stone	Years of usage	Usage	Mineral fiber content
Örencilik stone	Stone quarried from the hills west of village	1940–1980	Present in 70% of all homes. For walls	None
Keyrek	Quarried from the far hills west of village	1940–1965	For walls	None
Rock stone	Stone cut from the caves and cavities over the village	1930–1960	For storerooms, 90% made from this stone	None
Akkusak stone (Figures 2, 3)	Stone quarried from a hill 1 km north of the village. Nodules in pores	1900–1960	For walls of houses	Erionite within the nodules of the stone
Akkoy stone (Figure 3)	Obtained from a village 6 km west of Karain	1940–1965	For big houses and mosque	None
Water stone (Figure 3)	Quarry site unknown	1900–1960	Walls of some houses	Erionite within nodules
Incesu stone (Figure 3)	Obtained from a site 2 km west of village. Rigid and dark-colored stone	1940–1970	Garden walls of some of the houses	None
Urgup stone	Obtained from Urgup	1970–	Newly built houses	None
Soil for stucco purposes	From Boyali village	1940–1970	Inner walls	None

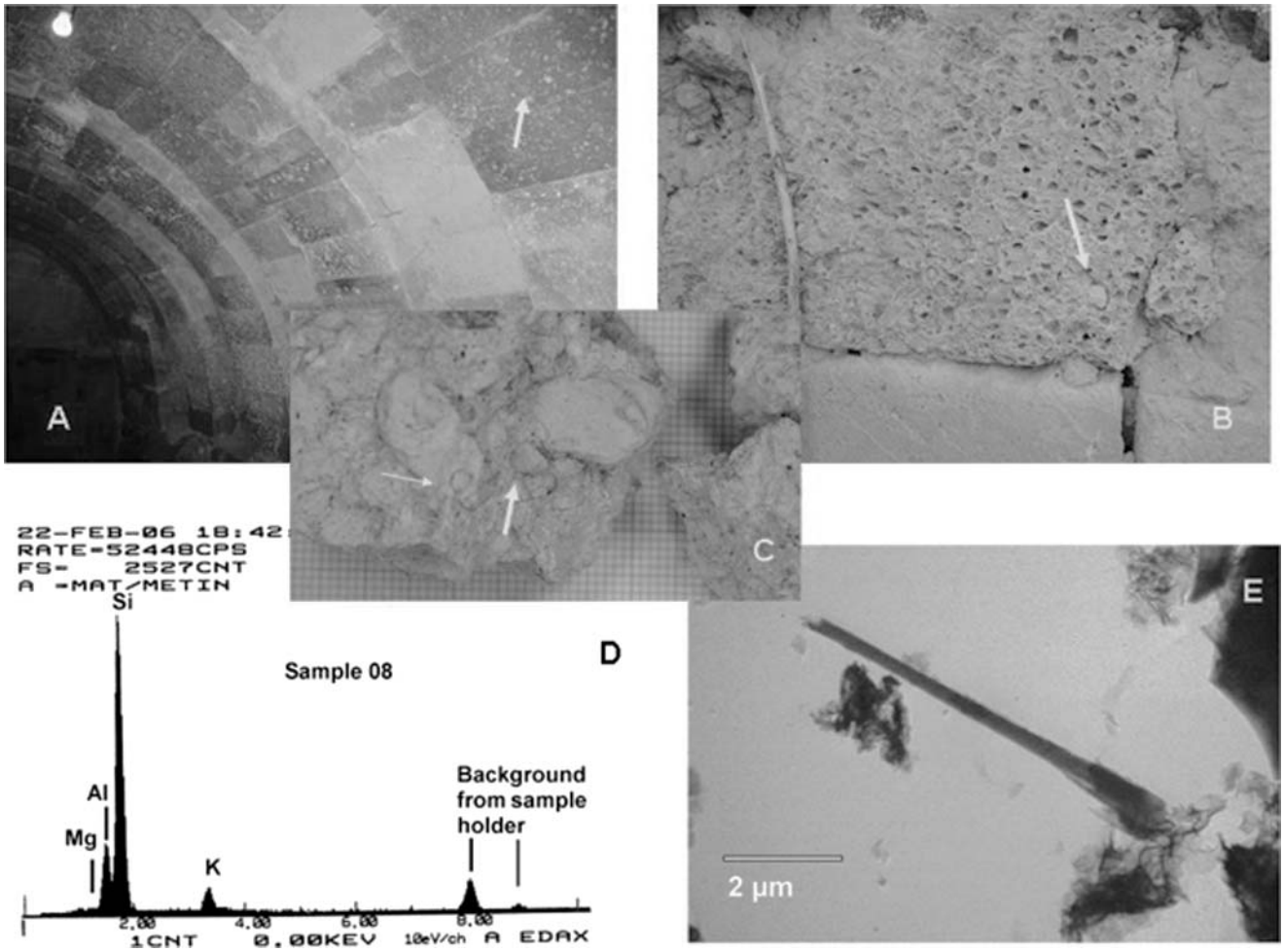

Fig. 2. **(A) Archway of a room built with Akkusak stone. (B, C) Close views of Akkusak stone: empty or filled (*arrows*) nodules. Erionite occurs in stone powders within these nodules, which crumble in time, releasing the fibers. The main stone structure remains. (D) Energy dispersive x-ray spectra showing erionite from Akkusak stone. (E) Electron microscopic view of an erionite fiber from the same sample.**

women had a steeper dose-response curve than men.[24] Thus, we need further studies to confirm whether women might be more prone to develop MM than men.

Duration of stay in the village

An analysis of mesothelioma incidence rates based on duration of stay in the village and on gender is given in Table 3 and Figure 2. There were no mesothelioma cases in villagers who had lived less than 20 years in Karain. The lowest mesothelioma incidence was found in villagers who had lived there for 20 to 29 years, and the highest rate was observed in those who had lived there for 30 to 39 years. Mesothelioma death rates in those who had lived for more than 40 years in the village were not significantly higher than those with shorter stays. In other words, continued living in the village after 40 years did not significantly increase the risk of mesothelioma, and after 50 years, the risk may decrease. Thus, there seems to be a dose-response curve up to a certain point, after which more exposure does not further increase the risk.

Immigrants to the village

Those who have immigrated to the village are of special interest. Between 1990 and 2006, 3 women who came to Karain as brides died from MM. This motivated us to investigate all brides who migrated to Karain from 1930 onwards for whom data were possible to attain. One fourth of this group were already dead, with MM being the cause of death in almost 70%. The median age of the brides who died from MM was 60 years, and their average stay in the village was almost 40 years. Thus, there was no difference between the native Karain villagers or the ones who migrated to the village in

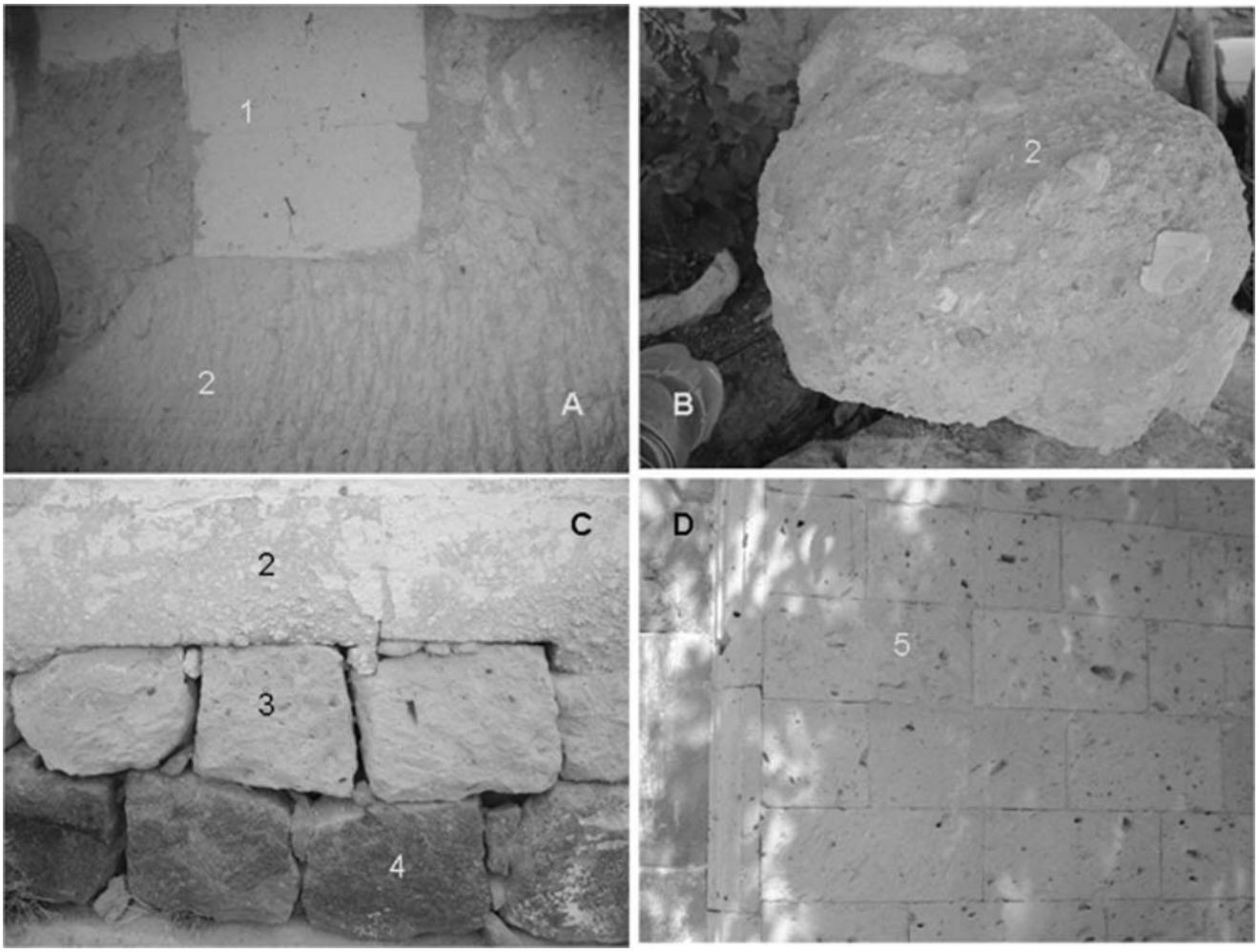

Fig. 3. **Other stone samples used for building in Karain village. (A) Orencilik stone (1), water stone (2). (B) A closer look at the water stone. Other types of stone structures that seem like nodules also exist in this stone sample. Water stone spreads out on the vast mid-section ground of the village. (C) A wall sample: rock stone (2), Orencilik stone (3), Incesu stone (4). (D) A wall built by using Akkoy stone.**

terms of MM risk. The women came from other villages, where MM is unknown.

Rocks used in construction of houses

Different homes were constructed from different stone types, only some of which contain erionite. Thus, many persons, even if they have lived for decades in the village, have had no exposure, or only very slight exposure, to erionite. The exposure takes place mainly or exclusively indoors with the Akkusak stone, which was commonly used in walls and arcs in the old houses. This stone has nodules with contents that easily turn into dust containing erionite. Outdoor erionite levels are very low, just as they are in Karlik village, where only 2 mesothelioma cases have been reported, one of whom was actually born in Karain.[3,10,16]

The Akkusak stone used to be mined from a stone ore approximately 2 m thick that surrounds a relatively high hill behind the village. Craftsmen used to go out to the ore, cut stone blocks of around 50 × 50 cm, and carry 2 to 3 at a time with help of mules or horses. From the 1960s onwards, other types of stones from spots closer to the village were used. Erionite has not been detected in these types of stones.

Genetics

From pedigree analyses carried out in the villagers, it was suggested that the disease is due to an autosomal dominant gene.[13] However, as the authors themselves acknowledged, there are difficulties in obtaining those pedigrees. Kin marriages are common, as are remarriages when the spouse has died. Because in those cases women take their husbands' family name, distinguishing children from different

marriages can be difficult as the years pass, and the margin of error is high. There are no population or health records in Turkey that go back to the 5th and 6th generations.[25] Furthermore, if 50% or more of all deaths in a village are due to mesothelioma, drawing any conclusions from clusters of the disease in certain families is difficult.[25] A high erionite exposure in one house could cause a high MM risk in many generations of the family living there (and in any brides moving in).

Sporadic clusters of mesotheliomas in blood relatives have been reported in the literature. However, it is only a small portion of all mesothelioma cases, and almost always there is a common exposure history. The conclusion of most authors is that a large genetic component is unlikely.[26,27]

Conclusion

The extreme MM risk in Karain village is due to indoor exposure to erionite in certain houses. Those born in the village, as well as those migrating to it (mainly as brides), suffer the same risk. In this field study, we did not found any data on genetic susceptibility to MM; however, the data from this and other studies are not sufficient to make a judgment concerning whether genetic susceptibility can play a facilitating role, but our findings indicate that such a role is probably fairly minor compared to erionite exposure.

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For comments and further information, address correspondence to Muzaffer Metintas, MD, Professor, Department of Chest Diseases, Eskisehir Osmangazi University Medical Faculty, Eskisehir, Turkey.

E-mail: muzaffermetintas@gmail.com

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