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The epidemiologic relationship between pleural mesothelioma and asbestos exposure

by MARKKU NURMINEN, statistician¹

NURMINEN, M. The epidemiologic relationship between pleural mesothelioma and asbestos exposure. *Scand. j. work environ. & health* 1 (1975) 128—137. This paper describes an investigation of 85 notifications of either probable or possible mesothelioma to the Finnish Cancer Registry from 1953 through 1969. The investigation covers characteristic epidemiologic features and the possibility of the mesothelioma being connected with occupational or other exposure to asbestos. The incidence rate of pleural mesothelioma was estimated at 1.1 per million per year. The male/female ratio was 1.3:1, which greatly differed from that for malignant neoplasms of the bronchus or lung in Finland in 1960. The mean age at death from mesothelioma was over 7 years lower than that for bronchial carcinoma. The ratio of the crude incidence rates for the urban and rural populations was 4.2; the corresponding ratio for cases of carcinoma of the bronchus or lung was 1.2 in Finland in 1960. The last occupations of the 82 deceased persons, obtained from the death certificates, were divided into three categories according to possible asbestos exposure. Exposure was present or probable in 9 (11.0 %) cases, 28 (34.2 %) had a possible exposure, and in 33 (40.2 %) cases exposure was absent or unlikely. The occupation of 12 (14.6 %) persons was unknown. Additional information of possible exposure history was obtained by interviewing the relatives of 10 mesothelioma patients. For half of the persons a definite, although in some cases trivial, exposure to asbestos could be ascertained. For the other five persons no exposure, either occupational, neighborhood or domestic, to asbestos could be traced. The residential distribution of the 85 persons with mesothelioma revealed no clustering of cases.

Key words: cancer epidemiology, pleural mesothelioma, asbestos exposure.

In epidemiologic studies patterns of disease in human populations are described and their causes sought. These goals are attained by observing the temporal-spatial distributions of disease and by demonstrating associations between different events and states in individuals. The purposes are usually expressed in general terms, but, when dealing with a particular (e.g., occupational) health hazard, the range of methods is limited by the nature of the causes sought and by the frequency (rate) of the occurrence of the disease.

Epidemiology is concerned with risk indicators, i.e., characteristics of people or their environment which reflect the individual probability (risk) of being affected, and with the possibility of manipulating risks. In assessing the causality of risk indicators the disease frequency is related to its various correlates, personal characteristics, and/or environmental exposures. Finally epidemiologic evidence is used to evaluate the effects of preventive measures.

An epidemiologic approach may assist in situations not easily solvable by customary methods, and indeed this type of approach seems to help when searching for the etiology of uncommon diseases like pleural mesothelioma. [For a detailed consideration of this and related matters the reader can consult Knox (12).]

The purpose of this article is to review the epidemiologic relationship between

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pleural mesothelioma and asbestos exposure and to present some recent findings from a study of the epidemiology of pleural mesothelioma in Finland.

RELATIONSHIP BETWEEN PLEURAL MESOTHELIOMA AND ASBESTOS EXPOSURE

The possibility of a relationship between pleural mesothelioma and asbestos exposure has been hypothesized for many years. Welder (32) first noted an association between asbestosis and pleural mesothelioma in 1943. His observation was followed by reports of a case of pleural mesothelioma in an asbestos worker suffering from asbestosis (31) and a case of peritoneal mesothelioma and asbestosis (16). Later Wagner et al. (30), in their retrospective investigation, reported a history of exposure to crocidolite asbestos for almost all the cases of primary malignant mesothelioma of the pleura they found in the northwest Cape Province of South Africa. Besides mesotheliomas noted as a result of occupational exposure in the asbestos mining industry (30), an increasing number of cases has been observed since 1960 in plants manufacturing brake linings or asbestos textile and friction material, among insulators and ladders in construction work, and in the shipbuilding industry (3, 17, 20).

Investigations from different countries have also revealed mesotheliomas due to possible domestic or neighborhood exposure to asbestos. Direct domestic exposure to dust from clothing worn by family members who worked with asbestos has been the only recognized contact with asbestos in several cases (17). In other cases the dusty surroundings of an asbestos factory or mill were a possible source of neighborhood exposure (20). In Finland the prevalence of plaques of the pleura was found to be high in the general population living near the anthophyllite factory at Paakkila, which is an open quarry and a fiber mill (11). Here the asbestos dust is not only airborne but is also present in the soil (14).

A register of cases of mesothelioma kept in England since 1962 provides further statistical evidence of a geographical concentration of cases in ports and other cities with factories handling large

amounts of asbestos (29). This clustering of mesotheliomas is, however, likely to be due to occupational rather than general environmental exposure, and the role of macroenvironmental exposure, i.e., the potential hazard of urban air contamination, as a cause of the reported differences in incidence of mesothelioma between urban and rural areas has not been established.

TYPES OF STUDIES CONDUCTED CONCERNING PLEURAL MESOTHELIOMA AND ASBESTOS EXPOSURE

Studies investigating the problem of "pleural mesothelioma and asbestos exposure" are generally case-history studies. This approach yields the most information because the outcome is so rare. Material is gathered from hospital records, autopsy series, files of death certificates, cancer registries, or from special collections of mesothelioma cases (mesothelioma registers). The data from the hospital records of mesothelioma cases may be used to characterize the clinical features of this tumor and to point out the difficulties in making a definite diagnosis, but case histories seldom provide any information of personal or environmental exposure (8). More valuable are studies of the amount and type of asbestos bodies in the lungs of persons with a mesothelioma (possibly by cell type) as well as investigations of the frequency of asbestosis in large autopsy materials or in representative samples of cases in occupational groups known to have been exposed to asbestos (9). Consulting only death certificates for information may result in an underestimate of the true mortality from mesothelial tumors (21), but a mesothelioma register should provide (a) a record of the annual incidence of mesothelioma associated with asbestos exposure, (b) trends in prevalence rates, (c) information on tumors occurring without any known or suspected occupational exposure, and (d) leads to prevention based on epidemiologic evidence (7).

Epidemiologic studies of asbestos and neoplasia usually provide information on more than one type of cancer. In a prospective study of a cohort of workers at an asbestos factory, for example, uncer-

tainties in the differential diagnosis of peripheral lung carcinomas and pleural mesotheliomas and between peritoneal mesotheliomas and other intra-abdominal cancers were clearly present (21). Such problems call for close cooperation between epidemiologists and pathologists, especially in an epidemiologic project directed toward a single type of tumor (1).

FREQUENCY OF PLEURAL MESOTHELIOMA

Even if the diagnostic criteria for pleural mesothelioma are assumed to be standard, the reported frequencies of pleural mesothelioma may vary greatly from one material or population to another owing to the differences in their composition and the criteria for inclusion in the study. For example, Hägerstrand et al. (9) reported the rate of mesothelioma to be 2.7/1,000 for an extensive 10-year autopsy material at a general hospital in Malmö, Sweden. For subjects who have inhaled asbestos dust, the reported frequencies from northern Italy range from 7/1,000 to 76/1,000 (25). Still higher frequencies of mesothelioma (11 %) have been reported for patients who have died from asbestosis (13). In southeastern Pennsylvania 34 cases of pleural mesothelioma, diagnosed between 1958 and 1963, were reported from 152 hospitals serving a population of over 6 million people (17). From these data the annual incidence rate can be estimated as one case per million. The incidence of definite mesotheliomas in England, Wales, and Scotland was 2.3 cases per million per year (7). Markedly greater incidences were calculated for areas with substantial industrial use of asbestos.

MESOTHELIOMA AND TYPES OF ASBESTOS EXPOSURE

The main commercial types of asbestos are chrysotile (white) and the distinct varieties of the amphiboles: crocidolite (blue), amosite (brown), and anthophyllite (white).

Recent epidemiologic work indicates that the different types and uses of asbestos are not equally hazardous. Exposure to anthophyllite is not known to

cause mesothelioma, but this may well be due to the small size of the cohorts followed (22). Also, exposure to chrysotile alone is very rarely a probable cause. In most of the cases exposures have been to crocidolite and/or amosite with or without chrysotile (29). Present evidence suggests that crocidolite carries a higher risk of mesothelioma than the other types of asbestos. It has been postulated that this difference in risk is due to the smaller average diameter of the crocidolite fibers (27). Especially if the dust reaches the pleura through direct penetration from the lungs, then the fineness of the fibers may serve as an explanation of the excess risk from crocidolite.

RECENT FINDINGS FROM FINLAND

In connection with a larger research project (10) an epidemiologic investigation was performed to study pleural mesothelioma on a national basis in Finland. More specifically, the characteristic epidemiologic features of pleural mesothelioma and the possibility of pleural mesothelioma being connected with occupational or other exposure to asbestos were of major interest in the study.

Materials and methods

The material for this study was taken from the files of the Finnish Cancer Registry (Institute for Statistical and Epidemiological Cancer Research) for the years 1953 through 1969. The information on all pleural cancers was carefully reassessed as was that on the cancers of neighboring organs (lungs, etc.) if the histologic diagnosis had been a sarcoma. Because of their extremely rare occurrence peritoneal mesotheliomas were not included in this study, however. On the basis of the information gathered the cases were classified into three categories: (a) those cases (51 persons) in which the mesothelioma diagnosis was probable; (b) those cases (34 persons) in which the diagnosis was uncertain but possible in light of available information; and (c) those cases that were probably not mesotheliomas of the pleura. Consideration of the probable and possible cases separately did not alter the results of the study,

Table 1. Number of pleural mesotheliomas reported to the Finnish Cancer Registry from 1953 to 1969 according to year of diagnosis and sex.

Year	Male	Female	Total
1953	1	—	1
1954	—	2	2
1955	1	1	2
1956	2	1	3
1957	—	1	1
1958	2	2	4
1959	1	—	1
1960	2	2	4
1961	2	3	5
1962	2	2	4
1963	2	4	6
1964	7	1	8
1965	5	5	10
1966	1	1	2
1967	4	3	7
1968	10	3	13
1969	6	6	12
Total	48	37	85

and the age at diagnosis, sex ratio, residential scatter, and urban/rural distribution were similar in the first two groups. It was thus decided to combine the first two groups and reject the third group.

The Central Statistical Office of Finland supplied the death certificates of the 81 persons (3 alive, 1 death certificate untraced) who had been classified into the first two groups. Besides information on the underlying cause of death, additional information on contributing causes of death, last occupation, and on the last place of residence could be obtained from the death certificates.

The Institute of Occupational Health (Department of Epidemiology and Biometry) conducted a study of the lifetime occupational and residential history of 10 persons who had died of mesothelioma. Since the subjects had died before the investigation began, relatives had to be interviewed to attain information on the occupational history, possible domiciliary exposure to asbestos, and smoking habits of the deceased. There were several unsuccessful attempts to locate the whereabouts of relatives before a sample of 10 interviews could be completed. No systematic data were available concerning the presence or absence of asbestos fibers or bodies in the sputum, lungs, or tumor tissue.

Results

Since there was a total of 85 cases of pleural mesothelioma (probable or possible) listed in the Finnish Cancer Registry from 1953 to 1969 (table 1), the annual incidence can be estimated as 1.1 per million, a figure which agrees with the rate found in Pennsylvania (17). The number of new (notified) cases has been increasing in Finland since 1953, however. The cumulative totals are 9 up to 1957, 33 up to 1963, and 85 up to 1969; and the number of new cases detected each year is now over 10.

The sex ratio (males: females) was only 1.3:1. This figure greatly differs from that for malignant neoplasms of the bronchus and lung [ICD 162—163 (33)] in Finland in 1960, about 12:1 (6), and the ratio of mesothelioma in men and women noted in England, 5:1 (7). The sex difference for carcinoma of the bronchus is generally attributed in part to the difference in smoking habits, but tobacco is not known to be an important factor in the development of mesothelioma.

The age of the 82 persons at death ranged from 3 to 93 years. The median age at death for both sexes was in the interval from 55 to 59 years [table 2; Grundy and Miller (8) can be consulted for reports of childhood cases]. For comparison the age distributions at death for all pleural mesotheliomas and for carcinoma of the bronchus and lung for male and female patients combined (5) are presented in fig. 1. The mean age at death from mesothelioma is over 7 years lower than that for bronchial carcinoma. Greenberg and Lloyd Davies (7) have reported a similar result.

Table 2. Distribution of 82 persons with pleural mesothelioma according to sex and age at death.

Age, years	Male		Female	
	No.	%	No.	%
< 35	4	8.5	3	8.6
35—44	5	10.6	3	8.6
45—54	9	19.2	10	28.6
55—64	13	27.6	12	34.2
65—74	14	29.8	5	14.3
≥ 75	2	4.3	2	5.7
Total	47	100	35	100

Fig. 1. Distribution of 82 persons with pleural mesothelioma reported between 1953 and 1969 according to their age at death and the age distribution of persons with bronchial or lung cancer in 1960.

Fig. 2. Survival time of 85 mesothelioma patients after pleural mesothelioma was diagnosed.

The clinical course of the disease appeared to be incurable and rapid. The mean survival time of all persons with pleural mesothelioma from the time of diagnosis was approximately 5 months, 74 % died within a year of the onset of symptoms, and only three persons survived for more than 2 years (fig. 2).

According to information obtained from death certificates, notifications to the Finnish Cancer Registry, and interviews, the ratio of the crude incidence rates for the urban and rural populations was 4.2. The corresponding ratio for cases of carcinoma of the bronchus and lung in 1960 was 1.2 (table 3).

The last occupations of the 82 deceased persons, obtained from the death certificates, were divided into the following three categories according to possible asbestos exposure: (a) present or probable, (b) possible, and (c) absent or unlikely. Nine persons (11.0 %) were thought to belong to the first group, 28 (34.2 %) to the second group, and 33 (40.2 %) to the third group. The occupation of 12 persons (14.6 %) was unknown (table 4).

In order to scrutinize for possible exposure history, a random sample of 10 subjects was taken from the entire series of 85 definite or probable mesothelioma diagnoses. Table 5 lists information obtained through an interview. The data show that two persons out of ten had migrated from a rural area or village to a town or city. For half of the persons a defi-

Table 3. Comparison between the frequency of pleural mesothelioma and new cases of bronchial and lung cancer in Finland in 1960 by place of residence.^a

Place of residence and ratio	Subjects with pleural mesothelioma/million/year	New cases of bronchial and lung cancer in 1960/million ^b
Urban	2.2	342.5
Rural	0.5	284.2
Ratio ^c	4.4	1.2

^a As written on notifications to the Finnish Cancer Registry or on death certificates.

^b Cancer Incidence in Finland VIII/1963, Helsinki, 1967.

^c Calculations are based on the mean population of Finland in 1960 (4).

Table 4. The last occupation recorded on the death certificates of 82 subjects with pleural mesothelioma according to asbestos exposure.

Exposure to asbestos	Occupation	No.
Present or probable	Foreman in asbestos factory, insulator, railroad engineer, railroad fireman, shipyard worker, pipe fitter, scrapyard assistant, foundry worker, railroad plater	9
Possible	Concrete worker, 2 construction workers, common laborer, brick factory worker, 2 road workers, factory worker, 2 workers, 7 farmers, agricultural technician, farmhand, sawmill manager, janitor, cloth cutter, machine driver, moulder, lever box man (railroad), truck driver, carpenter, laundrywoman	28
Absent or unlikely	2 painters, judge, managing chief (sulfuric acid factory), railroad station manager, army captain, bank official, book-keeper, 2 managing directors, bureau chief, agent, musician, elementary schoolteacher, tailor, student, 3 tradesmen, 3 nurses, midwife, boardinghouse keeper, hostess, cook, seamstress, restaurant assistant, technical assistant, maid	33
Unknown	Unknown	12

nite, although in some cases trivial, exposure to asbestos was ascertained. For the other five persons no exposure, either occupational, neighborhood or domestic, to asbestos could be traced. Also there was no systematic pattern in the smoking habits to suggest that cigarette smoking could be an important factor in the development of pleural mesothelioma. The patients' medical histories, where mentioned, did not contribute any information.

The residential distribution of the 85 persons with mesothelioma is plotted in fig. 3. The distribution corresponds with the population density of Finland and reveals no clustering of cases. There were no mesothelomas reported from the communities surrounding the anthophyllite asbestos mine at Paakkila in the county of Kuopio, a finding which concurs with earlier reports (18, 22).

Discussion

In examining the concept of the causal relationship between asbestos and malignancy, some problems arise. For example, one characteristic of occupational cancer is the long latent period from the first exposure to the appearance of the cancer. The average observed latent period for asbestos-induced cancer is 18 years (23). Even if exposure to asbestos is considered an etiologic factor, the exposure need not

necessarily be occupational. Fibers may be emitted from factories, be released in traffic from brake shoes and clutch plates, or be airborne from open asbestos mines or construction sites, e.g., from insulating material and plaster board (26, 29, 30). Several autopsy series have also revealed asbestos bodies in the pulmonary tissue of a high percentage of urban dwellers (4, 15, 28). Exposure can even take place at home, from floor tiles for example (19). Such nonoccupational exposure could have accounted for at least one person (no. 4, table 5) in the present series.

It is also possible that mesothelioma of the pleura is not induced by asbestos. The absence of residential clustering among the cases in Finland is a feature against environmental influence. On the other hand the migration of people in Finland has been massive in the last few decades. But even if asbestos fibers are not involved, other unsuspected environmental agents may be present.

The yearly increasing number of notified cases of mesothelioma (table 1) could be a reflection of a wider use of pleural mesothelioma as a diagnosis. It is one of the most difficult tumors to diagnose. According to different sources the histological pattern and macroscopic appearance vary greatly. Thus it is possible that a cancer, which in fact is a mesothelioma, can be classified as another type of malignant tumor. The reverse

Table 5 Exposure history of 10 persons with pleural mesothelioma.

Patient no.	Sex	Year of birth	Year of death	Residence	Occupation or workplace	Cigarettes/day	Domestic exposure	Relevant history
Asbestos exposure likely or confirmed								
1	M	1900	1969	Urban	Railroad plater in engine room	< 10	No	Asbestos used to insulate engines
2	M	1915	1968	Rural/urban	Different insulation jobs	> 20	No	Insulated roofs, boiler rooms, ships; often handled bitumen tar
3	M	1924	1969	Sub-urban	Worked in asbestos factory	> 20	Wife worked in the same factory	Worked at mass grinding and waste carrying; later engine man and shiftwork foreman; mixed asbestos exposure for 25 years
4	F	1910	1960	Rural	Farm work, bookkeeping	1—2	No	Did repair work on own house and handled asbestos boards
5	M	1897	1969	Urban	Railroad engineer	"Smoked"	Father also a railroad engineer	Worked at cleaning up and repairing engines; work place drafty and hot; work room air smoky and full of coal dust
Asbestos exposure untraced								
6	M	1921	1959	Urban	Cloth cutter	10—20	Wife also worked in dress factory	Dust present from cloth cutting
7	M	1904	1969	Urban	Police chief, shopkeeper	10	No	Suffered from bronchitis and allergic asthma caused by dusts
8	F	1916	1967	Urban	Farm work, hospital nursing	No	No	Worked in different nursing duties from 1941 on; last profession specialized roentgen nurse
9	F	1901	1971	Urban	Worked in candy factory and as a nurses aid	> 20	—	Complained of smoky air in park near factory shipyard located in next block
10	F	1919	1962	Rural/urban	Kitchen work, laundry work	No	No	Complained of humid and drafty air in laundryroom

is also possible: a diagnosis of mesothelioma may sometimes be made in cases where the tumor in fact belongs to one of the other categories. A diagnosis of mesothelioma can be made only from a microscopic specimen. In advanced cases a histological study is seldom performed, and the tumor is probably regarded as originating in the lung tissue. On the other hand one can consider a tumor to be of mesothelial origin on the basis of X-ray findings, but they are not sufficient for a definite diagnosis (2).

When investigating a rare disease like mesothelioma, case-history studies provide a major advantage in that a greater sampling fraction of the cases is obtained than in prospective cohort studies. In this particular study all notified cases of pleural mesothelioma in Finland during a 17-year period could be included. Partly for this reason it was thought useful on this occasion to study a single type of mesothelial cancer.

On a death certificate or on a notification to a cancer registry the place of residence and occupation relates to the person's last. Unfortunately this kind of occupational data is often either recorded in terms that are too general (e.g., "foreman," patient no. 3 in table 5) or totally uninformative ("housewife"). This lack of explicitness may explain in part why only 11 % of the occupations listed on the 82 death certificates could be connected to asbestos, while in half of the 10 cases in which relatives were interviewed an asbestos exposure was found which might have acted as a causative factor in the etiology of mesothelioma.

It has been shown that there is a higher incidence of lung cancer in asbestos workers than in the general population (22). But with mesothelioma there is less epidemiologic evidence for a dose-response relationship which would support the idea of causation. In the present series of pleural mesothelioma only one person with asbestosis was observed. Exposure may be so slight as to be inadequate for asbestosis (3). Such a situation would infer that even exposure which is generally trivial and remote is a potential health hazard (24). It follows that even visiting or having lived in the neighborhood of an asbestos factory or mine may be potentially dangerous. This may be

Fig. 3. Distribution of the 85 persons with mesothelioma (●) according to place of residence at the time of diagnosis (diagnosed between 1953 and 1969) and the location of the asbestos mine at Paakkila (x). Thirty persons resided in Helsinki.

so, but it should be reflected by higher incidence rates for pleural mesothelioma since the number of occupations in which exposure may occur is large.

The fact that no mesotheliomas associated with exposure to anthophyllite asbestos have been observed among the miners at Paakkila may well be due to the small amount of data gathered (22). In a retrospective mortality study based on 22,000 person-years the incidence rate

would have had to have been about 45 cases per million per year in order to produce one case of mesothelioma. This rate is markedly greater than the highest rate (26 cases per million per year) calculated in England (7).

CONCLUDING REMARKS

That there is some association between asbestos and mesothelioma seems likely, but pure probability is not enough to prove it. There is therefore a need for a deeper evaluation of hypotheses relating asbestos and pleural mesothelioma.

Because therapy is of little or no benefit to pleural mesothelioma, emphasis should be placed on its etiology in the hope that identifying causes of the neoplasm may lead to prevention.

Since it is possible that pleural mesothelioma is induced by asbestos or may be caused by some unsuspected environmental agent, a physician should always inquire thoroughly into the patient's history for any unusual exposures when a new case is diagnosed.

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