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EXCESS OF MESOTHELIOMAS AFTER EXPOSURE TO CHRYSOTILE IN BALANGERO, ITALY

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ABSTRACT

Context: Chrysotile from the mine in Balangero, Italy, is considered to be tremolite-free. In a cohort study of miners and millers only two pleural cancers were reported, a finding considered to contribute evidence that chrysotile has a low potency for inducing mesothelioma. However, follow-up ended in 1987 and white-collar workers and employees of sub-contractors were not studied.

Population and methods: To complete the case ascertainment, we searched the Registry of Malignant Mesotheliomas of Piedmont for records of cases among: mine employees; employees of subcontractors or of other firms transporting or refining Balangero asbestos, asbestos ore or mine tailings; individuals exposed to air pollution from the mine or living with mine employees; and individuals exposed to mine tailings from Balangero.

Results: We identified 4 new cases of pleural mesothelioma among blue-collar workers in the mine, in addition to the two reported in the cohort study. Thus, 6 mesotheliomas occurred, compared to 1.5 expected ($p < 0.01$). We also identified 3 mesothelioma cases among white-collar employees at the mine, 5 in workers in the mine hired by subcontracting firms, and 3 among workers processing Balangero chrysotile outside the mine. Finally, 10 additional cases were identified due to non-occupational exposure or exposure to re-used mine tailings.

Conclusions: The cluster of 14 mesothelioma cases among workers who were active in the mine and 13 among other people exposed to Balangero chrysotile adds further evidence to the carcinogenicity of tremolite-free chrysotile.

INTRODUCTION

The carcinogenicity of chrysotile is established, although the issue of its potency relative to amphiboles for inducing mesotheliomas remains unresolved, with estimates ranging from 1:3 to 1:500.[1, 2] A related controversy is whether tremolite fibre contamination, rather than chrysotile, could be entirely responsible for mesothelioma causation.[3] Chrysotile from the Balangero mine (Piedmont, northern Italy) is tremolite-free and contains trace amounts of balangeroite, a non-asbestos fibrous mineral, similar in shape to amphiboles.[4, 5]

A study on workers of the Balangero mine reported only two deaths from pleural cancer up to 1987.[4, 6] This study has been regarded as contributing to the evidence that chrysotile has relatively low carcinogenic potency.[2] Published reports did not, however, include clerical workers or employees of subcontractors, and four cases of malignant mesothelioma, one in a worker engaged at the mining site by a subcontractor, have been described after 1987.[7-9]

In Piedmont a registry of malignant mesotheliomas (RMM) has been maintained since 1990.[10] We report on a survey of data in the RMM, conducted to identify cases etiologically related to the mine, including cases among non-occupationally exposed persons.

POPULATION AND METHODS

The plant

The Balangero mine, active from 1917 to 1985, was an open-pit operation, flanked by a mill for opening, separating and mixing fibres of different length. Amiantifera, the company that owned the mine, officially ceased its activities in 1990. Asbestos and the mine tailings, which are crushed serpentine rocks left over after fibre extraction and which still contain up to 1% chrysotile fibres by weight, were taken away by railway and lorries. A cohort of miners and millers employed for at least one month by Amiantifera and active in 1946 or hired thereafter was established by Rubino *et al* and studied further by Piolatto *et al*. [4, 6] The cohort did not include white-collar workers or employees of sub-contractors. Fibre measurements during mining activities did not begin until 1969, and Rubino and coworkers experimentally reproduced working conditions for the period 1946-1975. They used these simulated conditions to estimate average fibre concentrations for different jobs and calendar periods, as well as individual cumulative exposures.[6] Occupational exposure was in the range of 100-400 ff/mly for about 30% of workers, and > 400 for another 30%.[4, 6] Fall-out from the mine affected the surrounding towns but, apart from anecdotal descriptions of episodes of very high air pollution in the literature, few measurements are available of asbestos fibre concentrations in the general environment.[8, 11-12] Mine tailings from Balangero were used in several areas of Piedmont as ballast for road and railroad construction and for courtyard paving.

Identification of cases

Many asbestos industries were located in Piedmont, a region of 4.5 million inhabitants.[13] Since 1990, the RMM has accounted for newly diagnosed cases of malignant mesothelioma among residents; cases occurring in 1980-1989 were registered retrospectively.[10] Structured interviews with cases or respondents were conducted to obtain information on life-long occupational and non-occupational exposure to asbestos. Initially interviews were conducted only with persons enrolled in surveys and case-control studies.[14-15] Over the years, the RMM has increased its efforts to obtain exposure data, which are now available for approximately 50% of all mesotheliomas diagnosed between 1990 and 2001. Through the network of regional registries connected with the National Registry of Mesotheliomas the RMM can identify persons exposed in Piedmont that were living in other Italian regions at the time of diagnosis.[16]

Industrial hygienists performed qualitative and quantitative assessment of asbestos exposure for all successfully interviewed cases. They based their assessment on descriptions of the relevant exposure circumstances and on available knowledge of the industrial and non-industrial settings involved. Records have been kept of all settings where exposures occurred. From the RMM records we extracted cases occurring in the following groups: employees of Amiantifera or of its subcontractors at the Balangero mine; employees of other firms transporting or refining asbestos,

asbestos ore, or tailings from the Balangero mine; individuals either exposed to the fall-out of dust from the mine (environmental exposure) or living with an employee of the mine (household exposure); and individuals reporting exposure to mine tailings from Balangero. Cases occurring in all but the last two groups ideally belong to well-defined occupational populations, even if we could not explicitly list these populations as we lack their employment rolls. Cases occurring in the last two groups belong to the general population. Persons living in the four towns closest to the mine (Balangero, Corio, Coassolo, Lanzo) were considered to have environmental exposure. Sharing a home with an employee of the mine who brought home his working clothes was classified as household exposure. Exposure to mine tailings was assumed for individuals who reported in the interview that they handled such materials or lived in proximity of places where they had been dumped or used for pavings. We did not include cases among workers at industries manufacturing asbestos-based products using Balangero asbestos, because most of these workers were also exposed to asbestos from other sources.

Calculation of the expected number of cases in the cohort of miners and millers

Because we had no access to the files of the mortality cohort study on Balangero miners and millers, we did not know the age distribution of its 631 members alive at the last follow-up in 1987.[4] We estimated the 1988-2006 person-years of observation by applying the following conservative assumptions: no mortality up to 31 December 2006, and all cohort members at least 60 years of age in 1987. We then computed the expected number of cases on the basis of the average incidence of malignant pleural mesothelioma (10.4/100 000 per year) for the period 1990-2001 among men aged 60 or older in the appropriate province (Turin). Reference rates were obtained from the RMM. The corresponding exercise could not be done for non-manual workers and for workers not employed by Amiantifera because their numbers were unknown.

RESULTS

Cases associated with exposure to chrysotile

Among 2992 malignant mesothelioma cases registered in Piedmont residents in the period 1980 – 2007, information on exposures was collected and assessed for 1432 subjects. By reviewing exposure assessment records, we identified 25 cases possibly related to exposure to chrysotile from the Balangero mine, bringing to 27 the overall number of cases considered in the present report.

In the accompanying tables, the exposure patterns of these cases are summarised in brief descriptions of all occupations and circumstances considered to have entailed exposure. Unexposed jobs and life events were not reported. The sentence “no other asbestos exposure at work” recorded for a case meant that the individual held other jobs, apart from those mentioned explicitly, and that the rater performing the exposure assessment considered them unexposed.

Of the nine cases of malignant mesothelioma in employees of Amiantifera (Table 1A), the first two are those reported by Rubino et al. (1979) and Piolatto et al. (1990). Case 3, first diagnosed in 1985, was not included in these studies, perhaps because he became a manager in the last part of his career. Four cases occurred among manual workers after the follow-up was closed (cases 4–7), one case was a white-collar worker (case 8), and one was a manual worker who later became a technical staff member (case 9).

Five cases occurred in employees of firms subcontracted by Amiantifera, who reported having worked at the same site, being engaged in the same production processes and using the same machinery as employees of Amiantifera (Table 1B).

Table 1A. Cases of malignant mesothelioma among workers employed by Amiantifera at the Balangero mining site

<i>Case</i>	<i>Sex</i>	<i>Age</i>	<i>Year</i>	<i>Site</i>	<i>Diagnosis</i>	<i>Source of case</i>	<i>Routes of exposure</i>
1	M	51	1975	Pleural	Cytol	Piolatto et al. 1990	Blue-collar worker at Amiantifera (1940-1973). No further data currently available.
2	M	62	1977	Pleural	Histol	Piolatto et al. 1990	Blue-collar worker at Amiantifera (1942-1967). No further data currently available.
3	M	64	1985	Pleural	Histol	RMM	Blue-collar worker at Amiantifera, (1954-1985): miner in the first years of employment, later technical staff and lastly manager.
4	M	68	1989	Pleural	Cytol, ICC	RMM	Blue-collar worker at Amiantifera (1936-1941 and 1942-1944): miners' aid, and later rock driller, then miller and fibre mixer. No other asbestos exposure at work.
5	M	73	1992	Pleural	Histol, IHC	RMM	Blue-collar worker at Amiantifera (1942-1969) as miners' aid and later miller. No other asbestos exposure at work.
6	M	77	1994	Pleural	Clinical	RMM	Blue-collar worker at Amiantifera (1938-1965). No further data currently available.
7 ^a	M	67	2002	Pleural	Cytol, ICC	RMM	Blue-collar worker at Amiantifera as plant electrician (1964-1965). Electrician in a steel mill (1953-1955), in railway coach construction (1955-1958), in an iron foundry (1959-1963 and 1966-1971), and in a motor vehicle assembly plant (1971-1989).
8	M	76	2005	Pleural	Clinical	RMM	White-collar worker, then manager at Amiantifera (1956-1985). No other asbestos exposure at work.
9	M	78	2006	Pleural	Histol, IHC	RMM	Blue collar worker at Amiantifera 1959-1967, asbestos bagger. White collar worker at Amiantifera 1967-1987. No other asbestos exposure at work. Lived in proximity of the mining area (1959-1987).

Abbreviations. Cytol: cytological confirmation, Histol: histological confirmation, IHC/ICC: immune staining pattern suggestive of a mesothelial neoplasm, based on histological or cytological material, respectively; RMM: Registry of Malignant Mesotheliomas

^a Possible exposure to other types of asbestos

Table 1B. Cases of malignant mesothelioma among workers employed by sub-contractors at the Balangero mining site

<i>Case</i>	<i>Sex</i>	<i>Age</i>	<i>Year</i>	<i>Site</i>	<i>Diagnosis</i>	<i>Source of case</i>	<i>Routes of exposure</i>
10	M	36	1989	Pleural	Histol	RMM	Bricklayer and roofer, engaged in building an asbestos mill at the mining site (1968-1972). Lift mechanic (1967-1968). No other asbestos exposure at work. Lived inside the mining site (1968-1972).
11 ^a	M	59	1992	Pleural	Histol, IHC	RMM	Blue-collar worker at a sub-contractor, working at the mining site as miners' aid (1949). Bricklayer (1949-1957), worker in a nylon production facility (1957-1959), worker in the curing department of a tire production plant (1963-1977), marble cutter (1979-1989).
12	M	68	2003	Pleural	Histol, IHC	Riboldi et al. 2004	Blue-collar worker at a sub-contractor, working at the mining site as lorry driver, carrying asbestos ore from the mine to the mill and tailings from the mill to the dumping site (1955). No other asbestos exposure at work.
13	M	74	2003	Pleural	Histol, IHC	RMM	Blue collar worker at a sub-contractor transporting asbestos from the Amiantifera mine to different industries, 1967-1989. Furnace worker in a steel mill 1966-1967.
14	M	72	2006	Pleural	Cytol, ICC	RMM	Blue collar worker at a sub-contractor as lorry driver, carrying asbestos from the Amiantifera mine, 1958-1973. No other asbestos exposure at work. Lived in proximity of the mining area (1933 – 2006).

Abbreviations. Cytol: cytological confirmation, Histol: histological confirmation, IHC/ICC: immune staining pattern suggestive of a mesothelial neoplasm, based on histological or cytological material, respectively; RMM: Registry of Malignant Mesotheliomas

^a Possible exposure to other types of asbestos

Three cases were never engaged at the Balangero mining site, but had worked with asbestos, asbestos ore, and mine tailings from the mine (Table 2). Cases 15 and 17 had worked at a mill outside the mining site that was not owned by Amiantifera, where low-grade ore yielding short fibres was treated and asbestos was separated, mixed, and packaged. Case 16 repeatedly handled materials from the Balangero mine: he worked on extracting nickel from “sterile” Balangero serpentinite and on a project for “wet” extraction of asbestos fibres.

Table 2. Cases of malignant mesothelioma in workers never employed at the Balangero mining site, but occupationally exposed to chrysotile from the mine

<i>Case</i>	<i>Sex</i>	<i>Age</i>	<i>Year</i>	<i>Site</i>	<i>Diagnosis</i>	<i>Source of case</i>	<i>Routes of exposure</i>
15 ^a	F	53	1990	Pleural	Histol, IHC	RMM	White-collar worker at a mill outside the mining site treating Balangero ore: office in the yard of the factory (1957-1990). The mill also treated tremolite-contaminated talc from local mines. Lived in proximity of the mining area (1937-1990).
16 ^a	M	56	1996	Pleural	Histol, IHC	RMM	Researcher and teacher at the Turin Institute of Technology (1964-1969). Analysed ore from the Balangero mine and built/managed pilot plants for ore exploitation (1964-1966, 1968-1969 and 1987). Engineering consultant (1969-1997). Sampled air in brake/clutch lining production plants (1978-1983).
17 ^a	M	68	2001	Peritoneal	Histol, IHC	RMM	Asbestos hand bagger (1950-1961) at a mill outside the mining site treating Balangero ore. The mill (but not the worker) also treated tremolite-contaminated talc from local mines. Lived in proximity of mining area (1933-1972).

Abbreviations. Histol: histological confirmation, IHC: immune staining pattern suggestive of a mesothelial neoplasm, based on histological material; RMM: Registry of Malignant Mesotheliomas

^a Possible exposure to other types of asbestos

Five cases occurred in the population living in the neighbourhood of the mining area (Table 3). Case 18 also reported household exposure. Finally, five cases occurred among persons exposed to mine tailings from Balangero at work or at home (Table 4). Three were women who lived for a long time in areas where the surroundings were paved with tailings from Balangero.

Table 3. Cases of malignant mesothelioma due to household or environmental exposure

<i>Case</i>	<i>Sex</i>	<i>Age</i>	<i>Year</i>	<i>Site</i>	<i>Diagnosis</i>	<i>Source of case</i>	<i>Routes of exposure</i>
18	F	55	1981	Pleural	Histol	RMM	No definite/likely occupational exposure. Husband asbestos packer at the mining site, work clothes cleaned and washed at home (1948–1973). Lived in proximity of the mining area (1926–1981).
19	M	78	2003	Pleural	Histol, IHC	RMM	No definite/likely occupational exposure. Lived in proximity of the mining area (1925–1926 and 1983–2003).
20	F	79	2003	Pleural	Histol, IHC	RMM	No definite/likely occupational exposure. Lived in proximity of the mining area (1935–2003).
21	F	69	2003	Pleural	Histol, IHC	RMM	No definite/likely occupational exposure. Lived in proximity of the mining area (1943 – 1980).
22	F	75	2007	Peritoneal	Histol, IHC	RMM	Farmer 1944–2002, leaves collected in the surroundings of the mining area used for cattle litters. Lived in proximity of the mining area (1936 – 2007).

Abbreviations. Histol: histological confirmation, IHC: immune staining pattern suggestive of a mesothelial neoplasm, based on histological material; RMM: Registry of Malignant Mesotheliomas

Table 4. Cases of malignant mesothelioma among persons exposed to mine tailings used outside mine

<i>Case</i>	<i>Sex</i>	<i>Age</i>	<i>Year</i>	<i>Site</i>	<i>Diagnosis</i>	<i>Source of case</i>	<i>Routes of exposure</i>
23	F	52	1995	Pleural	Histol, IHC	RMM	Corn mill owner. Possibly used asbestos-contaminated bags discarded from the Balangero mine (1961–1995). Lived in a town where Balangero tailings were widely used as road ballast (1943–1995).
24 ^a	F	47	1996	Pleural	Histol	RMM	Employed by Italian railways (1970–1991), where Balangero mine tailings were used as ballast up to the mid-1970s. No other asbestos exposure at work. Lived (1948–1996) in proximity of railway tracks where Balangero mine tailings had been used as ballast.
25 ^a	F	74	1998	Pleural	Histol	RMM	No definite/likely occupational exposure. Lived in a house with Balangero tailings as gravel substitute in the garden (1980–1998). Possible fall-out from an asbestos textile workshop 600 m from home (1978–1990).
26	F	39	2000	Pleural	Histol, IHC	RMM	No definite/likely occupational exposure. Lived in a district where Balangero tailings were used as road ballast (1982–2000).
27 ^a	M	74	2001	Pleural	Histol, IHC	RMM	Employed by Italian railways as track maintenance worker (1951–1986), where Balangero mine tailings were used as ballast. No other asbestos exposure at work.

Abbreviations. Histol: histological confirmation, IHC: immune staining pattern suggestive of a mesothelial neoplasm, based on histological material; RMM: Registry of Malignant Mesotheliomas

^a Possible exposure to other types of asbestos

Expected number of mesotheliomas in the cohort of miners and millers

The expected number of cases cannot be computed with precision without knowledge of the age distribution of the cohort of miners and millers. Piolatto et al. (1990) reported that 0.3 deaths from pleural cancer were expected between 1946 and 1987.[4] Since pleural mesothelioma incidence is very close to mortality from pleural cancer, we assume that 0.3 cases would be expected during the same period. Based on our calculations, further 1.2 cases are expected in 1988-2006, giving a total of 1.5 cases expected between 1946 and 2006. In blue-collar employees of Amiantifera 6 cases were recorded (cases 1, 2, and 4-7), corresponding to a standardized incidence ratio (SIR) of 4.00, with a 95% confidence interval (95%CI) of 1.47-8.71. We excluded the following cases from the number of malignant mesotheliomas observed in the cohort: case 8 because he was a clerk, cases 3 and 9 because, even if they served some years as manual workers, they became clerks and staff members and may not have been included in the cohort study, since this was restricted to miners and millers.[4, 6]

DISCUSSION

Information on exposure is available for 50% of all cases in the RMM, so additional cases due to the exposures of interest may exist among those whose personal histories are unknown. Despite this limitation, our survey allowed the identification of a cluster of malignant mesotheliomas in persons who were exposed to chrysotile from Balangero but not, or only to a limited extent, to other types of asbestos.

The expected number of mesothelioma cases in the cohort of Balangero miners and millers may have been overestimated in our calculations, first because we had to make some conservative assumptions to compute the number of person-years accrued during 1988-2006, and secondly because we used the population of Turin province as a reference. We had to approximate the calculation of person-years as we had no access to the individual records of the cohort members alive in 1987, when Piolatto and coworkers ended their follow-up study.[4] The population of Turin province may bias the mesothelioma SIR estimate towards the null, because it includes substantial numbers of former workers of asbestos industries.[13] Nevertheless, it is preferable to the alternatives: national incidence rates are unavailable for the calendar period considered, and estimates based on regional rates would be even more biased, due to the overwhelming influence of the peculiar epidemiological situation of Casale Monferrato.[14, 15] Thus, an SIR of 4.00 (95%CI 1.47-8.71), based on 6 observed cases, can be tentatively estimated for manual workers hired by the firm running the mine. In the most recent update of the mortality study, the standardised mortality ratio (SMR) for pleural cancer was reported to be 6.67 (95%CI 0.8-24.1), based on 2 observed deaths.[4] Both deaths could be confirmed as due to pleural mesothelioma, and they correspond to cases 1 and 2 in the present report. Current and earlier risk estimates are in agreement, if their confidence intervals are taken into account. Opportunities for occupational exposure to asbestos of Amiantifera employees outside the mine could be identified only for case 7, a man who worked as an electrician in other plants where asbestos use was possible.

No data were available to estimate expected cases of malignant mesothelioma among non-manual workers or employees of subcontracting firms. However, the detection of three and five cases in these groups, respectively, can hardly be attributed to chance. In particular, regarding the occurrence of malignant mesothelioma in non-manual employees (cases 3, 8 and 9), it is important to note that cases 3 and 9 were manual workers in their first years of employment. Regarding case 8, there are strong suggestions that substantial levels of airborne asbestos fibres were present in all the areas of the mining site. One of us observed a case of fatal asbestosis in a woman (diagnosed in 1989, dead in 1993 at age 63) who never worked at the mine but lived in a house inside the Amiantifera premises, close to the fibre separation plant (R Calisti, unpublished data). The administrative offices were located in the same area.

Thus, our present findings indicate that Balangero chrysotile miners and millers experienced increased risk of malignant mesothelioma. In addition, the results suggest that, in workplaces entailing exposure to asbestos in which some activities are carried out by subcontracting firms, any

assessment of the burden of disease caused by asbestos should include workers hired by the subcontracting firms, for which nominal rosters for use in conventional cohort studies are rarely collected.

We identified three new cases among workers employed by subcontractors or consultants to Amiantifera who had never worked at the mining site but who used or were in close contact with its ore, its products, or its tailings (Table 2). Their common exposure feature is Balangero chrysotile, although cases 15 and 17 may also have been exposed to fibrous tremolite.

Cases 18–22 suggest an etiological role of exposure to Balangero chrysotile in the general environment. Asbestos fibres have recently been found in the lungs of animals raised in the Balangero area, where the mining site was by far the most important source of asbestos fibres. This is still true today, due to incomplete remediation of the mining site.[17]

Cases 23–27 neither worked at the mine nor reported circumstances corresponding to our definitions of environmental or household exposure. They were however exposed to Balangero mine tailings used as ballast. Possible exposure to tremolite may have played a role in cases 23 and 27: ballast from Balangero was used for beds of railway lines up to the mid-1970s, but it was later replaced by other serpentinites, some of which were contaminated with tremolite.

The hypothesis has been advanced that chrysotile itself would not induce malignant mesotheliomas and that their occurrence in Quebec miners and millers would be due to contamination by fibrous tremolite.[3, 18] The occurrence of mesotheliomas in individuals with exposure to Balangero chrysotile is important, because no tremolite has been detected in it.[4] Instead, balangeroite is present, especially in serpentinites at the northern side of the mine, and represents 0.2–1% by weight of extracted fibres. Recognised in 1983 as a new mineral, it is a fibrous magnesium-iron silicate, appearing as bundles of brownish fibres strictly associated with long-fibre chrysotile.[5, 19] It is morphologically similar to amphiboles, and it produced nitrite accumulation, lipid peroxidation, and nitrous oxide synthase activation in a human lung epithelial cell line, similarly to crocidolite.[19, 20] Thus it exhibited a potential for producing oxidative cellular damage *in vitro*. However, it is unclear what role these factors may play in the induction of human mesothelioma. Furthermore, balangeroite has never been tested for carcinogenicity in long-term animal experiments. Therefore, in light of current knowledge, it cannot be considered a carcinogen, nor it can be implied to cause mesotheliomas instead of chrysotile.

In a meta-analysis of occupational cohort studies, chrysotile carcinogenic potency in inducing mesothelioma was estimated to be 2–3 orders of magnitude less than that of amphiboles.[2] The major contribution to this assessment came from the results of the cohort study on Quebec chrysotile miners and millers.[18] Supporting evidence was provided by the fact that, worldwide, in other cohorts – including that of Amiantifera workers – no or very few cases were found.[4, 21] Our assessment of the burden of mesotheliomas caused by chrysotile from Balangero is based on incomplete data. Nevertheless, the overall picture linking Balangero chrysotile to malignant mesothelioma is less reassuring than previously reported. Our findings also raise concern about the risks due to the continuing presence of mine tailings on railroad tracks, road beds and pavings, and perhaps to the incomplete remediation of the mining site.

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