Decreasing Prevalence of Pleural Calcifications Among Metsovites With Nonoccupational Asbestos Exposure*

Carmen Manda-Stachouli, MD; Yotanna Dalavanga, MD; George Daskalopoulos, MD; Christina Leontaridi, MD; Mitos Vassiliou, MD, PhD; and Stavros H. Constantopoulos, MD, FCCP

Study objectives: Twenty years ago, we reported on a very high prevalence of pleural calcifications (PCs) and malignant mesothelioma among inhabitants of Metsovo, in northwestern Greece. It was shown that both abnormalities were related to asbestos exposure from a whitewash containing tremolite. The fading use of this material has resulted in a decreased incidence of mesothelioma (one third of the original incidence). The aim of the present study was to examine whether PCs among Metsovites has followed a similar trend.

Design: Retrospective study.

Settings: University Hospital of Ioannina, a tertiary teaching hospital, “G. Hadjikosta” Hospital, a tertiary hospital in Ioannina, and Metsovo Health Center, a primary care center in the town of Metsovo.

Patients: Chest roentgenograms of 307 Metsovites, obtained between from 1998 to 2002 were examined. The prevalence of PCs was compared to the one noted 20 years ago.

Results: A significantly lower prevalence of calcifications was observed now among younger Metsovites (< 60 years of age). In both studies, there was an increasing rate of PC with age.

Conclusions: The findings of the present study strengthen the incrimination of the whitewash containing tremolite in the development of PCs in Metsovites. The withdrawal of its use in the area has resulted in a null prevalence of PCs in individuals < 40 years old.

(CHEST 2004; 126:617–621)

Key words: Metsovo; nonoccupational asbestos exposure; pleural calcifications; pleural plaques; tremolite

Abbreviations: CXR = chest roentgenogram; PC = pleural calcification

An epidemiologic investigation performed in the Metsovo area of northwestern Greece (population around 5,000) 20 years ago revealed that more than half of the adult population presented with pleural calcifications (PCs).1,2 Soon after (from 1981 to 1985), in the same area a mesothelioma “epidemic” was observed (ie, an incidence 300-fold higher than expected).3 Both phenomena were attributed to “luto,” a whitewash containing tremolite, that was used by practically all Metsovites from 1940 to 1950 and was gradually abandoned.4 In 1950, it was still used by 88% of the population, in 1960 by 68%, in 1970 its use had dropped to 37%, and in 1980 to 15%.5 Now its use has been completely substituted for by modern materials. The incidence of mesothelioma in the area of Metsovo, following the fading use of luto, has dropped between 1985 to 1994 to one third of the original incidence.6 It is well-established that both mesothelioma and PCs are the result of exposure to asbestos (eg,
tremolite) and other asbestiform fibers like erionite,\textsuperscript{7,8} Silica, talc, mica, and other minerals also may cause PCs, but this may be due to contamination from asbestos.\textsuperscript{9,10} Therefore, it would be particularly interesting to examine the evolution of PC prevalence in the Metsovo area 20 years after the first epidemiologic investigation. The results of this study in parallel with the already established decrease of mesothelioma incidence would further elucidate the impact of the nonoccupational use of asbestos on the respiratory system.

**Materials and Methods**

**Study Design**

Three hundred seven chest roentgenograms (CXRs) were collected from the records (from 1998 to 2002) of Metsovo Health Center, “G. Hadjikostas” General Hospital, and Ioannina University Hospital. These CXRs belonged to inhabitants of the four villages (ie, Metsovo, Milea, Anilio, and Votonossi) where PCs were first observed from 1978 to 1982.\textsuperscript{1,2} As was done in the previous study, patients were classified into five age interval groups (Table 1).

**CXR Evaluation**

All CXRs were carefully evaluated for the presence of PCs (Fig 1) by two of us (C.M.S. and S.H.C.), independently and then in joint session. In order to have results that were comparable with those from 1980, only posteroanterior CXRs were evaluated. The prevalence of PCs was calculated as the percentage of the total number of examined CXRs for each group (Table 1).

**Statistical Analysis**

The $\chi^2$ test was applied in order to examine the difference in the overall prevalence of PCs between the two studies (ie, from 1978 to 1982 and from 1998 to 2002). The significance of PC prevalence between men and women in the present study also was examined with the $\chi^2$ test. The $\chi^2$ test for multiple outcomes was used in order to examine the significance of differences in PCs between the two periods (ie, 1978 to 1982 and from 1998 to 2002) at the same age intervals as well as between males and females in the present study. A Bonferroni correction was used in order to define the source of significance. The level of significance was set at 95% (ie, $p < 0.05$).

### Table 1—Number and Prevalence of PCs in Metsovites\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>30–39</td>
<td>6/21 (28.6)</td>
<td>0/15 (0.0)</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>40–49</td>
<td>25/56 (44.6)</td>
<td>8/36 (22.2)</td>
<td>$&lt; 0.01$</td>
</tr>
<tr>
<td>50–59</td>
<td>38/58 (65.5)</td>
<td>13/49 (26.5)</td>
<td>$&lt; 0.01$</td>
</tr>
<tr>
<td>60–69</td>
<td>30/42 (71.4)</td>
<td>71/101 (70.3)</td>
<td>$&gt; 0.05$</td>
</tr>
<tr>
<td>≥70</td>
<td>30/37 (81.0)</td>
<td>86/106 (81.1)</td>
<td>$&gt; 0.05$</td>
</tr>
<tr>
<td>Total</td>
<td>129/214 (60.3)</td>
<td>178/307 (58.0)</td>
<td>$&gt; 0.05$</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Values given as No. (%), unless otherwise indicated.

### Results

Of the 307 CXRs examined, the evaluation of the two readers differed on 11 occasions (11 of 307 CXRs: 3.6%). In all 11 cases, a consensus was reached in the joint session. The prevalence of PCs in Metsovites from 1978 to 1982 and from 1998 to 2002 according to age group is presented in Table 1, and is graphically depicted in Figure 2. The percentage of PCs in each group according to sex is shown in Table 2.

Most of the individuals examined (82.7%) came from Metsovo, which is the capital of the area. The same was true in the older study (78.9%).

PCs were slightly more frequent among men than women in all studied age groups, except for those individuals ≥70 years of age. This difference was statistically significant only in the group of individuals 60 to 69 years of age (Table 2). A similar male predominance in PCs was observed in our previous work.

Comparisons concerning the prevalence of PCs according to age group show that it was significantly lower in the present study for the age groups 30 to 39 years ($p < 0.001$), 40 to 49 years ($p < 0.01$), and 50 to 59 years ($p < 0.01$). The corresponding differences for the older groups (ie, those 60 to 69 and ≥70 years) were not significant ($p > 0.05$). The youngest person with PCs in the present study was 42 years old vs 29 years old during the study from 1978 to 1982. It should be highlighted that no PCs were observed in the group that 30 to 39 years old in the present study, while in the former study 6 of 21 Metsovites of the same age had PCs. The overall prevalence of PCs, although lower now, is not significantly different from that of 1978 to 1982 (178 of 307 persons [58.0%] vs 129 of 214 persons [60.3%], respectively; $p > 0.05$). Nevertheless, in the old study most individuals (63.1%) were <60 years old, while in the present study that age group constitutes the minority (63.1% vs 32.65%, respectively; $p < 0.001$).

### Discussion

Pleural plaques are the most common manifestation of asbestos exposure.\textsuperscript{7–11} They are often calcified and are thus easier seen on CXRs, even those of poor quality.\textsuperscript{12,13} The surprisingly high prevalence of calcified pleural plaques was the striking finding that led us to discover the asbestos exposure of Metsovites 20 years ago.\textsuperscript{1,2} CXRs were the only available screening test then, and not all of them were of good quality. Therefore, we could refer with certainty only to calcified plaques, and not to simple pleural plaques. As a consequence, the presence of PCs was used thereafter as the hallmark of asbestos exposure in this population, and this is what we used in the
present study in which we compared the prevalence of PCs in Metsovites from 1978 to 1982 with that from 1998 to 2002.

The populations of the two studies had to be different. It is practically impossible to repeat now a general population study. The inhabitants of Metsovo think that their problem is solved since we have already proven the causative role of luto in their increased prevalence of PCs and mesothelioma. Now, Metsovites react to any type of publicity, because it gives a negative picture and can harm the tourism to the village, even though we reported¹⁴ long ago that there was no more asbestos exposure in Metsovo. This reaction remains a serious obstacle for

**Figure 1.** CXR of an inhabitant of Metsovo with characteristic PCs.

**Figure 2.** The percentage of PCs in Metsovites, according to age group from 1978 to 1982 (black columns) and from 1998 to 2002 (gray columns).
new epidemiologic research in the area involving the general population. Therefore, we used the only available alternative, the evaluation of CXRs from the records of the Metsovo Health Center and the two Hospitals in Ioannina.

We think that, despite this obligatory difference in the design, comparisons between the two studies are not unsuitable. There is no relation between bilateral scattered PCs, like those we have seen in individuals in Metsovo, and any disease entity, other than exposure to asbestos. Since we have attributed PCs to asbestos exposure, their presence is no longer a cause for hospitalization, and thus no patient in the present study was admitted to the hospital because of PCs. Furthermore, if such PCs are related to any other unknown disease, then the population of the present study would have an additional reason to present with PCs. Therefore, if anything, the present study would underestimate than overestimate the decrease in PCs prevalence among Metsovites.

In the earlier work, we had already suggested that Metsovites were exposed to asbestos since birth. The presence of PCs in young persons (one 29 years old, and six in the age group 30 to 39 year) was the indirect evidence of their early exposure to asbestos. According to Hillerdal, in areas where the population is exposed from birth, the first pleural changes will appear after the age of 30 years, and the prevalence then increases with age.

Given the documented increase of PC prevalence with age, a comparison between the two populations in terms of total numbers is not appropriate. The percentage of Metsovites > 60 years of age in the present study is much higher than that in the previous one (67.4% vs 36.9%, respectively; p < 0.001). Therefore, comparisons are meaningful only between groups of the same age, and they offer interesting results.

The youngest age group in the present study (30 to 39 year of age) has null prevalence of PCs. They were born between 1960 and 1969, when luto was being used by only around half of the population, and for only a few additional years, since 10 years later its use had practically stopped. On the contrary, 28.6% of persons in the same age group in the previous study had PCs. They were heavily exposed, as they were born between 1940 and 1949, when luto was used in most households, and its use continued for 3 or 4 more decades.

The middle age groups of the present study (i.e., 40 to 49 years and 50 to 59 years) are rather mixed groups regarding asbestos exposure. They were born between 1940 and 1959, when the decline in luto use had started. On the contrary, middle-aged Metsovites in the older study were born between 1920 and 1939, when luto was still used by all households. These facts also could explain the significant difference in the prevalence of PCs between the two studies in these age groups (current study, 22% and 27%, respectively; former study, 45% and 66%, respectively).

Finally, the almost identical prevalence of PCs in our older age groups (i.e., 60 to 69 years and ≥ 70 years) suggests that, for the development of PCs in Metsovites, the time since the first exposure or perhaps the fact that the exposure started from birth was possibly more important than the cumulative exposure to asbestos. This suggestion also is supported by our previous findings, which confirmed that asbestos bodies remained in the lungs of Metsovites even 4 or 5 decades after the end of the exposure to luto. The older groups in the two studies were exposed to asbestos practically since birth, but the cumulative exposure in the present study is roughly 20 years shorter. If the cumulative exposure was equally important, persons in the older groups of the present study should have a lower frequency of PCs.

The number of individuals examined from the other small villages in the Metsovo area is too small to make meaningful comparisons. On the contrary, the comparison of PCs between men and women is of some interest, since in both the present study and in the older one men predominate slightly. This is in agreement with the results of large epidemiologic studies and a similar study by Baris et al in a small Anatolian village that was environmentally exposed to tremolite. A larger study by Yazicioglou et al in a different area of Turkey with the same exposure gave, however, only a marginal male predominance. These conflicting results make any attempt to explain this slight male predominance very difficult.

Our thesis is that the population of Metsovo had been exposed to tremolite from luto whitewash since childhood. There is no asbestos in the atmosphere and practically no asbestos in the soil of the area. Metsovo is located outside the Pindos serpentine zone, and Metsovites were traveling to get the material from the neighboring hills inside the zone.
The exposure was associated with crashing the tremolite-containing material at home, resulting in a high fiber release with a concentration > 200 particles per cm³ in home air. Therefore, the exposure started immediately after birth.

The pattern of the decreasing prevalence of PCs incriminates luto further as the offending agent and, more specifically, breathing luto since childhood while crashing it into powder. Since the use of luto was practically abandoned after 1975 to 1980, and since there is no luto in the area around Metsovo, we believe that the exposure has ended. Therefore, the end of the mesothelioma epidemic is expected in a few decades, and PCs seen on the CXRs of Metsovites born after 1975 to 1980 should show no PCs. Nevertheless, we will be able to state this with certainty only when Metsovites born from 1975 to 1980 are at least 30 years old, since that is the length of time that PCs need to appear. If Metsovites do not present with PCs (on chest CT scans) and asbestos fibers (found in BAL fluid), the final chapter of Metsovo lung will have been written. The evaluation of such a population will be possible between 2005 and 2010. This is when we hopefully will be able to report the end of this asbestos exposure epidemic in Metsovo.

REFERENCES
9 Baris YI. Asbestos and erionite related chest diseases. Ankara, Turkey: Semih Ofset Matbaacilik Ltd, 1987; 57–60
10 Gibbs GW. Etiology of pleural calcification: a study of Quebec chrysotile asbestos miners and millers. Arch Environ Health 1979; 34:76–83
14 Constantopoulos SH. There is no asbestos in the atmosphere of Metsovo: large quantities of fibers are released during processing “luto soil” [abstract]. Proceedings of the 14th Panhellenic Medical Congress, Athens, Greece, 1988; 120