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The epidemiology of asbestos-related diseases

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Summary Asbestos has been recognised as a potential health hazard since the 1940s. Of the two major species of asbestos; white asbestos (chrysotile) and blue asbestos (crocidolite), both of which are hazardous. The workers at extraction facilities are at the greatest risk of exposure to asbestos and, therefore, the development of asbestos-related diseases, commonly mesothelioma. However, other individuals at a high risk of exposure include asbestos-cement workers, insulation workers and ship-yard workers. Environmental exposure to asbestos can occur as a result of living in areas either characterised by natural outcrops of asbestos or asbestos-related materials, or those close to asbestos-producing or -using plants. Unfortunately, man-made fibre alternatives to asbestos, such as rock and slag-wool and glass wool, have also been shown to have a detrimental effect on human health. A characteristic of mesothelioma is that there is a long latency period (20–30 years) before the signs and symptoms of the disease become apparent. In addition, diagnosis of the disease can be difficult. The use of biological markers, such as tissue polypeptide antigen, may play a useful role in the early detection of the disease in individuals at risk.

1. Introduction

It was in 1960 that the potential hazards to human health from exposure to asbestos fibres were indicated by a publication, by Wagner et al. [1], who reported several cases of pleural mesothelioma in miners working in South African mines contaminated with asbestos. Shortly afterwards, non-occupational cases were also reported [2] and this led to the initiation of research in the asbestos-producing countries. This birth was in fact a re-birth, as abundant scientific material was already available in the late 1930s and early 1940s [3]. Isolated cases of lung cancer occurring in asbestosis patients had been published both in the USA and in Britain since 1935, and in 1938 in Germany, Nordmann wrote a paper on ''The occupational cancer of asbestos workers'' [4], while in the same time Wedler was preparing his paper on the first primary cancers of the pleura in asbestosis patients, and considered them to be of occupational origin [5]. Despite the war conditions, these

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data were known in Britain and in the USA, where Hueper wrote that ''asbestos was unquestionably carcinogenic'' [6]. These facts, however, remained concealed.

Due to its remarkable properties, mainly its resistance to chemical damage and to heat, asbestos has found numerous applications contributing to its industrial and economical interest. After its carcinogenic properties were shown, the concept emerged of innocuous white asbestos and harmful blue asbestos. Indeed, asbestos is a generic name covering several different fibrous minerals. In short, there are two major species of asbestos: the serpentines comprising the curly and soft chrysotile fibres (white asbestos) and the amphiboles (blue asbestos) with a series of subvarieties such as crocidolite(blue asbestos), amosite (brown/grey asbestos) and tremolite, presenting themselves as hard needle-shaped rods. Closely linked to asbestos is erionite, another fibrous material. The concept prevailed that chrysotile was harmless, but this has now been disproved [7]. According to Stayner et al. [7], it seems prudent ''to treat chrysotile with virtually the same level of concern as the amphibole forms of asbestos''.

The use of asbestos covers a wide range of applications, so in this article, we shall consider occupational exposures, environmental exposures both of natural origin and as a consequence of the proximity of some industrial plants, and finally a series (often domestic) in which exposure to asbestos is rather unexpected. A separate section will be devoted to the asbestos situation in Poland. The restriction or ban of the use of asbestos in some countries has spurred the development of replacement materials: we shall consider the effects on health of man-made mineral fibres (MMMF). In concluding our review, we shall consider the role of biomarkers in assessing the effects in humans, as well as their potential use in preventive interventions, in the light of predictive time-trend incidences due to the (very) long incidence periods of asbestos-related cancers.

2. Effects of occupational exposures

2.1. Miners and millers

The first group of people at risk of being exposed to asbestos is of course the workers of the extraction facilities: the effects are strongly dependent on the type of the extracted fibres. The major chrysotile mines are located in Quebec, Canada (Thetford Mines), in Balangero (Italy), in British Columbia; in Cyprus, and natural outcrops are reported in Corsica. In the latter two locations, chrysotile is contaminated with minute quantities of tremolite, making evaluation more complicated. When pure chrysotile is involved, the effects are further influenced by the smoking status of the miner (see later). What is very clear from several studies is that exposure to chrysotile alone induces asbestosis, lung cancer and mesothelioma. Case and Dufresne [8] reported on 438 deceased male miners or millers from Thetford Mines; among these autopsied cases they observed some degree of asbestosis and either pleural plaques or pleural thickening in over 50% of men; 35.4% died of lung cancer and 5% of pleural mesothelioma. The authors mention the selection bias linked with autopsied cases, as in the same population an epidemiologic evaluation identified 11.2% lung cancer and 0.9% mesothelioma. Nevertheless, the carcinogenicity of chrysotile was unequivocally demonstrated. An increased prevalence of non-malignant respiratory symptoms was also observed [9]. In Balangero miners, several cases of mesothelioma have also been reported, and a general excess of lung cancer and mesothelioma has been observed.

In South Africa, from where Wagner's 1960 report [1] originated, both amosite and crocidolite are mined. However, mixed exposures, mainly to gold and silica, are also observed. In 1981, among 7317 male employees of the mines, 3212 were exposed only to amosite, 3430 only to crocidolite and 675 to both [10]. One thousand two hundred and twenty-five of the cohort had died at the time of the review (17%), representing an excess of 331 over the expected number of deaths among white South African males. Asbestos-related deaths were of mesothelioma, lung cancer and other respiratory diseases, 30 cases being due to mesothelioma (pleural 22, peritoneal 8) and 65 to tumours of the trachea, bronchus and lung. Exposure to crocidolite produced more severe health effects than that to amosite (or mixed); the incidence per 100,000 subject years for mesothelioma was 7.8 after exposure to amosite and 44.6 after exposure to crocidolite.

The only asbestos-related mineral mined in Australia was crocidolite at the famous Wittenoom mine in Western Australia; this was closed in 1966. The workforce consisted of 6505 men and 411 women, and a health survey was carried out at the end of 1980, at a time when 820 deaths had occurred in men and 23 in women [11]. In men, significant excess death rates were observed for all neoplasms including mesothelioma (32 deaths), cancer of the trachea, bronchus and lung (standard mortality rate (SMR) 2.64), cancer of the stomach (SMR 1.90), pneumoconiosis (SMR 25.5) and some digestive diseases, e.g. peptic ulceration (SMR 2.36).

In this cohort, nearly equal numbers of deaths from lung cancer and from mesothelioma were observed, whereas the lung cancer/mesothelioma ratio is generally considered to be around 3.5; this might be an extra indication of the aggressiveness of crocidolite towards mesothelioma. It has been stated that the Wittenoom fibres are of particular concern as they are of a finer diameter than those in South Africa [12]. The prevalence of mesothelioma cases in Australia was probably the highest in the world. The prevalence of radiological signs of asbestosis among Wittenoom miners and millers is believed to be at nearly 20% [13].

2.2. Other occupational exposures

Exposure to asbestos has been found in many occupations, the major contributions coming from the primary asbestos production or manufacture industries, from the building industry generally and from shipping-related activities. The distribution of occupational mesothelioma cases in an asbestos mining country are shown in the paper by Ferguson et al. [12], based on a total of 456 subjects. The major findings are presented in Table 1.

Numerous other occupations may also involve asbestos exposure, albeit to a lesser degree. Such occupations include the staff of coal-fired power stations, mechanics repairing motor vehicles (brakes, clutch), carpenters and woodworkers, electricians, welders, etc. Exposure may occur in unexpected places, as in the case of a market-gardener who died from mesothelioma: after a thorough investigation it was found that he used to pin his orders on an asbestos-containing board standing near his desk.

As can be inferred from Table 1, contact with asbestos-cement leads to a high rate of mesothelioma. The mortality for all causes has been evaluated in a 1465 strong worker cohort in Sweden [14] and the relative risk (RR) compared with that in a cohort of 762 referents, over the 1927—1986 period. The following RRs in the heavy worker cohort compared to the reference group have been observed: All causes: 1.2; non-malignant respiratory disease: 2.6; all malignancies 1.6; respiratory cancer: 2.5; respiratory cancer except mesothelioma: 1.8; mesothelioma: 7.2; gastro-intestinal cancer: 1.2. The pattern for cancer morbidity remained similar over the period 1958—1986. Lower gastro-intestinal tract cancer was slightly elevated, which was confirmed in a comparison with the general population in the same region. With regard to mesothelioma, the authors emphasise that every fibre-year/ml of exposure in a time frame of for 40 years or more before diagnosis has a major impact on the relative risk. In the highest exposure categories, the mesothelioma rates correspond to lifetime risks of as much as 5—10%. The figures of Albin et al. [14] are confirmed by other studies. In all studies, the very long latency period is underscored, with highest frequencies 40 and more years after onset of exposure. Predictive diagnostic symptoms for the development of mesothelioma will be considered below.

Among the other high-risk occupational categories are insulation workers. In a prospective study, 17,800 insulation workers in the USA and Canada were followed up from 1967 to 1984. During the observation period, 356 workers died of malignant mesothelioma with histopathological

Table 1 Distribution of asbestos-related occupations

Occupational activity	Number of cases	Proportion (%)
Asbestos production or manufacture		
Mining and milling	34	26.1
Asbestos-cement production	49	
Asbestos-cement transport	3	
Asbestos insulation manufacture and installation	27	
Asbestos product manufacture	6	
Building		
Construction/maintenance/demolition (general)	14	13.2
Employment of asbestos-cement	46	
Shipping		
Construction/demolition/maintenance (on shore)	76	23.2
Stevedoring	19	
Others	11	
Railways		
Rolling stock fabrication, repair and maintenance	42	9.2

confirmation of their disease (134 pleural mesothelioma and 222 peritoneal) [15]. As the incidence of mesothelioma in the general population (and confirmed by necropsy) was very low (0.01—0.07%), it was easy to identify asbestos as the causative factor, subsequent to its ever increasing use in the industry. The incidence of mesothelioma is expected to increase further in the coming years. The high proportion of peritoneal mesothelioma in this series remains unexplained; however pathological examinations could have improved the accuracy of this difficult diagnosis.

Shipyard workers represent another high-risk category, with relative risks extending from 10.3 to 18.1 according to working conditions and smoking status, as reported in an US study [16]. The annual age-adjusted incidence rate per 100,000 population among white males was 2.7, which was about four times higher than for the controls living in the same area. In Italy, high mesothelioma incidences are observed in regions where shipyards are established.

It is worthwhile mentioning that many unsuspected causes of exposure to asbestos exist, for instance the re-use of bags having contained asbestos. Among the occupations known to carry some risk of exposure, a few merit particular attention: railway staff, not only in construction, maintenance and repair of the rolling facilities, but also station masters and attendants exposed to asbestos fibres released by brakes; urban street police officers exposed to particles released by brakes; car mechanics; iron and metal workers, etc.

3. Effects of environmental exposures

3.1. Of natural origin

Some regions are characterised by natural outcrops of asbestos or asbestos-like minerals that may exert an effect on the health of local dwellers.

In Corsica (north-eastern part), a strong suspicion over environmental asbestos effects was aroused when, during the course of the follow-up of the former miners of a chrysotile mine, it was observed that in the unexposed control group 3.8% of the subjects presented with bilateral pleural plaques on radiographical examination [17]. Fifty-three subjects with bilateral pleural plaques and born in north-eastern Corsica were identified; they were all born in villages located on asbestos outcrops. In a village exposed to asbestos, 41% of the inhabitants had bilateral pleural plaques, versus 6% in an unexposed village. Tremolite concentrations were markedly higher in exposed villages. Malignant mesothelioma caused by childhood environmental exposure to asbestos was observed in eight patients. Table 2 gives their characteristics.

Table 2 Occupations of environmentally exposed subjects in Corsica

Gender	Age (years)	Occupation	Fibre content
M	67	Farmer	High
F	62	Winegrower	High
M	81	Farmer	High
F	68	Farmer	High
M	41	Engineer	Medium
F	46	Nurse	ND
M	84	Wood carrier	ND
M	81	Clerk	ND

ND: not determined.

Similar observations have been made in Cyprus and in north-western Greece (the so-called ''Metsovo'' lungs); in Cyprus, tremolite seems to be the culprit.

However, by far the most extensive studies on natural environmental exposures to asbestos and asbestiform fibres have been carried out in Turkey, and notably in the Central Cappadocian area. Malignant mesothelioma is common in some villages of Central Cappadocia and has been the subject of many investigations by Baris and his team. Whereas many cases of mesothelioma could be attributed to asbestos exposure, it appeared that this was not the only implicated mineral fibre, the other cause being erionite, a natural fibrous zeolite, which can be found in volcanic tuffs and is an environmental contaminant in Cappadocia. Three ''erionite villages'' (Karain, Tuzköy and Sarihidir) are built upon and into volcanic rocks containing erionite [18]. Their mesothelioma burden is appalling ([19] and personal communication). During the period 1970—1987, 217 people died in Karain village and among them 125 of malignant disease. Pleural mesothelioma accounted for 108 cases, peritoneal mesothelioma for 1 case, and lung cancer for 6 cases. In Tuzköy village, 277 deaths were identified between 1980 and 1988, with 131 of them (47%) being due to malignant disease, including 59 cases of pleural mesothelioma, 33 of peritoneal mesothelioma and 20 of gastro-intestinal malignancies. Peritoneal mesothelioma was frequent in females (M:F ratio 1:2). Mesotheliomas are also reported in New Caledonia, in the South Pacific, due to spreading of asbestos-containing materials on the walls of the small huts of blue-collar workers. This practice can be found in many buildings worldwide.

Table 3 Mesothelioma incidence in and around Casle Monferrato (Italy)

Place of residence	No. of observed mesothelioma cases (male + female)	Incidence rate (%) per 100,000 residents	
		Male	Female
Casale Monferrato	49	11.4	10.2
Neighbouring villages	4	5.1	–
Distant villages	7	1.5	0.6
Controls[a]	49	1	0.3

[a] Controls were subjects from the cancer registry of Varese province who had not been exposed to asbestos.

3.2. Secondary to anthropologic activities

The proximity of asbestos-producing or asbestos-using industrial plants has a clear effect on the health outcomes amongst the local population. In Italy, geographic clusterings of mesothelioma are observed in the population living around industrial facilities using asbestos, mainly shipyards. A comprehensive investigation has been carried out among the inhabitants of the town of Casale Monferrato (Piedmont) near which the major Italian asbestos-cement plant is located [20]. Its most relevant results are presented in Table 3 (for mesothelioma). Similar mesothelioma clusters have been observed in Britain, in the US and elsewhere; of particular concern is abandoned asbestos-containing rubbish.

It should not be overlooked that many common household utensils contain some amount of asbestos, e.g. protective gloves, hair driers, ironing boards, etc. they should be in perfect condition not to let any asbestos escape.

The hazards linked to making buildings fireproof have already been discussed.

4. Exposure to asbestos (and derived products) in Poland

Several studies on the health effects of exposure to asbestos have been carried out in Poland during the last decades, bearing in mind that no asbestos is mined in Poland and that the incidence of mesothelioma, considered asbestos-specific, is very low in Poland. The very low incidence of mesothelioma is reflected in the small reported number of annual cases (120). This is comparable to the low incidence observed in Hungary (78 cases annually) and in Romania (133 cases), and it is much lower than that in Western countries [20]. The observed mesothelioma cases result from industrial pollution generated by the only four active asbestos-cement plants in Poland (presently closed down). However, in at least one case, production wastes were made available to the local community, particularly to the workers of the factory, and used for the hardening of roads, paths, farmyards, etc., or as construction material components. In this way, workers living in the vicinity prolonged their exposure, but the general population was also exposed to an environmental pollution. The majority of the asbestos used in the plants was of the chrysotile type (85%), the rest being crocidolite.

Two major studies have been performed on the exposed worker cohorts [21,22]. The first study [21] involved a cohort of 1526 workers from one plant having been employed for at least 3 months between 1959 and 1985, and observed until the end of 1996; 1356 were males and 170 females. SMRs were calculated for the 306 workers who had died, the reference population being the general population of Poland. The most important results are given in Table 4. The overall mortality was similar to that of the reference population, both in males and females. However, a two-fold excess in cancer mor-

Table 4 Mortality from cancer in asbestos-cement plant I

Cause of death	Standardised mortality rate (95% CI)	
	Male	Female
All cancer	99 (79–123)	216 (112–377)
Trachea, bronchus, lung	99 (66–142)	671 (138–1961)
Pleura M	8135 (3532–12738)	20292 (2435–73254)
Colon	301 (121–620)	0
Pancreas	59 (7–213)	989 (120–3573)

Table 5 Mortality from cancer in asbestos-cement plants II and III

Cause of cancer death	Male			Female
	<9 years' exposure	10–19 years' exposure	>20 years' exposure	
All cancer	90 (67–119)	75 (49–111)	109 (54–195)	89 (43–164)
Trachea, bronchus, lung	79 (44–130)	94 (47–168)	77 (16–225)	382 (79–1116)
Pleura M	0	3606 (437–13206)	16646 (34209–48606)	11275 (1368–40714)
Colon	261 (71–668)	229 (28–827)	412	NA
Pancreas	261 (71–668)	0	0	NA

NA: not available.

tality was observed in women. Remarkable is the absence of an excess in lung cancer deaths in men.

A second study involved 3116 workers (from other plants): 2525 males and 591 females [22]. SMRs were calculated relative to the duration of employment (for males); the results are presented in Table 5. In this study also, general mortality was lower than expected, revealing a ''healthy worker effect''. Altogether these figures should be considered with caution, due to the long latency period of mesothelioma (30–40 years). The study cohort is still ''young''. The incidence of mesothelioma incidence is predicted to further rise for several years. Also, the subject numbers on which some of the conclusions are based are small, with poor statistical strength, and further studies are needed.

One of the conspicuous findings of this evaluation is the lack of mortality increase due to lung cancer in men, and the question arises as to whether there is an intervention of some unrecognised protective factor, maybe of dietary origin. A higher mortality for colon cancer has been reported in other series.

The problem of the underestimation of occupational cancers has been raised [23] and will be considered below.

5. Exposure to man-made mineral fibres

In the search for replacement materials for asbestos artificial fibres have been developed, including rock and slag-wool and glass wool. Ceramic and other fibres are also in industrial use, and they have been considered to be harmless with regard to human health. An international investigation involving 13 manufacturing plants in seven European countries was initiated under the auspices of International Agency for Research on Cancer (IARC, Lyon, France) and its findings published in 1984 [24]. The main results are presented in Table 6. This study has been further extended from 1983 to 1990 or 1991; a total 22,002 production workers (18,769 males) were included, and divided in three subcohorts: rock/slag wool; glass wool and continuous filament production [25]. SMR was significantly elevated in rock/slag wool and glass wool as summarized in

Table 6 Standard mortality rates for lung cancer in the man-made mineral fibre industry in relation to the time since first employment

Cause of death and time since first employment	Observed deaths	Expected deaths	SMR (95% confidence interval)
All causes	515	524.4	98 (90–107)
All neoplasms	126	128.8	98 (82–117)
Cancer of trachea, bronchus and lung			
≤19 years	27	29.8	91 (60–132)
20–29 years	12	4.7	124 (64–217)
≥30 years	11	5.7	195 (97–348)
Diseases of the respiratory system	38	45.5	83 (59–115)

SMR: standard mortality rate.

Table 7 Extension of mortality study in man-made mineral fibres

Cause of death	Whole cohort	Rock/slag wool	Glass wool
All causes	114	118	107
All cancers	113	114	111

All figures are statistically significant at $P < 0.05$.

Table 7. Similar observations are reported from the US, with SMRs of 120.

New grounds for concern appear after the discovery of defective cigarette filters causing the release of cellulose acetate-fibres during smoking [26]. The size of these fibres is similar to that of carcinogenic asbestos fibres.

6. Discussion

Due to space limitations, some aspects of the asbestos problem have received little or no discussion. Among them should be mentioned the difficulty of mesothelioma diagnosis, the potential usefulness of some biomarker determinations, the consequences of the very long latency period for mesothelioma after an initial exposure, and the predictable increase in incidence of mesothelioma in spite of restrictions in the use or banning of asbestos. The diagnosis of pleural mesothelioma is conspicuously difficult and a firm diagnosis should always be based on clear histopathological findings, despite evocative radiological findings. In the case of peritoneal mesothelioma, the diagnosis may even be more controversial. Albin et al. [14] have emphasised the interest of complementary immunohistochemical examinations, especially in the differential diagnosis with pulmonary adenocarcinoma, as advocated by Carson and Pinkus [27] and by Otis et al. [28]. In 12 of their cases for which sufficient material was available, Albin et al. [14] found no expression of carcinoembryonic antigen (CEA) in pleural mesothelioma, a consistent expression of CAM 5.2 (anti-cytokeratin) antigen and a mixed expression of vimentin. These observations should be considered in parallel with our own findings of tissue polypeptide antigen (TPA) as a biomarker characteristic of the mesothelial cell [29]. TPA is a cytoskeleton marker expressing antigens corresponding to cytokeratins 8, 18 and 19. It is very differently expressed by mesothelioma and lung cancer, due to different carcinogenesis mechanisms. As soluble forms of TPA and CEA (and other antigens) are present in serum, their assessment may be very helpful in the differential diagnosis of undetermined neoplasms. In a blind evaluation of sera belonging to 24 mesothelioma, lung cancer and asbestosis patients, we have correctly identified all of them, relying only on serum biomarker assessments [30]. As modifications in serum biomarker levels appear very early and well ahead of radiological or pathological signs, they may play an important role in the early identification of exposed subjects and enhance the efficiency of preventive interventions directed against the occurrence of mesothelioma or lung cancer [31]. The mean levels of serum TPA (in U/l) are as follows: controls (males) 36.5; asbestosis cases 118; lung cancer 240, mesothelioma 358. The interest of the biomarker determinations is underscored by the results of Table 8. This relates to a small cohort of 19 active workers in a French asbestos-cement plant. Of these 19 workers, only one presented with radiological signs of asbestosis. But abnormal biomarker values were detected in five workers, including the one with radiological signs. As shown in the table, the biomarker results are predictive of development of mesothelioma in two workers, and of lung cancer in two others. The long latency period for the development of mesothelioma makes these findings very important; they should be extended to environmentally exposed populations.

In all exposed subjects a complete review should be carried out, including the most modern achievements in molecular biology, as underscored by Niklinski et al. [32]. No longer can prognostic eval-

Table 8 Serum CEA and TPA values in asbestos-exposed workers

Identification	CEA (ng/ml)	TPA (U/l)	Smoking status	Predictive of
1[a]	6.86	170.1	+	M
2	11.21	12.6	+++	LC
3	2.07	108.9	−	−
4	1.74	274.9	−	M
5	7.38	43.4	+	LC

CEA, carcinoembryonic antigen; TPA, tissue polypeptide antigen; M, mesothelioma; LC, lung cancer.
[a] Radiological signs of asbestosis.

uations with regard to the outcomes of asbestos exposure be based solely on radiological findings or on counts of fibres in the inhaled air. The more important finding is that an increasing incidence of mesothelioma may be expected despite a reduction in the use of asbestos. While it appears from the data presented in Table 5 that the mean latency period for mesothelioma is at least 20 years, robust estimations put the median latent period at at least 32 years post-initial exposure [34]. This has far-flung consequences, as the restrictions, or total bans, on the use of asbestos occurred around 1985. This means that the incidence of mesothelioma can be expected to increase until at least 2020. There have been attempts to evaluate the potential increase in mesothelioma incidence over the coming decades. In Germany, extensive studies were undertaken under the direction of Woitowitz to determine the impact of radiological findings of asbestosis as risk factors for the development of lung carcinoma [33].

As a conclusion, it should be standard procedure to follow-up all subjects who have had at least some exposure to asbestos, and to use the best available techniques in the prevention, diagnosis and treatment of mesothelioma.

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