Genetic Predisposition to Fiber Carcinogenesis Causes a Mesothelioma Epidemic in Turkey

A. Umran Dogan,[1,5] Y. Izzettin Baris,[2] Meral Dogan,[3] Salih Emri,[4] Ian Steele,[6] Amira G. Elmishad,[7] and Michele Carbone[7]

[1]Department of Geological Engineering, Ankara University; [2]Chest Diseases Division, Guven Hospital; Departments of [3]Geological Engineering and [4]Pulmonary Medicine, Hacettepe University, Ankara, Turkey; [5]Department of Chemical and Biochemical Engineering, University of Iowa, Iowa City, Iowa; [6]Department of the Geophysical Sciences, University of Chicago, Chicago, Illinois; and [7]Thoracic Oncology Program, Cardinal Bernardin Cancer Center, Loyola University, Maywood, Illinois

Abstract

Malignant mesothelioma in the western world is often associated with asbestos exposure. It is a relatively rare cancer that causes ~2,500 deaths yearly in the United States and 1,000 deaths yearly in the United Kingdom. In contrast, among people born in the Cappadocian (Turkey) villages of Tuzkoy, Karain, and "Old" Sarihidir, ~50% of deaths are caused by malignant mesothelioma. This epidemic has been attributed to erionite exposure, a type of fibrous zeolite mineral commonly found in this area of Turkey. In these three villages, malignant mesothelioma occurs in certain houses but not in others. The hypothesis was that a unique and more carcinogenic erionite was present in certain houses and caused malignant mesothelioma. We determined the X-ray diffraction pattern and the crystal structure of erionite from malignant mesothelioma villages and compared the results with the erionite samples from nearby non–malignant mesothelioma villages and from the United States. We found the same type of erionite in Cappadocian villages, with or without a malignant mesothelioma epidemic, in households with high or no incidence of malignant mesothelioma and in the United States. Pedigree studies of the three malignant mesothelioma villages showed that malignant mesothelioma was prevalent in certain families but not in others. When high-risk malignant mesothelioma family members married into families with no history of it, malignant mesothelioma appeared in the descendants. Genetically predisposed family members born and raised outside the malignant mesothelioma villages did not seem to develop malignant mesothelioma. In summary, pedigree and mineralogical studies indicate that the malignant mesothelioma epidemic is caused by erionite exposure in genetically predisposed individuals. This is the first time that genetics is shown to influence mineral fiber carcinogenesis. (Cancer Res 2006; 66(10): 5063-8)

Introduction

A mesothelioma (malignant mesothelioma) epidemic occurs in three villages in Cappadocia, Turkey: Tuzkoy (population ~1,400), Karain (population ~1,600), and "Old" Sarihidir (the village was abandoned between late 1950s and early 1960s when the population was ~250). This epidemic has been linked to erionite exposure (1–4). Erionite is a fibrous zeolite mineral formed by alteration of volcanic rocks, such as those found in the Cappadocian region of Turkey and in other geologically similar areas of the world. Its structure is composed of a (Si and Al) O_2 three-dimensional framework where each O atom links two (Si and Al) atoms (5). The framework contains cavities or "cages" of characteristic geometry in which cations, including K, Ca, Na, and Mg, reside. Also found in these cages are variable amounts of water and hydroxyl ions. The stoichiometry is nominally $K_2Ca_{1.5}NaMg(Al_8Si_{28})O_{72} \cdot 28H_2O$ but varies considerably and with the cations occupying several positions within the cages (see below). In 1997, the International Mineralogical Association recommended a new nomenclature for zeolite minerals (6). Three types of erionite were identified and differentiated based on differences in the amount of Ca, Na, and K, which are the predominant large cations, and to the low amounts of Mg, Fe, Sr, and Ba in the structure. It was recommended that published literature about previous erionite analyses should be relied upon only if quantitative analyses were done and if the balance error (E%) was ≤10% (see Materials and Methods; refs. 6, 7). Because the previous studies that linked erionite to the malignant mesothelioma epidemic in Cappadocia did not calculate the balance error or its crystal structure, it is unproven that the mineral identified as the cause of the epidemic was indeed erionite and not a closely related mineral (5).

It has been shown that even very limited exposure to Cappadocian erionite fibers is sufficient to cause malignant mesothelioma (8–10). Erionite is a chemical carcinogen and mutagen (11) and animal experiments have shown that erionite is more potent than crocidolite in causing malignant mesothelioma (12). It has been suggested that erionite increases the balance between cell proliferation and apoptosis and that a lower amount of erionite compared with crocidolite asbestos is required to induce c-Jun mRNA, a mechanism that has been linked to fiber carcinogenesis (13). We reported previously that malignant mesothelioma in the villages of Tuzkoy and Karain occurs predominantly in certain families, whereas families living in nearby houses do not develop malignant mesothelioma (1, 14). Nearby villages, such as Karlik, 1.5 km from Karain, do not experience excess malignant mesothelioma. These differences have been attributed to the absence of erionite in Karlik and/or to the presence of a putatively "different" type of erionite in certain houses in the nearby malignant mesothelioma villages (1). The hypothesis that a more oncogenic type of erionite caused the malignant mesothelioma epidemic in certain villages but not in others seemed supported by the observation that erionite is present in California, Nevada, Oregon, etc., as well as in several European countries. However, outside of Cappadocia erionite has not been linked to malignant mesothelioma (1, 15). In this study,

we did quantitative mineralogical analyses to test the hypothesis that there were differences in erionite samples from the malignant mesothelioma villages versus erionite samples from non–malignant mesothelioma villages or from the United States and within the same malignant mesothelioma village among different houses. In addition, we did pedigree analyses in the three malignant mesothelioma villages to test the hypothesis that genetic predisposition, rather than erionite carcinogenesis, caused the malignant mesothelioma epidemic. Our data indicate that erionite and genetics together influence the malignant mesothelioma epidemic.

Materials and Methods

Mineralogical studies. The mineral samples were collected from the villages of Tuzkoy, "Old" Sarihidir, Karain, and Karlik. Because erionite is a minor component in rock samples, separation and concentration is required before chemical analysis. This was accomplished by a tedious hand-picking process for each of the 70 samples, as the grain size is $\sim 7 \times 50$ μm rods or fibers. The samples were studied with an optical microscope to verify the presence of fibrous material and with a scanning electron microscope (SEM) to determine the morphology of the fibrous crystals. The purity was estimated using energy-dispersive spectroscopy (EDS) and SEM observation of the morphology of individual micron-sized fibers and by powder X-ray diffraction (XRD). These samples of concentrated erionite were then sent for chemical analysis using the inductively coupled plasma-mass spectrometry (ICP-MS) technique at the ACME Analytical Laboratories (Vancouver, British Columbia, Canada). The H_2O content was determined as described (16). An erionite sample from Rome, OR was used as a control. Of the 70 samples, 17 analyses showed acceptable balance errors; 53 samples contained additional minerals and are not discussed further. It is not unusual to have to discard $\sim 80\%$ of the mineral samples collected, because it is impossible when taking a rock sample to be certain of its purity.

The balance error is defined as: $E\% = [(Al + Fe^{3+})_{obs} - Al_{th}] / Al_{th} \times 100$, where $Al_{th} = Na + K + 2 (Ca + Mg + Sr + Ba)$ (6, 7). Its use was recommended in 1970 (7), but only recently its value has been universally accepted. The balance error checks that the results obtained are compatible with the chemical composition and the structure of the mineral, preventing erroneous interpretations of the data.

All diagnosis of malignant mesothelioma, including clinical records, radiology, and pathology, were either originally made (because most of these individuals were their patients) or carefully reviewed by members of our team.

Results

Pedigree analyses revealed that in the malignant mesothelioma villages malignant mesothelioma was more frequent in certain families compared with others. However, in some families, malignant mesothelioma developed among individuals who married into the affected family. For example, in one family, 17 of 30 members died of malignant mesothelioma (Fig. 1, family 1). Among the 17 malignant mesothelioma, 5 occurred in individuals who married into this family. This finding argued against genetic predisposition and suggested instead that either an infectious agent caused or contributed to malignant mesothelioma or a more carcinogenic type of erionite was present in this family house (multigeneration families often live in the same house because of economic constraints).

Using the PCR followed by Southern blot hybridization with radioactive probes, we tested 10 malignant mesothelioma samples from malignant mesothelioma Cappadocian families for SV40. SV40 is the only infectious agent that has been linked to malignant mesothelioma (17). All Cappadocian samples tested negative,

whereas 2 of 5 of the U.S. malignant mesothelioma samples analyzed in parallel tested positive (data not shown; for Methods see ref. 18), supporting previous studies indicating that SV40 is not present in Turkish malignant mesothelioma (18, 19).

Next, we tested the hypothesis that some houses in the malignant mesothelioma villages contained a type of erionite with some chemical difference that could possibly account for increased carcinogenicity. We collected representative erionite samples from Tuzkoy, Karain, and "Old" Sarihidir and in the non–malignant mesothelioma village of Karlik for chemical analysis. Standard erionite (control) from Rome, OR was analyzed in parallel. Erionite samples were also taken from houses with high incidence of malignant mesothelioma and houses with no incidence to test the hypothesis that the clustering of malignant mesothelioma in certain households and villages was caused by differences in the
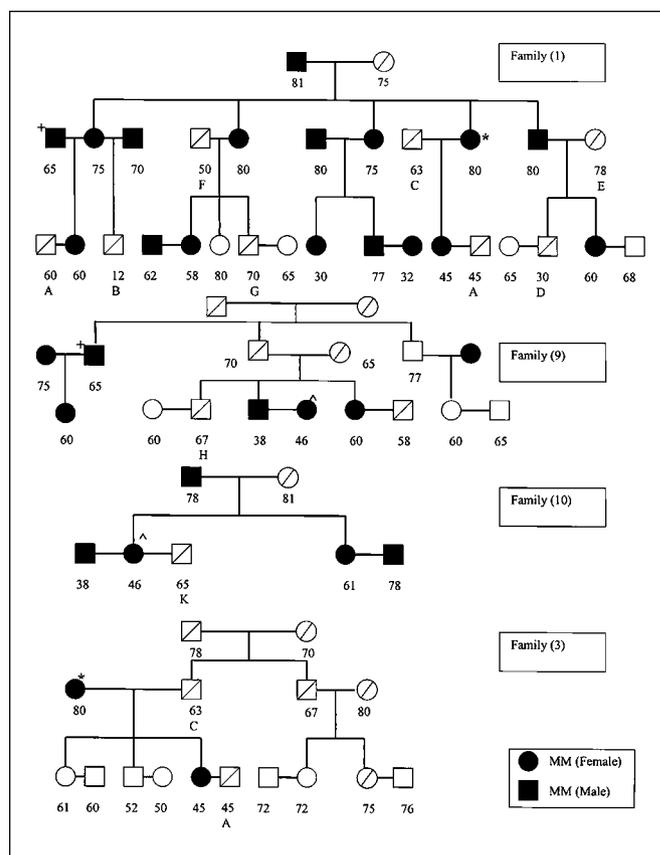

Figure 1. Family 1: Pedigree from the now abandoned village of "Old" Sarihidir showing a family of 30 in which 17 died of malignant mesothelioma (*black symbols*), 4 died of other cancers [osteosarcomas (*B*), leukemia (*D*), prostate cancer (*F*), and pancreatic cancer (*G*)], 4 died of reasons other than cancer [2 traffic accidents (*A*), 1 intestinal occlusion (*C*), 1 congestive hearth failure (*E*), and 1 unknown reason (first generation, female; *F*)], and 4 are alive (*white symbols*). Five malignant mesothelioma developed in individuals who married into the family. They were also from malignant mesothelioma families. *Bottom*, representative examples. Family 9: Pedigree of the family of origin of 65-year-old male (+) marrying into family 1. Seven of the 17 people of this two-generation pedigree died of malignant mesothelioma, 1 of liver cancer (*H*), and 5 unknown. The deaths for malignant mesothelioma include a 46-year-old female (^) who married into family 9. The family of origin of this woman (family 10) has a very high incidence of malignant mesothelioma: 5 of the 7 family members died of malignant mesothelioma and 1 of lung cancer (*K*); the remaining cause of death is unknown. Family 3: When members of family 1 (*) marry into a non–malignant mesothelioma family, malignant mesothelioma appears in the descendents. *A*, traffic accident; *C*, intestinal occlusion; the other causes of death were not cancer related but could not be established with certainty.

presence or type of erionite. A representative SEM image of erionite from Karlik, a non–malignant mesothelioma village, is shown in Fig. 2. Erionite fibers are formed by bundles of individual fibrils with a diameter of ~0.5 μm, measuring 5 to 6 μm in diameter, and are 30 to 40 μm long. There were no appreciable differences in size among samples from different villages or from Oregon (control). Chemical analyses provided a quantitative composition, a mineral formula (based on 72 oxygens) and the balance error (Table 1). As required (6, 7), only the 17 analyses for which the balance error was <10% and which showed <0.8% Mg were accepted (see Materials and Methods). The results show SiO_2 concentrations slightly above values usually determined for erionite (~68% versus ~60%); likewise, the values of H_2O are lower. It remains possible that the technical approach we used (ICP-MS for bulk analyses and SEM-EDS for individual mineral analyses) compared with electron probe microanalysis (EPMA) of individual fibers of previous studies (16) may account for some differences. However, this hypothesis seems unlikely because, in parallel, we tested a sample of Oregon erionite and we obtained results comparable with those reported (refs. 6, 7, 15, 16; Table 1). Therefore, the erionite from these Cappadocian villages has high SiO_2 that, however, seems irrelevant to carcinogenesis because it is not associated with any one village (i.e., it is a characteristic of the erionite of both malignant mesothelioma and non–malignant mesothelioma villages). The content of Fe_2O_3 was higher in the malignant mesothelioma villages and in the control erionite from Oregon compared with the non–malignant mesothelioma village of Karlik (Table 1). Iron content has been linked to asbestos carcinogenesis (20). However, it is unclear if the differences detected here could be related to carcinogenicity because the highest amount of Fe_2O_3 was found in the erionite sample from Oregon (Table 1), a region where, thus far, erionite has not been associated with malignant mesothelioma. In summary, there is an apparent chemical feature shown by high SiO_2 and Fe_2O_3 and low H_2O that makes Cappadocian erionite slightly different compared with other analyzed samples. Minor to trace elements (Mn, Ti, Cr, and P) were detected and there were no significant difference in samples from the four villages. Only trace
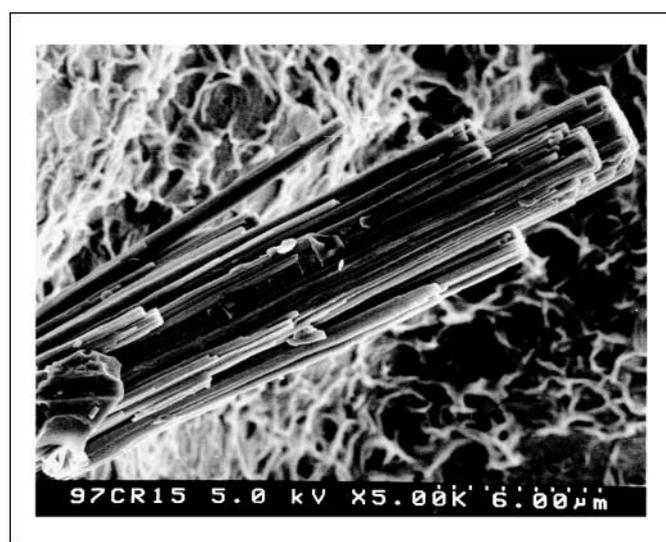

Figure 2. Representative SEM image of erionite from a sample taken in the non–malignant mesothelioma village of Karlik. The accelerating voltage used was 5 kV. Bar, 6 μm. Note the individual fibrils (0.5 μm in diameter) forming the erionite bundles (~5 μm in diameter).

to undetectable amounts of Ba and Sr were found. Using powder XRD, we compared the diffraction pattern of two erionite enriched samples from Tuzkoy, N-25-1 and N-25-2, with three reference erionite diffraction patterns included in the Joint Committee of Powder Diffraction Spectroscopy reference database and with the diffraction patterns of erionite from Pine Valley, NV and Rome, OR. With minor exceptions, the agreement among the patterns was very good. The diffraction technique must be used on a bulk sample, and although it is specific for erionite, it has some limitations. (*a*) The presence or absence of amorphous material, specifically Si-rich glass from which erionite forms, may not be recognized. (*b*) Minor crystalline contaminant material at levels <5% are difficult to recognize. (*c*) Some specific phases with a similar structure to that of erionite (specifically the mineral offretite) are either not possible or extremely difficult to recognize (16). We addressed this concern by using the Advanced Photon Source Synchrotron (APSS) at the Argonne National Laboratory (affiliated with the University of Chicago), the only facility in the United States that can perform this type of analyses. The crystal structure of a single grain from sample N-25 from the village of Tuzkoy measuring 7 × 7 × 25 μm was determined (Fig. 3) and the results identified this grain as erionite and confirmed the absence of offretite.

Because we did not identify any particular mineralogical differences among erionite from malignant mesothelioma villages compared with erionite from non–malignant mesothelioma villages or from Oregon, and given the ubiquity of environmental exposure within each village, the obvious question is why there is such variability in risk. An additional hypothesis to account for the observation shown in Fig. 1 (family 1) of a very high incidence of malignant mesothelioma in family members and in those who married into this malignant mesothelioma family was that also those who married into this family had genetic predisposition to develop malignant mesothelioma.

We constructed 18 family pedigrees from "Old" Sarihidir, 4 of them are shown in Fig. 1. Malignant mesothelioma was found with various incidences (two or more) in 10 of 18 families and most of these families were related; 4 families had only one case of malignant mesothelioma; no malignant mesothelioma occurred in the 4 remaining families. We also prepared 3 family pedigrees from the village of Karain and 3 from Tuzkoy: 5 of them had multiple cases of malignant mesothelioma; 1 pedigree from Tuzkoy had a single case of malignant mesothelioma.

We found that those who married into a malignant mesothelioma family (Fig. 1, family 1) and who developed malignant mesothelioma were also from malignant mesothelioma families (Fig. 1, families 9 and 10). When members of a family with high incidence of malignant mesothelioma married into families with no history of malignant mesothelioma, descendents developed malignant mesothelioma (Fig. 1, family 3).

To test the hypothesis that genetics alone could cause malignant mesothelioma in certain families, we identified 24 descendants from family 1 ages 26 to 45 years who were born and raised outside the village of "Old" Sarihidir after the village was abandoned. No malignant mesothelioma developed in this group; instead, three malignant mesothelioma cases were observed in the same age group among 29 members of family 1 who were born and raised in "Old" Sarihidir and thus exposed to erionite (Fig. 1). The estimated odds ratio between the two groups is 6.47, indicating that individuals born and raised in "Old" Sarihidir are at 6.5 higher risk to develop malignant mesothelioma compared with family

members born and raised outside this village. Although it will take a few more years to confirm that the incidence of malignant mesothelioma is lower in family members born outside "Old" Sarihidir, and it may take 20 to 40 more years to see whether they develop malignant mesothelioma at all, these findings are consistent with a model of cocarcinogenicity between genetics and erionite.

Discussion

Our results indicate that the malignant mesothelioma epidemic in three Cappadocian villages is caused by the interaction among the chemical carcinogen erionite with genetics. Using SEM, chemical analyses, XRD, EDS, and APSS (see Materials and Methods), we determined for the first time the crystal structure and chemical composition of erionite from the Cappadocian malignant mesothelioma villages and compared the results with the erionite from nearby non–malignant mesothelioma villages and from Oregon. All chemical analyses were verified determining the balance error (see Materials and Methods). These studies showed that Tuzkoy has predominantly erionite-Na; Karain, "Old" Sarihidir, the non–malignant mesothelioma village of Karlik, and Rome, OR (control) have predominantly erionite-K (Table 1). The three

malignant mesothelioma villages have about the same incidence of malignant mesothelioma ($\sim 50\%$ of deaths). Within the same village, no differences in composition or in presence of erionite were found among houses with high and low or no incidence of malignant mesothelioma; all the houses tested contained erionite. Therefore, we found no evidence to support the hypothesis that the composition or textural features of erionite show consistent differences among the four villages (three malignant mesothelioma villages and one non–malignant mesothelioma village) that could account for the striking different incidence of malignant mesothelioma among these nearby villages. We are in the process of purifying erionite from different Cappadocian villages to verify in future experiments in tissue culture and in animals that these samples and erionite samples from the United States have similar biological effects.

In parallel to the mineralogical analyses, we did pedigree studies in the malignant mesothelioma villages. The results showed that malignant mesothelioma was prevalent in certain families and absent in others and that when members of non–malignant mesothelioma families married into a malignant mesothelioma family some of the descendents developed malignant mesothelioma (Fig. 1).

Table 1. Mean chemical composition of erionite from malignant mesothelioma villages compared with that of the non–malignant mesothelioma village of Karlik and control erionite from Oregon

n	Tuzkoy	"Old" Sarihidir	Karain	Karlik	Rome, OR	
	8	3	3	3	1	Ref. 22
SiO_2	67.89	65.82	68.19	70.49	60.70	60.81
Al_2O_3	12.57	13.13	12.58	11.84	12.32	13.59
Fe_2O_3	1.28	1.36	1.50	0.86	3.39	3.63
Na_2O	3.18	1.74	2.36	2.21	2.16	1.90
K_2O	3.86	3.98	4.01	5.54	4.71	7.17
MgO	0.59	0.85	0.64	0.63	1.12	0.80
CaO	1.88	1.98	2.12	1.07	1.67	1.54
MnO	0.05	0.05	0.06	0.05	0.05	0.00
TiO_2	0.15	0.21	0.19	0.09	0.48	0.00
Cr_2O_3	0.002	0.001	0.003	0.002	0.007	0.00
P_2O_5	0.02	0.04	0.05	0.02	0.07	0.00
H_2O	8.30	10.80	8.13	6.93	13.06	10.57
Total	99.76	99.96	99.83	99.75	99.74	100.04
Cations based on 72 oxygens						
Si	29.05	28.82	29.06	29.70	27.93	27.54
Al	6.35	6.78	6.33	5.88	6.68	7.25
Fe^{+3}	0.41	0.45	0.49	0.28	1.17	1.24
Na	2.63	1.48	1.95	1.81	1.93	1.67
K	2.11	2.22	2.18	2.98	2.76	4.14
Mg	0.38	0.55	0.41	0.40	0.77	0.54
Ca	0.87	0.93	0.98	0.48	0.82	0.75
$Si + Al + Fe^{+3}$	35.81	36.04	35.88	35.85	35.78	36.03
E%	−6.53	8.33	−0.27	−5.92	−0.25	1.26
Species	-Na	-K	-K	-K	-K	-K

NOTE: Mean compositions and number of cations based on 72 oxygens for erionite from four Cappadocian villages, including the malignant mesothelioma villages of Tuzkoy, "Old" Sarihidir, and Karain and the non–malignant mesothelioma village of Karlik. The number of samples averaged (n) is indicated as is the balance error (E%) for each average analysis. One erionite (control) sample from Rome, OR was analyzed in parallel with the Cappadocian samples. The results obtained from this control Oregon sample are further compared with a published analysis of a similar sample from Rome, OR (column 7; ref. 22).
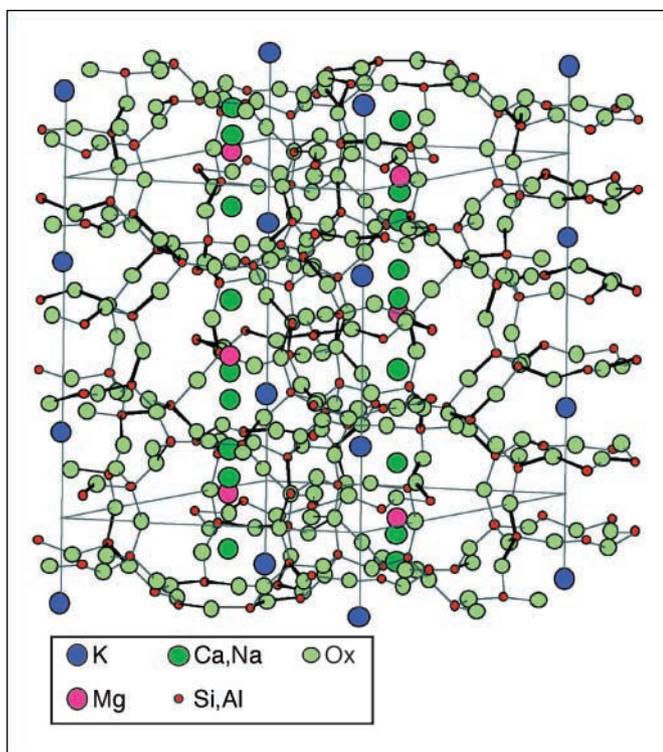
Figure 3. Crystal structure of erionite from Tuzkoy. *Red circles,* Si and Al atoms each surrounded by four oxygen (*light blue*) atoms to form a tetrahedron. Each of the four oxygen atoms is bonded to another (Si and Al) atom forming a three-dimensional tetrahedral framework. Within the framework are cavities or cages in which cations (Ca, K, Na, and minor Mg, Ba, and Sr) reside. In erionite, there are two types of cages, a large cage and a small cage. In addition to listed cations, H_2O is present in the larger cage. The positions of these cations and other species are poorly constrained but exist along a vertical column and are represented by the *dark green* and *pink circles* in the large cage. In the small cage, K (*dark blue*) is the predominant cation. Although the Si / (Si + Al) ratio can vary from ~0.75 to 0.80, the sum of the cation charges must be equal to the number of Al atoms; a test of any zeolite analysis is this match and values within 10% (also termed balance error) are considered reliable. Deviations can be caused by mixed mineral phases or substitution of cations not included in the analysis. Large openings in the cage walls allow cations and other molecules to move with relative ease through the structure.

Our findings do not call into question the fact that a large body of literature indicates that erionite is a potent carcinogen capable of causing malignant mesothelioma. It is certainly possible that some individuals have or would have developed malignant mesothelioma because of erionite exposure alone. However, we found that exposure to erionite causes an excess of malignant mesothelioma in certain families compared with others. The alternative hypothesis is that the malignant mesothelioma epidemic is not related to erionite at all but that was caused by a founder mutation that has reached a high frequency in this isolated population. The evidence against this hypothesis includes the following: (*a*) The strength of the evidence that erionite is a potent carcinogen (9–13). (*b*) Such high frequencies of genetic variation with uniformly high penetrance would be unlikely to show such a limited geographic distribution. The high frequency of

disease within certain villages implies a locally high frequency for the genetic variation increasing risk of malignant mesothelioma, approaching 50% for dominant models and 75% for recessive models. These very high frequencies are much more supportable when penetrances for susceptible individuals are high only in the presence of potent carcinogens, and very low otherwise, than if penetrances are uniformly high as would be expected for a strictly genetic model of susceptibility. The latter would not be expected to be restricted to certain villages or households but much more widespread. (*c*) The observation that individuals from high-risk families who were born and raised outside the high-risk region seem to revert to a much lower risk. (*d*) The fact that we identified five families with only a single malignant mesothelioma, which is compatible with sporadic malignant mesothelioma caused by erionite exposure.

Therefore, the malignant mesothelioma epidemic in Cappadocia seems to be caused by the interaction between genetics and erionite exposure. This situation is somewhat reminiscent of aflatoxin B1 exposure and hepatitis B virus infection in causing hepatocellular carcinoma. Both agents increase the risk, but together they have a multiplicative carcinogenic effect (21). Here, rather than a viral infection and a toxin, we have a mineral fiber (erionite) and a genetic factor that together cause an unprecedented high incidence of malignant mesothelioma. At the same time, the observation that the same type of erionite was found in Oregon and in Cappadocia underscores the potential risk for malignant mesothelioma through erionite exposure in the western world. Therefore, the risk of contracting sporadic malignant mesothelioma because of exposure to erionite in the western portion of the United States and in some European countries should not be underestimated.

In summary, this is the first time that genetic predisposition is shown to influence mineral fiber carcinogenesis. We propose that our data may have general implications for understanding why among many people exposed to carcinogenic mineral fibers only few develop disease. We hypothesize that the same gene(s) is altered following erionite and asbestos exposure in sporadic malignant mesothelioma. We propose that the isolation of this putative malignant mesothelioma susceptibility gene(s) would lead to novel preventive and therapeutic approaches that should benefit patients in Cappadocia and in the western world.

Acknowledgments

References

1. Carbone M, Kratzke R, Testa JR. The pathogenesis of mesothelioma. Semin Oncol 2002;29:2–17.

2. Mossman BT, Bignon J, Corn M, Seaton A, Gee JB. Asbestos: scientific developments and implications for public policy. Science 1990;247:294–301.

3. Baris YI, Sahin AA, Ozesmi M, et al. An outbreak of

pleural mesothelioma and chronic fibrosing pleurisy in the village of Karain/Urgup in Anatolia. Thorax 1978;33: 181–92.

4. Artvinli M, Baris YI. Malignant mesotheliomas in a

small village in the Anatolian region of Turkey: an epidemiologic study. J Natl Cancer Inst 1979;63:17–22.

5. Dogan AU, Dogan M, Emri S. Erionite. 2nd ed. In: Wexler P, editor. Encyclopedia of toxicology. Oxford: Elsevier; 2005. p. 237–41.

6. Coombs DS, Alberti A, Armbruster T, et al. Recommended nomenclature for zeolite minerals; report of the Subcommittee on Zeolites of the International Mineralogical Association, Commission on New Minerals and Mineral Names. Can Mineral 1997;35:1571–606.

7. Passaglia E. The crystal chemistry of chabazites. Am Mineral 1970;55:1278–301.

8. Pass HI, Vogelzang N, Carbone M. Mesothelioma cancer: principles and practice of oncology. 7th ed. In: De Vita VT, Hellman S, Rosenberg SA, editors. Philadelphia: Lippincott Williams and Wilkins; 2005.

9. 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;2:984–7.

10. Baris I, Simonato L, Artvinli M, 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.

11. Okayasu R, Wu L, Hei TK. Biological effects of naturally occurring and man-made fibres: *in vitro* cytotoxicity and mutagenesis in mammalian cells. Br J Cancer 1999;79:1319–24.

12. Wagner JC, Skidmore JW, Hill RJ, Griffiths DM. Erionite exposure and mesotheliomas in rats. Br J Cancer 1985;51:727–30.

13. Timblin CR, Guthrie GD, Janssen YW, Walsh ES, Vacek F, Mossman BT. Patterns of c-fos and c-jun proto-oncogene expression apoptosis and proliferation in rat pleural mesothelial cells exposed to erionite or asbestos fibers. Toxicol Appl Pharmacol 1998;151:88–97.

14. Roushdy-Hammady I, Siegel J, Emri S, Testa JR, Carbone M. A genetic-susceptibility factor and malignant mesothelioma in the Cappadocian region of Turkey. Lancet 2001;357:444–5.

15. Mumpton FA. A reconnaissance study of the association of zeolites with mesothelioma occurrences in central Turkey. USGS Open File Rep 1979;55:79–954.

16. Passaglia E, Artioli G, Gualtieri A. Crystal chemistry of the zeolites erionite and offretite. Am Mineral 1998;83:577–89.

17. Gazdar AF, Butel JS, Carbone M. SV40 and human tumors: myth association or causality? Nat Rev Cancer 2002;2:957–64.

18. De Rienzo A, Tor M, Sterman DH, Aksoy F, Albelda SM, Testa JR. Detection of SV40 DNA sequences in malignant mesothelioma specimens from the United States but not from Turkey. J Cell Biochem 2002;84:455–9.

19. Emri S, Kocagoz T, Olut A, Gungen Y, Mutti L, Baris YI. Simian virus 40 is not a cofactor in the pathogenesis of environmentally induced malignant pleural mesothelioma in Turkey. Anticancer Res 2000;20:891–4.

20. Robledo R, Mossman B. Cellular and molecular mechanisms of asbestos-induced fibrosis. J Cell Physiol 1999;180:158–66.

21. Carbone M, Klein G, Gruber J, Wong M. Modern criteria to establish human cancer etiology. Cancer Res 2004;64:5518–24.

22. Eberly PE, Jr. Adsorption properties of naturally occurring erionite and its cationic-exchanged forms. Am Mineral 1964;49:30–40.

AACR American Association
for Cancer Research

Genetic Predisposition to Fiber Carcinogenesis Causes a Mesothelioma Epidemic in Turkey

A. Umran Dogan, Y. Izzettin Baris, Meral Dogan, et al.

Updated version	Access the most recent version of this article at: http://cancerres.aacrjournals.org/content/66/10/5063

Cited articles	This article cites 20 articles, 4 of which you can access for free at: http://cancerres.aacrjournals.org/content/66/10/5063.full#ref-list-1
Citing articles	This article has been cited by 16 HighWire-hosted articles. Access the articles at: http://cancerres.aacrjournals.org/content/66/10/5063.full#related-urls

E-mail alerts	Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions	To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions	To request permission to re-use all or part of this article, use this link http://cancerres.aacrjournals.org/content/66/10/5063. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.