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### 3 Asbestos, asbestosis and cancer

#### Exposure criteria for clinical diagnosis

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#### Industrial use of asbestos

Occupational exposure to asbestos constitutes a major health hazard in all industrialized countries of the world. In Western Europe, North America and Australia the manufacture and use of asbestos products peaked in the 1970s. Since then the annual consumption has dropped from about two million tons (2.5 kg per capita) to the current level of 250 000 tons/year. In Japan, the demand for imported asbestos still exceeds 300 000 tons/year (2.3 kg per capita). The production and use have increased outside these areas. Asbestos cement makes up 85% of all commercial applications and other major uses include friction materials, floor tiles, gaskets, insulation boards and asbestos textiles. The life cycle of the products begins in the primary asbestos industry and continues with secondary manufacture, installation, usage and disposal (1). Worldwide millions of workers have been or are being exposed to asbestos in the workplace most often during the maintenance, repair and replacement of asbestos-containing materials.

The industrial use of asbestos is closely related to the subsequent health effects. Table 3.1 compares the current incidence of mesothelioma with the annual use of asbestos about two decades ago (2–15). The national indices are almost identical in these countries reflecting the similarity of technological applications, industrial structure as well as workplace conditions. Accordingly, the average use of 3 kg per capita will induce about 15 mesothelioma cases/million people, i.e., each 200 tons of produced asbestos will be responsible for one death from pleural or peritoneal mesothelioma. In the total population of 800 million inhabitants, about 10 000 mesotheliomas and 20 000 asbestos-induced lung cancers can be estimated to occur annually. The incidence has been expected to reach its maximum around the year 2010 in the United Kingdom (11) or in Finland (5). The highest annual incidence of mesothelioma has been registered in Australia, 36.5 cases/million men and 5.8 cases/million women as standardized to the age class of over 20 years (14). These data are consistent with the estimates that about 80% of all mesothelioma cases are associated with occupational exposure to asbestos and the remainder may be misdiagnoses or due to environmental, domestic or unknown occupational causes. The background rate of 1–2 mesothelioma cases/million people corresponds to about one case per 10 000 deaths. In some small cohorts of asbestos-exposed workers the proportional mortality may exceed 10%. About half of all mesothelioma cases will occur in construction, shipbuilding and transport workers; despite higher risks, less than

5% have been registered from the primary asbestos industry (3, 11, 16, 17, 18). About 5 to 7% of all lung cancers are attributable to occupational exposure to asbestos (2).

Asbestos-related health effects can be observed in the general population. In a representative sample of 8 000 Finns over 30 years of age, about 6.8% of the men and 2.0% of the women had bilateral plaques which indicated occupational exposure to anthophyllite and other types of asbestos (19, 20). In Finnish housebuilding workers such radiological findings were detectable in 17% of the 17 937 examined people. The risk expanded over all job titles (e.g. carpenters, plumbers, insulators, electricians) (21).

## Evaluation of work history

Lifetime job histories can be obtained in various ways, but the most common is a face-to-face discussion with the patient. This interview data may need to be supplemented with employment records and inquiries to their current or past workplaces. Check-lists of asbestos-containing materials and trade names are often presented as a part of the detailed questionnaire. In addition, technical and hygienic experts can advise on the probable level of asbestos exposure using measurement data or general knowledge. During the past 30 years, more than one hundred cohort studies have reported excess risks of mesothelioma and lung cancer in numerous asbestos-exposed populations (18, 22). Although most of the studies refer to the primary asbestos industries, they may serve as a general guideline on the characteristics of asbestos-related diseases.

In case-control studies of mesothelioma or lung cancer, the individual work histories have been classified in terms of exposure probability roughly as follows (23–27):

**Definite exposure:** Manufacture of asbestos products, asbestos spraying, insulation, demolition of old buildings

**Probable exposure:** Construction, shipbuilding, heating trades, pipefitting, sheet metal work

**Possible exposure:** Transport, railways, ship engine crew, firefighting, mining and quarrying, oil refining, chemical, paper and metal industries, car repair and general maintenance jobs

**Unlikely exposure:** Office work, agriculture and forestry, health care and education, telecommunication and textile industry.

In this evaluation, work periods over one month are taken into account. According to national or local circumstances, the above classification may need to be slightly modified. In general, heavy exposure has required at least one year employment in the asbestos industry, asbestos spraying and insulation work or 10 years of employment in the building construction and shipyard work with definite or probable intermittent exposure to asbestos (28).

In series of mesothelioma patients, the above crude classification has shown several-fold risks among definitely and probably exposed people in comparison to unlikely exposed (OR = 17.7 in Tuomi et al. 1991 (29), OR = 11.0 in Mowe et al. 1985 (23)). This system of exposure evaluation has also been validated by means of fibre analyses from lung tissue (26, 29) as well as by correlation with the prevalence of pleural plaques (19, 20).

In a German study of 324 mesothelioma cases, the male patients reported some occupational contact with asbestos products as follows: raw asbestos (8%), asbestos textiles (14%), asbestos board (11%), asbestos cement (25%), brake linings (10%), asbestos insulation (69%), asbestos-containing plastics (6%) and other materials (7%). In women, the most common contacts were raw asbestos (15%) and textiles (11%). Excess risks were observed for insulation work, removal of heat insulations and replacement of packings. None of the reported free-time activities entailed any significant risk. The odds-ratio analysis comprised 31 occupations and excess risks were found for sheet metal workers, pipefitters, electricians, metal workers, insulators and rubber manufacturers. Asbestos exposure was found for 80% of the mesothelioma cases, 53% of the hospital controls and 41% of the population controls. Cumulative fibre doses were estimated from work histories and job-related dust measurements that were available in Germany or in the international literature. In the highest exposure category, the odds ratio equalled about 100 (3, 30). In another series of 145 German mesothelioma patients, work histories reported asbestos production (19%), insulation work (18%), shipyard industry (10%), metal industry (14%) and use of asbestos cement (10%), friction materials (9%) or other uses (19%) (31).

In a large German study of 839 male lung cancer cases, asbestos exposure was assessed with personal interviews and self-reported check-lists. A standardized European questionnaire was developed including stringent guidance how to obtain detailed information from various jobs, tasks and work situations. About 41% of the cases and 34% of the controls reported some occupational exposure to asbestos. A cut-off of 2 400 lifetime hours was used as a definition of high exposure for each type of work. The highest smoking-adjusted risks were observed for insulation work (OR = 4.39), for machining of asbestos cement products (OR = 2.37) and for work in the asbestos industry (OR = 2.21). A smaller risk was associated with other asbestos-containing materials (e.g. brake and clutch linings, OR = 1.25) (32-34).

In contrast to the structured interview by trained experts, a simple direct question such as "Have you ever been exposed to asbestos?" does not seem to discriminate between the exposed and nonexposed persons. Nevertheless, a multicentre study of 1 793 lung cancers in the United States found a significant risk (OR = 1.8) among those who mentioned asbestos in the questionnaire of occupational exposures (35).

A Canadian case-control study in the Montreal area included 857 lung cancers among the total series of 4 263 cancers. In the multivariate analysis of the interviews, occupational exposure to chrysotile asbestos was related to excess risk of lung cancer (OR = 2.3) and mesothelioma (OR = 14.6). Inorganic insulation dust (OR = 10.7), amphibole asbestos (OR = 51.6) and work in the construction industry (OR = 10.7) were also implicated as a cause of mesothelioma. Substantial exposure was defined as at least 10 years of work duration accumulated up to five years before the onset of the disease (36).

In France, a work duration of 10 years in the manufacture of asbestos products, insulation work, asbestos removal, construction and shipbuilding industry have been considered significant enough for the diagnosis of lung cancer as an occupational disease (Code de la securite social, le decret no. 96-445). The Finnish compensation criteria require at least one year of heavy exposure (spraying, insulating) or at least 10 years of

moderate exposure (construction work) as an evidence for a two-fold risk of lung cancer. Parenchymal fibrosis and pleural changes are used as a proof of asbestos exposure but they are not a necessary requirement for the compensation. Smoking habits of the patient are considered irrelevant in the attribution of the risk, i.e., smokers and non-smokers are treated equally by the social security system (37).

Numerous publications and data bases of dust measurements are available for the exposure evaluation in terms of fibres/cm<sup>3</sup>. In clinical practice, it is rare that any exposure measurements have ever been made at the workplaces of a particular patient. Much expertise and training are therefore needed to translate the work history into a quantitative estimate of exposure. More than 27 000 results from the period of 1972–1991 have been compiled by the German Accident Insurance Institution (BIA). The data cover industry categories (manufacture of asbestos textiles, boards, packings, cement, friction materials), occupations (asbestos sprayer, car mechanics) and work operations (installation, grinding, cutting, boring and removal of building materials, repair of brakes and clutches). For diagnostic and compensation purposes, this documentation is used to assess the cumulative lifetime exposure of a patient when occupational disease can be suspected. A dosis exceeding 25 fibre-years/cm<sup>3</sup> has been estimated to cause a two-fold risk of lung cancer (38). In the United States, past occupational exposures have been surveyed and reviewed by the National Institute for Occupational Safety and Health (39). The percentage increase in lung cancer for a one-year exposure to 1 fibre/cm<sup>3</sup> ranged from 1 to 4% in a large series of epidemiological studies, irrespective of fibre type or industrial process (40).

In ambient air or in the built environment, typical concentrations of asbestos have been from less than 0.1 to 10 fibres/litre. The highest values refer to outdoor air near an asbestos factory or indoor air inside buildings with asbestos-containing materials (2, 41–44). These levels are negligible in comparison to airborne concentrations that may exceed 1 to 10 fibres/cm<sup>3</sup> at many industrial workplaces and occupational situations.

### **Asbestos fibres in tissue samples**

By electron microscopy, asbestos fibres have been detected in human lung tissue as early as in the 1940s (45). In asbestos-exposed workers, the concentrations may range over several orders of magnitude from less than 0.01 million to over 1000 million fibres/g dry tissue. About 1 or 2 days of crocidolite spraying or 1 to 4 months of insulation work may accumulate an amphibole level of 1 million fibres (>1 µm)/g dry tissue that can be measured several years later (46). Numerous studies have established a clear correlation between the pulmonary amphibole content and the duration or intensity of exposure. No such association was observed with chrysotile fibres which are removed from the lungs more rapidly (47, 48).

In a German study of 47 mesothelioma patients and 63 hospital controls, a lung burden of 0.1–0.2 million fibres (>5 µm)/g dry tissue has been estimated to predict a five-fold risk (49). About the same risk was observed also for an asbestos content of over 1 million fibres (>1 µm)/g dry tissue in Norway (OR = 8.5), in Finland (OR = 14.4) and in Australia (OR = 2.36) (23, 29, 50). The risk of mesothelioma was increased already at the level of general environmental exposure and slightly above the detection limit of the

electron microscopic method. A two-fold risk of lung cancer has been associated with a lung burden of 2 million amphibole fibres ( $>5\ \mu\text{m}$ )/g dry tissue (43). In a case-control study of 113 male lung cancer patients and 297 autopsy in Finland, a pulmonary concentration of 1 to 5 million and over 5 million asbestos fibres ( $>1\ \mu\text{m}$ )/g dry tissue increased the risk significantly (OR = 1.7 and 5.3, respectively) (28). Inevitably all numerical estimates of relative risk are largely determined by the chosen upper cut-off boundary of the reference population.

Table 3.2 lists 27 electron microscopic studies on the asbestos fibre levels in the general population or in operated or autopsied people without known occupational exposure to asbestos (3, 23, 25–26, 49–71). A reasonable agreement exists between these selected laboratories from Europe, North America, Japan and Australia. A parenchymal level of 0.1 million amphibole fibres ( $>5\ \mu\text{m}$ ) or 1 million asbestos fibres ( $>1\ \mu\text{m}$ )/g dry tissue are highly indicative of occupational exposure to asbestos. Such results may occur in 10–20% of the general population and less than 5% of the tissue samples taken from unlikely exposed persons. For the German and Japanese populations, an upper level of 3–5 million asbestos fibres ( $>1\ \mu\text{m}$ )/g dry tissue has also been proposed as an indicator of occupational exposure (42, 58). In Finnish urban men, the limit of 1 million asbestos fibres ( $>1\ \mu\text{m}$ )/g dry tissue was exceeded in 33% of the probably exposed ( $n = 64$ ), in 19% of the possibly exposed ( $n = 134$ ) and in 1% of the unlikely exposed ( $n = 80$ ). In the same autopsy series, bilateral plaques were found in 58% of the 300 men aged 33 to 69 years. More than 80% of the men with over 1 million asbestos fibres ( $>1\ \mu\text{m}$ )/g dry tissue had plaques. As a minimum estimate, about 43% of widespread plaques and 24% of all plaques were attributed to asbestos levels exceeding 0.1 million fibres ( $>1\ \mu\text{m}$ )/g dry tissue. The plaques were induced by occupational exposure to asbestos (mostly anthophyllite) and to a minor extent by domestic or environmental exposures (56).

In diagnostic practice, local and interlobar variations of fibre size or concentration are relatively unimportant. About two-fold differences have occurred when adjacent tissue sites or homogeneous samples have been analysed (25, 51, 60). Electron microscopy counting requires about  $1\text{--}2\ \text{cm}^3$  of parenchymal tissue without tumour, plaque or pleura. Within a particular type of asbestos, the fibre concentrations expressed as a defined size fraction (e.g. fibres longer than 1 or  $5\ \mu\text{m}$ ) are highly correlated and consequently the sizing and reporting of fibre levels must be decided on technical grounds. For example, serious sample contamination may prevent the counting of short chrysotile fibres below  $1\ \mu\text{m}$  in length (73). There are no measurable differences between smokers and nonsmokers and the fibre retention will not be altered significantly by any respiratory disease.

A majority of 19 studies listed in Table 3.3 have established a limit of 1000 asbestos bodies (AB)/g dry tissue as an indicator of occupational asbestos exposure (3, 24, 48, 57–59, 63–64, 66, 69, 74–82). Asbestos-body concentrations over 1000 AB/g dry tissue have been associated with uncoated fibre concentrations exceeding 0.1 million amphibole fibres ( $>1\ \mu\text{m}$ )/g dry tissue (69). The AB counting had a specificity of 92% and sensitivity of 68% when 3 000 AB/g was compared with 0.3 million amphibole fibres ( $>5\ \mu\text{m}$ )/g dry tissue. Accordingly 0.5–1% of the amphibole fibres were coated (31, 59). In a series of 90 asbestos workers from an Australian crocidolite mine, the geometric mean and range of different exposure measures were:  $17\ 500\ (63\text{--}2 \times 10^6)$  AB/g dry tis-

sue, 183 ( $<1-10 \times 10^3$ ) million fibres ( $>0.4 \mu\text{m}$ )/g dry tissue, 20.9 (0.03–497) fibre-years/ $\text{cm}^3$  and 20 (1–130) fibres/ $\text{cm}^3$  (83). In a German study of 41 mesotheliomas and 45 hospital controls, an odds-ratio  $\text{OR} = 3.65$  was associated with 50–500 AB/g wet tissue and  $\text{OR} = 57.16$  with over 500 AB/g wet tissue. The level of below 50 AB/g wet tissue was used as a reference (3). The continuation of this series (66 cases, 147 controls) gave the corresponding odds-ratios  $\text{OR} = 4.43$  and 38.2 (43).

When asbestos bodies were counted by light microscopy in bronchoalveolar lavage fluid obtained from 563 Belgian hospital patients, a limit of 1 AB/ml was exceeded in 84% of definitely exposed ( $n = 215$ ), in 54% of probably exposed ( $n = 16$ ), in 18% of nonexposed blue collar workers ( $n = 117$ ) and in 7% of nonexposed white collar workers ( $n = 115$ ). The highest values exceeding 1000 AB/ml BAL occurred in 5.5% of the patients with definite occupational exposure to asbestos. Among asbestosis patients ( $n = 59$ ) the mean level was 121 AB/ml BAL and ranged from below 0.1 to over 1000 AB/ml BAL (84). Among a subgroup of 100 consecutive patients, a good correlation was observed between the AB concentration in BAL and the AB concentration in lung tissue. In 70% of the cases, the tissue concentration was below 1000 AB/g dry tissue when less than 1 AB/ml was found in the lavage fluid (74). The same cut-off limits (1 AB/ml BAL and 1000 AB/g dry tissue) were exceeded in 33% and 100% of the definitely or probably exposed mesothelioma cases ( $n = 48$ ) from the Paris area. In contrast, the respective percentages were 12% and 36% among the unlikely or possibly exposed cases ( $n = 36$ ) (24). Both parenchymal and BAL concentrations were spread over six orders of magnitude from less than 40 to  $8.9 \times 10^6$  AB/g dry tissue in the parenchyma and from less than 0.05 to  $10 \times 10^3$  AB/ml BAL in another French series of 69 patients with suspected asbestos-related diseases. The cut-offs of 1000 AB/g dry tissue and 1 AB/ml BAL were recommended to distinguish occupational exposure (85). Table 3.4 gives a review of 8 studies related to AB levels in BAL from occupationally nonexposed (24, 53, 74, 84, 86–90).

In a Finnish series of 65 patients (59 lung cancers), quantitative relationship was established between four indices of asbestos exposure (work history, AB in BAL, AB in lung tissue, uncoated asbestos fibres in lung tissue). The values of 1 AB/ml BAL, 1000 AB/g dry tissue and 1 million asbestos fibres ( $>1 \mu\text{m}$ )/g dry tissue were exceeded in 60%, 74% and 52% of the subjects. The work histories revealed heavy or moderate exposure in 69% and the rest had possible or unlikely occupational exposure to asbestos. Three independent studies from Belgium, France and Finland showed that 1 AB/ml BAL predicts consistently 1 800–2 500 AB/g dry tissue (91). In 21 asbestos sprayers, a median spraying time of 1.4 years had produced about 500 AB/ml and accordingly, 1 AB/ml BAL would correspond to 1 to 2 days of crocidolite spraying as reported in an interview (92).

Various analytical methods have been used to detect coated or uncoated asbestos fibres in sputum, urine, pleura, lymph nodes, kidney and other organs (46, 80). Such analyses may verify suspected exposure to asbestos but lack of reproducibility or reference values prevents their application in diagnostic practice. In individual cases, none of these techniques can be used to exclude significant exposure to asbestos without compatible evidence from the work history or other sources of information.

## Summary

1. Occupational exposures to asbestos dust are widespread in all industrial countries. About 20 to 40% of adult men report in detailed interviews some past occupations and jobs which may have entailed asbestos exposure at work. In Western Europe, North America, Japan and Australia the use of asbestos peaked in the 1970s and currently about 10 000 mesotheliomas and 20 000 asbestos-induced lung cancers are estimated to occur annually in the population of about 800 million people.
2. Using structured questionnaires and check-lists, trained interviewers can identify those persons who have a work history compatible with a two-fold risk of lung cancer. In general, one year of heavy exposure (e.g. manufacture of asbestos products, asbestos spraying, insulation work with asbestos materials, demolition of old buildings) or 10 years of moderate exposure (e.g. construction, shipbuilding) may suffice. About 80% of mesothelioma patients have had some occupational exposure that exceeds or equals general environmental or domestic exposures.
3. Numerous dust measurements are available for the estimation of past asbestos fibre levels at typical workplaces and in the use of asbestos-containing materials. A cumulative limit of 25 fibre-years/cm<sup>3</sup> can be applied to attribute a two-fold risk of lung cancer to asbestos exposure. Estimated levels exceeding this guideline are also found in the cases of clinical asbestosis. Lower exposures from work-related, household and natural sources (below 0.01 f/cm<sup>3</sup>) may induce pleural changes (prevalence up to 2% in the adult population) and mesothelioma (incidence up to 1–2 cases/million people/year).
4. For clinical purposes, the following guidelines are recommended to identify those persons who highly probably have been exposed to asbestos dust at work:
  - over 0.1 million amphibole fibres (>5 µm)/g dry lung tissue
  - or over 1 million asbestos fibres (>1 µm)/g dry lung tissue
  - as measured by electron microscopy in a qualified laboratory
  - or over 1000 asbestos bodies/g dry tissue (100 asbestos bodies/g wet tissue)
  - or over 1 asbestos body/ml in bronchoalveolar lavage fluid
  - as measured by light microscopy in a qualified laboratory.

An increased risk of mesothelioma and pleural plaques may occur below or at these concentrations. A two-fold risk of lung cancer is related to the retained fibre levels of 2 million amphibole fibres (>5 µm)/g dry lung tissue or 5 million asbestos fibres (>1 µm)/g dry lung tissue.

5. Each laboratory should establish its own reference values. In individual cases, none of the tissue analyses can be used to exclude significant exposure to asbestos (especially chrysotile) without compatible evidence from work history or other sources of information.