資料 11

Proceedings of an International Expert Meeting on

New Advances in Radiology and Screening of Asbestos-Related Diseases

9–11 February 2000
Espoo, Finland

Organizer
Finnish Institute of Occupational Health

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People and Work • Research Reports 36

Finnish Institute of Occupational Health
Helsinki 2000

Asbestos and lung cancer: a selective up-date to *The Helsinki Criteria* for individual attribution

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Introduction

At a meeting held in Helsinki in January 1997, a group of 19 authorities from 8 nations that do not produce asbestos formulated a set of criteria for the diagnosis of asbestos-related diseases and their attribution to asbestos. Published later in the same year, in the *Scandinavian Journal of Work, Environment and Health* (1), the criteria for the attribution of lung cancer to asbestos have proven to be the most controversial outcome of the meeting – as anticipated by the participants and organizers.

In most published studies, there is a direct and linear relationship between the relative risk of lung cancer and cumulative exposure to asbestos, including chrysotile and the amphiboles, expressed as:

$$RR = 1 + K*E$$

where RR is the relative risk of lung cancer, E represents cumulative asbestos exposure, expressed as fibres/ml-years (fibre-years), and K is the industry-specific slope of the relationship (RR for the increase per 1 fibre-year of exposure) for lung cancer. The value of K varies across cohorts (e.g. 0.001–0.0005 in miners and for friction products manufacture, to 0.03–0.05 in cohorts of asbestos textile and insulation workers), whereas cohorts with mixed exposures usually have intermediate values (2, 3). Positive estimates for K have been obtained in all studies, but some are based on a small number of cases or deaths (2). Lung cancer risk does not appear to correlate with the types of asbestos (2). Some authorities suggest an 'average' value of K = 0.01 independent of fibre type, corresponding to an increase of 1% of the risk of lung cancer for every fibre-year of exposure (2). The figure of 4% mentioned in *The Helsinki Criteria* is intermediate between the K values of 0.03–0.05 for textile and insulation workers. As reported in different studies (e.g. see 4 and 5), the interactive effect in combination with tobacco smoke ranges from less than additive to supramultiplicative, but the model for insulation workers approximates a multiplicative effect (6, 7). If the multistage model of carcinogenesis holds, and asbestos and smoking act at different stages, then a multiplicative relationship follows (8).

The additive increase in RR for 25 fibre/ml-years exposure has been estimated at 1.5 for amosite factory workers (9); de Klerk et al (10) put the multiplicative increase in RR at

1.25 per $\log_e$ fibre-year – i.e. for 25 fibre-years the RR is 4; the additive increase in RR for 25 fibre-years would be about 1.25 (de Klerk, personal communication). In an earlier paper on the Wittenoom cohort, the multiplicative increase in RR per $\log_e$ fibre-year was estimated at 1.4 – i.e. exposure of 25 fibre-years would give an RR of 4.5 (11).

The Helsinki Criteria

For the individual case, *The Helsinki Criteria* set exposure estimates or correlates sufficient to increase the lung cancer RR to 2.0 or more, with an attributable fraction of > (2-1)/2 = 0.5, equating to a probability of causation of 50% – the civil standard of proof (4, 5). In the case of some occupational lung cancers, a relative risk of 1.1 (rather than 2) has been accepted as indication of a material contribution to causation rather than "the cause of" by civil courts (12, 13).

The Helsinki Criteria do not require the presence of asbestosis for attribution of lung cancer to asbestos, and instead focus upon cumulative exposure to asbestos as assessed clinically (e.g. estimated cumulative exposure) or pathologically (e.g. asbestos bodies or uncoated fibre concentrations within lung tissue).

"Because of the high incidence of lung cancer in the general population, it is not possible to prove in precise deterministic terms that asbestos is the causative factor for an *individual* patient, even when asbestosis is present. However, attribution of causation requires *reasonable* medical certainty on a probability basis that the agent (asbestos) has caused or contributed materially to the disease. The likelihood that asbestos exposure has made a substantial contribution increases when the exposure increases. Cumulative exposure, on a probability basis, should thus be considered the main criterion for the attribution of a substantial contribution by asbestos to lung cancer risk. For example, relative risk is roughly doubled for cohorts exposed to asbestos fibres at a cumulative exposure of 25 fibre-years or with an equivalent occupational history, at which level asbestosis may or may not be present or detectable."

Specifically, *The Criteria* include the following:

- The presence of asbestosis (e.g. asbestosis diagnosed clinically, radiologically – including high-resolution CT – or histologically);

  or

- A count of 5,000 to 15,000 asbestos bodies (ABs) or more per gram dry lung tissue, which is about equivalent to an uncoated fibre burden of 2 million amphibole fibres (> 5 micrometers in length) per gram dry lung tissue, or 5 million amphibole fibres > 1 micrometer in length per gram dry lung; this tissue count of ABs is also roughly equivalent to 5 to 15 ABs per ml of broncho-alveolar lavage fluid (e.g. see 14 and 15).

  The Criteria also recommend that when the AB concentration is < 10,000 per gram dry lung, the count be supplemented by an uncoated fibre burden analysis using electron microscopy.

These fibre counts relate only to the amphibole types of asbestos. *The Criteria* state that chrysotile does not accumulate within lung tissue to the same extent as the amphiboles, because of faster clearance rates; therefore, occupational histories (fibre-years of exposure) are considered probably to represent a better indicator of lung cancer risk from chrysotile than fibre burden analysis.

or

- Estimated cumulative exposure to asbestos of 25 fibre-years or more.

Clinical cases of asbestosis can be encountered at this level of exposure (16): e.g. Churg (17) indicates that the dose required for the development of asbestosis is in the range 25–100 fibre-years; in an autopsy study on South Carolina asbestos textile workers exposed to Canadian chrysotile, Green et al. (18) reported that asbestosis was usually present at 20 or more fibre-years of exposure, and a few cases were encountered at estimated cumulative exposures of 10–20 fibre-years. Rödelsperger (15) reported that an estimated cumulative exposure of 25 fibre-years correlates with the uncoated asbestos fibre concentrations given above (see also 19, discussed below):

"A relationship is demonstrated between asbestos fibre dose estimated from the interview and concentration of amphibole fibres from lung tissue analysis. From this a dose of 25 fibre-years corresponds to an amphibole fibre concentration of 2 fibres/microgram" (abstract and p. 307). (I.e. 2 million amphibole fibres per gram dry lung for fibres 5 micrometers in length or more; in Rödelsperger's study on mesothelioma patients (15), 25 fibre-years and the count of 2,000,000 uncoated fibres per gram dry lung corresponded roughly to an AB count of 1,500 per gram wet lung; for obvious reasons, these values could not be derived for the control patients).

or

- An occupational history* of one year of heavy exposure to asbestos (e.g. manufacture of asbestos products, asbestos spraying, insulation work with asbestos materials, demolition of old buildings) or 5–10 years of moderate exposure (e.g. construction or shipbuilding). *The Criteria* go on to state that a 2-fold risk of lung cancer can be reached with exposures lasting < 1 year if the exposure is of extremely high intensity. Again, the basis for this criterion derives from correlative studies whereby estimated cumulative dose is calculated from the work history (e.g. types of work carried out, and their frequency and duration) or correlation of the occupational history with asbestos fibre concentrations in lung tissue.

  (*Occupational history is the only means whereby latency can be assessed.)

and

- A minimum lag-time of 10 years.

Asbestos body and asbestos fibre content of lung tissue and lung cancer risk

In a study on the asbestos body (AB) and fibre content in resected lung tissue from 477 consecutive patients with lung cancer, de Vuyst et al. (20) found that a count of 5,000 or more ABs per gram dry lung correlated with "significant occupational" cumulative exposure; the figure of 5,000 ABs or more was considered to be about equivalent to 5,000,000 f/g dry lung. Thimpont and de Vuyst (19) also found that concentrations of ABs > 5,000/g dry lung do not occur in non-exposed control subjects and are always indicative of occupational exposure; about 50% of patients with > 5,000 ABs/g dry lung tissue have low-grade fibrotic lesions affecting small airways and the interstitium, and identifiable ABs in histological sections.

Lung cancer is now accepted in Belgium as an asbestos-related disorder if *one* of the following *major* criteria is present:

1. Asbestosis or bilateral diffuse pleural thickening.

2. Cumulative exposure ≥ 25 fibre-years.

3. AB concentrations in lung tissue or in BAL respectively ≥ 5000/g dry lung or 5/ml BAL.

4. A duration of at least 10 years' work in a limited list of jobs.

5. A minimum lag-time of 10 years.

Thimpont and de Vuyst (19) also referred to a series of *minor* criteria (insufficient by themselves for attribution): (i) pleural plaques; (ii) unilateral diffuse pleural thickening; and (iii) bronchiolar and peribronchiolar fibrosis without detectable ABs in lung tissue.

In a case-control study on AB concentrations in autopsy lung tissue with allowance for smoking, Mollo et al. (21) found a 4-fold increase in the RR for adenocarcinoma at a lower cut-off count of 1,000 ABs/g dry lung. In a stratified analysis from multiple comparisons, the RR was 5.59 for all cancers vs. controls and 17.75 for adenocarcinomas vs. controls (i.e. RR about 4 for 1,000–9,999 ABs per gram dry lung, with evidence of a dose-response effect, with higher RRs for counts > 10,000).

In 1995, Rödelsperger and Woitowitz (22) reviewed estimated dose-response relationships for lung cancer and mesothelioma in humans and in animal models, and they calculated the cumulative exposures for white South African amphibole miners:

"An average cumulative exposure of 15.2 fibre-years for amosite miners and 9.83 fibre-years for crocidolite miners can be obtained from the discussion in Sluis-Cremer et al (1992). Despite the fact that this estimated exposure is very low, the SMR [standardized mortality ratio] for lung cancer altogether increased to 1.72 (95% confidence interval CI = 1.32–2.21); for amosite miners the SMR amounted to 1.38 (90% CI = 0.97–1.91) and for crocidolite miners to 2.03 (90% C1 = 1.43–2.80)",

thereby suggesting that the RR or SMR for lung cancer may reach 2.00 with exposures < 25 fibre-years.

Exposure assessment

The cumulative exposure standard of 25 fibre-years or more is also applied in Germany (23) and Denmark, and job histories elsewhere in Scandinavia (asbestosis not required). Occupational histories also form the basis for attribution in France, as reviewed recently by Hindry (24).

In Australia, the New South Wales (NSW) Dust Diseases Tribunal and the Worker's Compensation Court have ruled repeatedly in favour of *The Helsinki Criteria* as basis for attribution, and in 1999 *The Criteria* were under consideration as a National Standard (25).

Because legal decisions now appear to favour a *Helsinki Criteria* approach, construction of databases such as described by Burdorf and Swuste (26) or *Faserjahre* (BK Report 1/97) will be essential for equitable compensation of lung cancer due to asbestos, when evidence of quantified exposure must be based on history.

The German system is based partly on a quantified exposure of 25 fibre-years, derived from a standardized work history and reference to a database of some 27,000 measurements covering a broad range of jobs, industries and time periods. This is, in turn, based on actual measurements and expert opinions.

The 90th percentile for a given job/industry is taken or a conventional value defined. The Dutch system uses a more qualitative approach with probabilistic assessments of the likelihood of different exposure levels. Without such systems, Boards and Tribunals will continue to spend inordinate time considering differing opinions of expert witnesses in determining past exposures. The aim of this system is to create a matrix that defines asbestos exposure by time, occupation and industry.

In association with each value, there will be assigned a level of confidence ranging from:

1. Direct measurement
2. Interpolated measurement
3. Measurement in a similar facility
4. Interpolation from a similar facility
5. Consensus estimate
6. Estimate for which no consensus could be reached.

Chest X-ray status for asbestosis and the risk of lung cancer

In a chest X-ray study on lung cancer in the Wittenoom cohort, de Klerk et al. (10) found an increase in the RR of lung cancer with increasing cumulative exposure to asbestos, in the absence of radiographic asbestosis, but the presence of asbestosis had an adjuvant effect on risk. In a study of asbestos-cement workers in Ontario, based on chest X-rays, Finkelstein (27) also found an increase in the RR of lung cancer in the absence of radiographic asbestosis (although this study has been criticized because no relationship to smoking was identified – apparently due to misclassification of smoking habits for some patients – and there was no "significant" dose-response effect).

Epidemiological studies and meta-analyses

Between 1993 and 1999, multiple epidemiological studies have reported on lung cancer risk in individuals exposed to asbestos. The Netherlands cohort study (28) found the RR to be 2.49 overall, with a value of 1.59 for low exposures, 0.96 for intermediate exposures, and 3.49 for high exposures (exposures divided into tertiles; in this study, the tertiles do not correspond to cumulative doses, but to probabilities of exposure); the RRs adjusted for age and other occupational factors were 1.82 [low], 1.29 [intermediate] and 2.72 [high]).

In 1997, Steenland and Stayner (29) summarized 24 epidemiological studies on lung cancer, published between 1979 and 1994. Across these studies, lung cancer SMRs varied from 0.9 to 5.0, with a mean value of about 2. An exposure-response relationship was demonstrated in 15 of these studies, with no such relationship in 4, and there was no information in 5. Van Loon et al. (28), in their report on The Netherlands cohort study, also referred to five studies on asbestos and lung cancer with RR estimates that varied from 2.0 to 4.1, among which only one reported a non-significant positive association between cumulative exposure to asbestos and risk of lung cancer.

There have been some attempts to carry out meta-analysis of published studies on quantitative dose-related lung cancer risk with asbestos exposure. The study of Lash et al. (30) illustrates the difficulty of this exercise when very heterogeneous studies are considered. The limitations of this type of study have been pointed out in reviews by Blettner et al. (31) and Ioannidis et al. (32). Accordingly, Blettner et al. (31) state that "... Meta-analyses from published data are in general insufficient to calculate a pooled estimate since published estimates are based on heterogeneous populations, different study designs and mainly different statistical models [abstract] ... Meta-analyses using published data are, therefore, restricted and seldom useful to produce a valid quantitative estimate or to investigate exposure relations such as dose-response (p. 8)...". It is possible that pooled data studies may give more valid answers, but in the asbestos-lung cancer field, industry differences may preclude this. (In a meta-analysis of 69 asbestos-exposed occupational cohorts, Goodman et al. (33) identified "... meta-SMRs of 163 and 148 (for lung cancer) with and without latency, with significant heterogeneity of results...".)

The summary estimate obtained from a random-effects model recommended by Lash et al. (30) has no population-specific interpretation; instead it represents the mean of a distribution that generates effects. Unlike a standardized rate ratio, it does not correspond to an average effect in a population.

Random-effects summaries give proportionally greater weight to small studies than do fixed-effects summaries. As a consequence, random-effects summaries will be more heavily affected by biases that more strongly affect small studies.

Lobar distribution of lung cancer, lung cancer in asbestosis versus diffuse interstitial fibrosis, and the South Carolina asbestos textile cohort

Lee et al. (34) addressed the lobar distribution of lung cancer in asbestos-exposed individuals and found that the tumours were predominantly located in the upper lobe (i.e.

they did not find the reversal of the upper lobe to lower lobe ratio reported in some other studies).

Churg (35) refers to a study in Japan by Nagai et al. (36) which identified lung cancer in 38% of patients with diffuse interstitial fibrosis (DIF) who were smokers, and in 11% of the same group who were non-smokers; the figure of 38% is roughly comparable to the high frequency of lung cancer development in asbestosis (e.g. see 5). Nonetheless, analysis of the paper by Nagai et al. (36) reveals some unusual data that call this figure into doubt: e.g. 88% of the tumours were peripheral in distribution and the diagnosis in 27 out of 31 cases was established by transbronchial biopsy of lung (in limited samples of this type, there is a problem in distinguishing between reactive broncho-alveolar epithelial proliferation that is an almost invariable accompaniment of DIF, from genuine lung cancer; in other words, the technique by which the diagnosis of cancer was made casts doubt on the figure).

From an analysis of death certificates in the United States, Wells and Mannino (37) found a 5% rate of association between DIF and lung cancer, in comparison to 27% for asbestosis and lung cancer.

Lung cancer rates in patients with progressive vs. non-progressive asbestosis might be claimed as evidence in favour of the fibrosis-cancer nexus. For example, Oksa et al. (38) identified 11 lung cancers in 24 patients with progressive asbestosis (46%; SIR = 37), in comparison to 5 of 54 non-progressors (9%; SIR = 4.3). At this stage, it should be emphasized that progression or severity of disease such as asbestosis is not the same as the presence or absence of the disorder (asbestosis); because the paper did not address a group of patients with comparable exposures in the absence of asbestosis, it does not by itself contribute information to the question of whether asbestosis is an obligate precursor for the cancer, or not.

In addition, the classical studies carried out by Dement et al. (39, 40) on South Carolina asbestos textile workers are worth mention (e.g. see 39); this cohort worked with Canadian chrysotile, and is known to have up to 30–50-fold higher K value than the Quebec chrysotile miners and millers – a difference that remains unexplained (41). Dement et al. (39) found an SMR of 2.59 and a standardized risk ratio of 2.63 (95% CI, 1.20–5.75) at 2.7–6.8 fibre-years of exposure, for white males. This estimated cumulative exposure is below the level at which Green et al. (18) – in an autopsy study based on the same cohort – found histologic asbestosis.

More recently, Case and Dufresne (42) have revisited the study reported in 1989 by Sébastien et al. (43) on the fibre content of lung tissue from the South Carolina textile workers in comparison to the Quebec (Thetford) miners/millers, concentrating on fibres > 18 micrometers in length; Case and Dufresne (42) reported that a significant amount of amosite/crocidolite fibres was found in the textile workers' lungs, with the implication that these commercial amphiboles, as opposed to chrysotile, might explain the difference in the K values for the two cohorts (there were only slight differences in fibre length, so that exposure to long fibres cannot explain the K differences). Green et al. (18) also reported a fibre burden study on the South Carolina textile workers, with a comparable control group: the textile workers had a higher lung content of chrysotile in comparison to the controls (geometric mean = 33,450,000 vs. 6,710,000 f/g dry lung), with a higher content of tremolite (3,560,000 vs. 260,000); the asbestos workers also