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Malignant Mesothelioma due to Environmental Exposure to Asbestos*: Follow-Up of a Turkish Cohort Living in a Rural Area

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Malignant Mesothelioma due to Environmental Exposure to Asbestos*

Follow-Up of a Turkish Cohort Living in a Rural Area

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Study objectives: **This study examines the incidence of malignant pleural mesothelioma (MPM) in a rural population of Turkey with environmental exposure to asbestos-contaminated soil mixtures (white soil).**
Design: **A field-based epidemiologic study.**
Setting and subjects: **A cohort of villagers (the "Eskisehir" cohort) from 11 villages around Eskisehir in central Anatolia, who had been environmentally exposed to asbestos due to the use of white soil.**
Measurements: **The mineral content and asbestos contamination of the white soil used in these villages was determined, as well as airborne fiber concentrations. Cohort members' details of age, sex, ambient exposure data, duration of residence in the villages, and hospital records, including pathologic diagnosis, were recorded.**
Results: **The Eskisehir cohort consisted of 1,886 villagers. During the observation time, 377 deaths occurred and 24 MPM cases were diagnosed. Average annual mesothelioma incidence rates were 114.8/100,000 for men and 159.8/100,000 for women.**
Conclusions: **These data indicate that the risk of mesothelioma is 88.3 times greater in men and 799 times greater in women, respectively, in comparison to world background incidence rates.**
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Key words: asbestos; environmental exposure; epidemiology; mesothelioma; pleural cancer

Abbreviations: AMIR = annual mesothelioma incidence rate; f/mL = fibers per milliliter; MPM = malignant pleural mesothelioma; mSIR = mesothelioma standardized incidence ratio

Malignant pleural mesothelioma (MPM) is a frequent cause of death in some parts of rural Anatolia in Turkey. In previous studies, it has been well demonstrated that environmental exposure to asbestos through the use of asbestos-contaminated soil mixtures causes a high risk of MPM in these rural regions.[1–3] These soil mixtures containing asbestos are commonly found surrounding these rural areas and are known in Anatolia as *aktoprak* (white soil) or *çorak*. The villagers in these mainly agricultural regions use this soil as a whitewash or plaster material (white stucco) for walls, as insulation and water proofing, for floors and roofs, for baby powder, and also in pottery.[1,4–6]

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Our clinic is a department of the Medical Faculty of Osmangazi University in Eskisehir, Turkey. The Eskisehir district is located in central Anatolia. The total population is 641,057, with 163,621 living

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within 403 villages. There is no occupational asbestos exposure in these areas; however, many patients with MPM, or other asbestos-related chest diseases, are admitted to our clinic each year from rural regions where the use of white soil has been widespread and continues to a lesser extent today. In our 1999 study,[3] it was determined that > 10,000 villagers remain exposed to asbestos-contaminated white soil.

Although the main consequence of environmental asbestos exposure is an increased risk of malignant mesothelioma, we do not yet know the actual mesothelioma rates from this type of environmental exposure. Therefore, our aim in the present study was to determine the mesothelioma rate in a cohort of villagers with the environmental asbestos exposure described. This exposure is also common in some other rural parts of the world.[7–10]

Materials and Methods

Eskisehir Cohort

The Eshisehir cohort was formed as follows: of the 403 villages of Eskisehir, we were able to acquire data, via a questionnaire, from 196 villages. We learned that white soil had been used in 140 villages and was still being used in 126 villages. We randomly chose 67 villages from these 126 villages. We were receiving patients from some of these villages already, and we collected white soil samples from them. We found tremolite or other types of asbestos fiber contamination in a total of 41 villages. A total of 10,120 people are still living in these villages and are still being exposed to asbestos.[3] By random sampling, we identified 11 of 41 villages: Gökdere, Dağküplü, Üçsaray, Kayi, Kadikuyusu, Tepeköy, Tatarcik, Kayi-M, Sekiören, Ömerköy, and Çalci. The 1,886 villagers ≥ 30 years old formed our study group, which we named the "Eskisehir" cohort.

This cohort was investigated in detail over a 10-year period from 1990 to 2000, using the muhtars' registers, state health center files, hospital records, and personal interviews with families by two researchers (a chest physician and an epidemiologist). The villagers' names, ages, length of time spent in their villages, dates of migration to the city, marriage status, occupations, dates and causes of death, and other details were documented. These data were completed with hospital and death records, including pathologic findings, to document all causes of death and verify mesothelioma diagnosis.

Since MPM cases for the Eskisehir province were referred to our department immediately on diagnosis, or suspicion of mesothelioma, all MPM cases were diagnosed and followed up in our department. All MPM cases had histologically confirmed malignant mesothelioma. The histopathologic examination of biopsy specimens from all cases was performed by faculty members in our pathology department. The samples were treated with hematoxylin-eosin, alcian blue, and mucicarmine histochemical stains. Immunohistologic confirmation of carcinoembryonic antigen and Leu-M1 were obtained in some samples, and carcinoembryonic antigen, vimentin, and keratin were obtained in others. Some samples were also examined by Dr. Allen R. Gibbs from Llandough Hospital, UK. We re-evaluated all MPM cases from this cohort and confirmed them with histopathologic records for this study.

Confirmation of Environmental Exposure

We visited these villages to collect samples of the white soil utilized by the inhabitants. In doing this sampling, our aim was to check for the presence of asbestos contamination that had been determined in the previous publications.[1,3] A mineral analysis of these samples was carried out by means of an x-ray diffractometer (Rint 2000; Rigaku; The Woodlands, TX), largely at the Gebze Institute of Higher Technology and the National Institute of Mineral Research (Ankara).

During white soil sampling, we also collected indoor and outdoor air samples (two samples for each environment) from all villages, for minerologic and quantitative analyses of asbestos fibers. Collection of samples was fulfilled on dry and sunny days during the summer. For this purpose, we used the SKC portable air collector pumps including the special MCE gridded filters that were 25 mm in diameter with 0.8-μm pore size for asbestos fibers (SKC Ltd; Dorset, UK). The pumps were set at a 2 L/min flow rate for an 8-h duration. After sampling, we removed the filters and placed them into a special cassette for transport. Air fiber concentrations were determined in the National Institute of Workers Health and Security, Ankara, by counting fibers > 5 μm long on these filters using a phase-contrast microscope and experienced specialists.[11]

Calculations

Every year of residence by a member of the Eskisehir cohort in villages during the period 1990 to 2000 was counted as a person-year. The years of migration, of MPM diagnosis, or of death were counted as half a year. If a person survived for ≥ 1 year after diagnosis of MPM, these years were disregarded.

For every year, the number of observation-years in each 5-year age group was calculated. The number of observation-years in each 5-year age group was multiplied by the MPM incidence rate of this particular 5-year age group of females and males in the given year.

These incidence rates used in our study were obtained from İzmir Cancer Registry-KIDEM (İzmir, Turkey), which is used as a reference for Turkey by the International Agency Research on Cancer.[12,13] Only the documents for 1993 to 1996 in the registry were suitable for evaluation; therefore, the 1993 to 1994 incidence rates were used for the years from 1990 to 1992, and the 1995 to 1996 rates were used for the years 1997–2000. The resulting data of expected MPM for each year and age group were added, giving the total number of expected cases in the cohort. This method has been used in other similar studies.[14,15]

The mesothelioma standardized incidence ratio (mSIR) was calculated by dividing the observed number of cases by the expected number of cases. The 95% confidence intervals of the mSIRs were calculated to assess statistical significance as follows: the SE of the natural logarithm of the mSIR was approximated by the inverse of the square root of the observed number of cases. The 95% confidence limits of the standardized incidence ratio were calculated as the natural logarithm of standardized incidence ratio adding percentage SE and multiplying by 1.96. After exponentiation, the exact 95% confidence limits indicated that the approximation was satisfactory.

Direct standardized average annual mesothelioma incidence rates (AMIRs), adjusted to the Segi standard population (World Health Organization 1990 world health statistics), were calculated as follows: age-specific rates (case No./person-year in groups of 5 years) were computed for the Eskisehir cohort. These rates were applied to the number of persons in the corresponding age group of the standard population, and the results were

summed. This sum was divided by the total number of persons in the standard population. Thus, the direct standardized average AMIRs were obtained.

Results

The white soil samples from 11 villages all contained asbestos fibers, a high rate of tremolite or tremolite-plus-actinolite-plus-chrysotile mixtures, as well as a lower rate of anthophyllite-plus-chrysotile mixtures. Indoor and outdoor air fiber concentrations were low. Indoor fiber concentrations were from 0.009 to 0.28 fibers per milliliter (f/mL) [mean, 0.089 f/mL]; and outdoor fiber concentrations were 0.009 to 0.04 f/mL (mean, 0.012 f/mL).

Age and sex characteristics of the cohort are on Table 1. There were 9393.5 person-years in the male group and 8791.5 person years in the female group. The number of deaths from any cause were 377.

Of the 1,886 villagers, 24 villagers (12 men and 12 women) had MPM between 1990 and 2000. Of these, 18 villagers died before the start of the study, 3 villagers died during the study, and 3 villagers were alive for the duration of the study period. Proportional mortality of MPM was 5.6% (21 of 377 deaths). The mean age of the patients with MPM was 56.5 ± 11.0 years (range, 36 to 76 years), 57.8 ± 9.7 years (range, 39 to 70 years) for male patients and 55.3 ± 12.4 years (range, 36 to 76 years) for female patients. As the patients had been exposed to asbestos from birth, the latency was equivalent to the age of the patient at diagnosis. The difference in latency between male and female patients was not significant ($p > 0.05$).

The average AMIRs per 100,000 people in our study group are seen in Table 2. During the observation period 1990 to 2000, only 0.228 cases of MPM were expected in the cohort among the male patients and 0.083 among the female patients. The observed numbers were clearly increased (Table 3).

Table 1—*Age and Sex Characteristics

Characteristics	Data
Persons in cohort	1,886
Male sex, No. (%)	997 (52.9)
Female sex, No. (%)	889 (47.1)
Out migrant	23
In migrant	98
Residents in villages	1,765
Mean age of the cohort, yr	59.2 ± 14.8
Male mean age, yr	59.2 ± 15.3
Range, yr	30–95
Female mean age, yr	59.2 ± 14.2
Range, yr	30–100

*Data are presented as No. or mean ± SD unless otherwise indicated.

Table 2—*Average AMIRs for MPM (per 10^5 Population)*

Subjects	Cases, No.	Average AMIR	Ratio to Turkey*	Ratio to World*
Male	12	114.8	191.3	88.3
Female	12	159.8	532.7	799.0

*The incidences of MPM for Turkey were those of 1996, and the whole world were those of 1993. The expected incidence for Turkey is 0.7 per 100,000 for male subjects and 0.3 per 100,000 for female subjects in Turkey; for the whole world, these data are 1.3 per 100,000 and 0.2 per 100,000, respectively.[13,22]

Discussion

Environmental exposure to asbestos as a cause of mesothelioma has been well documented in many studies.[1,3,7–9,16–18] However, the AMIR values of 114.8/100,000 for men and 159.8/100,000 for women that we established in a cohort of villagers who had been environmentally exposed to asbestos from birth through the use of white soil are the first values presented in the literature for such a cohort. Mesothelioma case series and incidence data from other similar types of exposure[19,20] in Turkey have been published. In a study[19] in the southeast part of Turkey, an incidence rate of 22.8 per million was reported. This is similar to industrialized countries such as Sweden.[21,22] A previous study[20] reported an incidence of 105.5 per million for the same region. The incidences reported in these previous studies were determined according to the mesothelioma cases established at a reference hospital serving the area population. Since these studies were not based on a well-defined cohort that can be followed up, the values reported cannot be considered fully accurate for incidences of the exposure types described. The values determined in our study as the annual mesothelioma incidence rates are, in fact, 50 to 60 times higher than the data given in those publications.[19,20]

In rural areas, there may be important differences not only in terms of the nature of environmental and occupational exposure but in individual characteristics. The host response to inhaled asbestos fibers is affected by various parameters, including the physical, chemical, or biological characteristics of the

Table 3—*Observed and Expected Rates of MPM in 1,886 Subjects*

Subjects	Observed, No.	Expected	mSIR	95% Confidence Interval
Male	12	0.228	52.63	29.88–92.64
Female	12	0.083	143.9	81.71–253.36

fibers; the cumulative fiber dose; latency; and individual host factors. However, MPM was a frequent cause of death in this well-defined group of former villagers of the present study. The incidence rates for both sexes are extremely high; as high, in fact, as those observed in occupationally exposed cohorts. In lower Normandy, for instance, the average annual incidence of mesothelioma was estimated at 88/100,000 in an asbestos factory, at a mean of 19/100,000 in a ship building and repairs industry, and 122.4/100,000 among workers in the textile and friction linings industry.[23]

In our study, the proportional mortality was 5.6%. This is equal to or slightly above the published data from workers occupationally exposed to asbestos. In crocidolite miners, the proportional risk was calculated to be 3.9%.[24] In another study from the same area (Wittenoom in western Australia), where there was a heavy contamination of the surroundings of the mine, including the village itself, the life-long risk of mesothelioma was calculated to be 6% for the work force.[25]

It is generally assumed that occupational fiber exposure levels are higher, on average, than indoor and outdoor environmental exposure levels. Hillerdal[26] reported recreated asbestos exposure levels of 25 f/mL with excursions to 1,000 to 2,000 f/mL for workers who were first exposed to asbestos in the past. Workplace measurements in the 1960s often showed peak exposures of 20 f/mL, which were substantially reduced over subsequent years.[26]

Airborne fiber concentrations can vary according to mining or milling of asbestos and the type of asbestos industry. However, estimated levels have always been observed to be higher than environmental levels.[27,28]

We found indoor air fiber concentrations ranging from 0.009 to 0.28 f/mL (mean, 0.089 f/mL) in villages using asbestos-contaminated white soil. In another study from Turkey, indoor air fiber concentrations in villages using asbestos-contaminated white soil were 0.14 f/mL before the floor was swept and 0.94 f/mL afterwards.[29] These ambient levels from villages in Turkey most likely underestimate true exposures for villages that would occur over a 24-h period, because the measurement of ambient levels may well be affected by environmental conditions. In a forming community, true airborne fiber levels may be higher during ongoing activities within or outside the home, such as the passing of a herd of sheep in the street. The application of white soil as whitewash is usually done each year with grinding of the soil to powder and suspending the powder in a water bucket. It was estimated that the airborne fiber level may increase up to 200 f/mL in the immediate environment during crushing.[30] In a newly whitewashed room, and while sweeping floors, the concentration can be quite variable, ranging from 0.02 to 17.9 f/mL.[26,31] Environmental levels will be low when there is no wind, during wet months or the rainy season rather than the dry periods or during windy weather. For this reason, in order to decrease fault, we resorted to undertaking air sample collections on dry and sunny days in the summer. Also, the airborne fiber levels that were determined in this study from villages may be lower than the actual concentrations of the fibers most likely to be the cause of the mesotheliomas in this patient cohort, because the membrane filter method that we used to estimate fiber concentrations has the restraint to count the invisible fibers of ≤ 0.25 μm in diameter that may be responsible for mesotheliomas.[32]

Even though environmental asbestos fiber exposure levels may be lower in comparison to occupational settings, the cumulative asbestos exposure levels may be similar to those from occupational settings. In general, occupational exposure durations are limited to approximately 2,000 h/yr and begin with employment. The exposure duration for a villager may be nearly 8,700 h/yr because the villager spends most of his time in the village, and this begins at birth.[31] For a 40-year-old man, the cumulative asbestos exposure duration will be $>$ 340,000 h, as compared with 80,000 h for the same duration (40-year working period) in an occupational setting. Thus, although the exposure dose in environmental contact may be low at any one moment, the cumulative exposure dose is unlikely to be lower than in occupational exposure. In fact, a study[31] in Turkey has reported fiber concentrations in the BAL fluids of environmentally exposed villagers to be no lower than the concentrations of the occupationally exposed villagers. This finding and its interpretation clearly demonstrate that the mesothelioma risk is as high for villagers exposed to asbestos as for those occupationally exposed. The impact of fibers for a child may very well be different in comparison to an adult. This may be one explanation for the increased AMIR.

The mesothelioma risk incurred through the use of asbestos-contaminated white soil in villages is higher than that induced by an environmental exposure of residents living near an asbestos mine. As mentioned earlier, in the township of Wittenoom, there was a formerly active crocidolite mine. At least 5,000 people lived in the township of Wittenoom without working in the mines. In 1993, 27 cases of mesothelioma had occurred among these people.[25,33] It has been estimated that 1.1% of children and 1.9% of female residents of Wittenoom have died or will

die from mesothelioma.[25] Among the workforce, this data was estimated to be 6%.[25]

In the cohort of 4,569 former residents with residences of ≥ 1 month, 27 cases of mesothelioma have been identified, giving an average AMIR of 26/100,000.[33] The data for our cohort are approximately five to six times higher. These data must be correlated with the average time spent at the villages. In Wittenoom, only 41% had an exposure of ≥ 2 years. Our patients, however, had spent most of their lives in the villages. The environmental exposure level in Wittenoom was estimated to be 1.0 f/mL from 1943 to 1957 and 0.5 f/mL between 1958 and 1966, when the mine was closed. These values were estimated from environmental measurements, the earliest of which were taken in 1966.[33]

We conducted a similar study some time ago on a cohort of villagers who had migrated from Karain Village in Turkey to Stockholm. The AMIR values determined for this erionite-exposed cohort were 298.1/100,000 for men and 400.9/100,000 for women. These were the highest MPM values to be published to date. We assume this result is related to the fact that the erionite in the vicinity of the Karain Village carries a stronger carcinogenic potential than asbestos.[21]

In the present study, the male/female ratio of MPM was similar and consistent with an environmental etiology. In rural areas, the whitewash process may be done by both men and women. According to agricultural custom, sometimes women and sometimes men, depending on who is free at the time, extract and grind the soil, dissolve it in water, and whitewash the walls. Sometimes the job is done in a mixed order, which means different tasks might be performed by different sexes. So, there is not a certain share of duties between them.[3] Within industrialized societies mesothelioma occurs most frequently in men due to previous occupational exposure.

The mean age of mesothelioma appearance, equaling the latency time, was approximately 56 years for both sexes in our series. It was found to be 56 years for 97 patients with MPM who lived in and around Eskisehir.[3] In another study from Turkey, for the environmental asbestos exposure series for Selçuk, the average age was 50 years, with one fourth of the patients < 40 years old.[18] The latency period in occupational exposure is generally 30 to 40 years,[23,34,35] and the mean age of the patients is ≥ 60 years.[23,36,37] These data suggest that the latency is longer for environmental exposure since the exposure begins at birth; therefore, the average individual in Turkey who presents with mesothelioma is approximately 50 to 56 years of age. The average worker in whom mesothelioma has developed at the age of approximately 60 years and who began work at age of 20 years has a latency of approximately 40 years. Thus, it seems that the latency time for mesothelioma caused by environmental asbestos may be longer than that caused by occupational asbestos. The reasons for the difference in latency between occupational and environmental exposure are not clear. One possibility is that on average, higher levels of exposure in occupational settings might thus shorten the latency time. It has been pointed out that latency was also dependent on exposure, varying from 29.6 years for insulators (with the highest exposure) to 51.7 years in women with domestic exposure.[26] Bianchi and coworkers[38] observed latency periods between 14 years and 75 years, with a mean of 48.8 years and a median of 51 years. In this study, the latency periods among insulators and dockworkers were shorter than those among other categories that are exposed less, again suggesting that latency may be related to intensity of exposure.[38]

In conclusion, the average annual mesothelioma incidence rates in our study indicate that the risk of mesothelioma for villagers exposed to asbestos through use of white soil is 88.3 times greater in men and 799 times greater in women, in comparison to world background incidence rates, and similar to occupationally exposed asbestos cohorts.

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