The "Helsinki Criteria" for Attribution of Lung Cancer to Asbestos Exposure

How Robust Are the Criteria?

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The "Helsinki Criteria" were put forward as "state-of-the-art" criteria for the diagnosis and attribution of certain lung and pleural disorders to asbestos exposure by a group which convened in Helsinki in 1997, and were further updated in 2004.[1,2] The Helsinki Criteria were purported to be the work of a "consensus conference" whose purpose was to develop guidelines for diagnosing individual cases of asbestos-related diseases. Interestingly, the documents that have resulted from the meeting bear a striking resemblance to the review articles written by Henderson et al[3,4] several years prior to the meeting, one of which in fact is not a scientific reference at all but a legal briefing book.[3] The recommended criteria are increasingly being used for medicolegal purposes, often by "experts" indiscriminately, with no specific knowledge as to how they were derived and how they should be applied. In fact, the article uses a considerable amount of medicolegal jargon and despite the appellation of "consensus conference" is clearly slanted toward a particular medicolegal viewpoint.

The most controversial issues are those related to the guidelines provided for lung cancer and its attribution to asbestos exposure. In this article we critically evaluate the criteria that the group proposed for lung cancer and examine their validity and robustness.

Lung cancer risk in relationship to asbestos exposure varies with cumulative exposure, industry, and fiber type. All the main histological types of lung cancer can be caused by exposure to asbestos, and at present there is no genetic test or marker that can separate asbestos-induced lung cancers from the mainstream. It is generally agreed among the scientific community that a lung cancer can be ascribed to asbestos exposure when it occurs in a setting of asbestosis and with an appropriate latency.[5,6] However, it is debatable and controversial as to whether a lung cancer can be attributed to asbestos exposure in the absence of asbestosis.

What epidemiologic evidence informs on the issue of asbestos-attributability of lung cancer? In 1991, a prospective longitudinal study of workers employed in the manufacture of asbestos cement products found that the excess risk of lung cancer was limited to those workers who had radiographic evidence of asbestosis.[7] A subsequent review of the literature on this subject, in 1996,[6] suggested that the weight of the scientific evidence supported this conclusion.

Recently, the results of 2 studies, originally designed to assess the efficacy of lung cancer prevention by β-carotene and retinol in high-risk populations (smoking and asbestos exposure), have challenged this conclusion. These studies now had an altered objective, said to address the question of whether elevated lung cancer risk due to asbestos exposure is limited to those with asbestosis. In both cases their answer was no.[8,9] However, neither study was initiated to answer this question, and both are associated with serious flaws in regard to their changed purpose. These chemoprevention studies were abandoned when it became clear that vitamin treatment did not reduce lung cancer risk, and indeed, in the Cullen study,[8] the intervention was discontinued ahead of schedule when evidence proved that "the vitamins did not prevent lung cancer and strongly suggested increased risk of lung cancer, an effect most pronounced among the asbestos workers." Not surprisingly, the results show that lung cancer risk was related to smoking, asbestosis, and airway obstruction, all associations which are generally accepted. Also, there was an inexplicable synergy between vitamin treatment and asbestosis in the associated lung cancer risk. Internal comparisons were done in regard to asbestos exposure, asbestos-related x-ray changes, smoking, and lung function. No quantitative exposure estimates were possible: years of exposure in asbestos-exposure jobs, 80% of them in shipyards and construction, were a crude surrogate of exposure.

Shipyard asbestos-exposure studies have often failed to show an overall excess lung cancer risk because the jobs have extremely variable and nonquantifiable asbestos exposures. Without valid exposure estimates, this variable cannot be accounted for, and dose-response relationships (in those without asbestosis) cannot be supported when assessment of exposure (dose) cannot be validated and is highly uncertain. X-ray results were generated by one (different)

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reader in each study center and pooled. Standard approaches to International Labour Organization readings for epidemiologic purposes requires a panel of the same 3 readers study-wide, with median readings used. The ascertainment of ''asbestosis'' in this study is therefore suspect and its putative absence of questionable reliability. The authors conceded all of these limitations of their study and concluded: ''Hence, we can neither affirm nor refute the contention that asbestosis obligatorily mediates the relation between exposure and cancer . . . .''

The Reid study[9] contains many of the same limitations, and others. The chemoprevention trial was not designed to answer the question posed in this article, resulting in a limited ability to provide a valid answer. Again, lung cancer risk was strongly related to smoking and asbestosis, and it is claimed that a dose-dependent lung cancer risk did not require the presence of asbestosis. However, as indicated, this claim is dependent on credible exposure estimates and identification of asbestosis in the study population. Almost half the study population is derived from former residents of the Wittenoom community, and general environmental fiber sampling must be considered inadequate for construction of individual cumulative exposures. The absence of panel chest x-ray readings (a single reader was used) is nonstandard in studying the epidemiology of mineral dust diseases. Importantly, the exposure effects studied were the consequence of pure crocidolite exposure. It has been found that asbestos-related lung cancer risk is 10- to 50-fold higher in amphibole-exposed individuals than following exposure to chrysotile.[10] Since the universe of asbestos-exposed workers contains almost none exposed *only* to crocidolite, any results from this study are clearly not generalizable.

The Helsinki Criteria state that the risk of developing lung cancer is materially increased (by a factor of 2), even without asbestosis, under the following conditions:

1. One year of heavy exposure (eg, manufacturing of asbestos products, asbestos spraying, insulation work with asbestos materials, demolition of old buildings) or 5 to 10 years of moderate exposure (eg, construction, shipbuilding).
2. Estimated cumulative exposures to mixed (amphibole plus chrysotile) asbestos fibers of 25 fibers per milliliter per year (fiber-years).
3. A lung fiber burden within the range recorded for asbestosis in the same laboratory.
4. Retained fiber levels of 2 million amphibole fibers (>5 μm) per gram of dry lung tissue or 5 million amphibole fibers (>1 μm) per gram of dry lung tissue, as determined by electron microscopic analysis.
5. Asbestos body concentrations determined by light microscopic analysis greater than 10 000 per gram of dry lung tissue.

Criteria 1 and 2 can be considered as clinical or anecdotal assessments of cumulative asbestos exposure and 3 through 5 as mineralogical estimates of exposure.

ESTIMATES OF EXPOSURE ANECDOTALLY

What really matters in terms of causing an asbestos-related lung cancer is the amount of fibers deposited in the lungs and their retention. Cumulative exposure estimates are a surrogate for this. Three of the major factors influencing deposition are the number of fibers in the breathing zone of the individual, fiber dispersal (clumped fibers are too large to be deposited), and fiber size distribution (a small increase in the percentage of thin fibers will increase percentage deposition considerably). No surveys of airborne measurements have taken these factors into account.

Anecdotal estimates are fraught with difficulties because an individual's estimate of exposure is subject to poor recall of what conditions were really like decades prior to the development of the lung cancer, poor appreciation of what was in the ''dust'' to which he or she was exposed, and perhaps exaggeration because there is the prospect of compensation. Some of these problems can be overcome to an extent by a structured questionnaire and expert knowledge of the industrial situations where the particular individual worked. However, in many cases, particularly in those with multiple employments, or in employments where no airborne measurements exist, there remain many uncertainties as to the relative amounts of asbestos exposure which took place. The terms light, moderate, and heavy exposure mean little outside particular industries and are used indiscriminately, particularly when translated across different industries. Helsinki proponents simply adopt the adjudication criteria incorporated in Finland without critical review of the underpinning scientific evidence. For example, shipbuilding is used in the Helsinki Criteria as an example of moderate exposure to asbestos, which after 5 to 10 years would result in a doubling of risk for lung cancer; in fact, there are many different trades within the shipbuilding industry, with many different levels of asbestos exposure. Several cohort studies of the shipbuilding industry have been performed, and these have demonstrated in the majority a risk of lung cancer that is less than 2-fold.[11–14] Moreover, if one looks at different industries the standardized mortality ratios for lung cancer vary considerably, and it is therefore questionable whether one should extrapolate the risks for asbestos related lung cancer derived from one industry to individuals employed in other industries.

Critical examination of the proposed 25 fiber-years level for attribution of lung cancer to asbestos reveals several weaknesses. First of all, it implies a false precision concerning the estimate. There are many methodological problems related to determination of the fiber-years level. Many of the estimates have been based on inadequate sampling techniques that have changed in the course of the years.

Second, the measurements of airborne fiber levels have been conducted by optical microscopic techniques. Direct comparisons between fiber levels determined by optical and transmission electron microscopic techniques have shown approximately a 10-fold greater amount for amosite and a 40- to 200-fold greater amount for crocidolite with the latter. It can be seen that equivalent optical counts obtained for amosite and crocidolite would in fact be 4 to 20 times higher for crocidolite than for amosite if transmission electron microscopy (TEM) techniques had been used.

Third, the document states that the

relative risk of lung cancer is estimated to increase 0.5% to 4% for each fiber-year of cumulative exposure and then proceeds to use the upper level of this boundary range for stating that the increase of lung cancer is 2-fold, with a cumulative exposure of 25 fiber-years. If, on the other hand, one took the lower boundary level of 0.5%, this would translate into an equivalent of 200 fiber-years. Even this is debatable because there are industries with substantial exposure to asbestos where no increase in lung cancer risk has been detected. In fact, the published estimated percent increases in relative lung cancer risk for different industries has been much wider, namely from 0.010% to 9.1%, with consequent doubling of relative risk at 10 000 fiber-years to 11 fiber-years exposure.[15]

This general Helsinki guideline takes no account of the different relative risks by industry and type of fiber exposure, important determinants of risk. It is wholly unsuitable to claim that lung cancer attribution may be made on the basis of a generic figure for cumulative asbestos exposure originating from a single epidemiological cohort when in fact risk assessment across different published epidemiological studies has indicated a variation of almost 3 orders of magnitude (0.01%–9.1%).

It has been stated that 25 fiber-years cumulative exposure represents the threshold level for the development of asbestosis from mixed dust exposure. In fact, the 25 fiber-year value probably only applies to amphibole exposure, and the value for chrysotile exposure is considerably higher, on the order of 200 fiber-years.[7] At the subjectively estimated 25 fiber-years exposure only a small minority of asbestos-exposed workers would appear to develop radiologically detected changes that may be interpreted as asbestosis. Of these, only a small percentage will subsequently develop lung cancer. It appears that it is merely coincidental that the Helsinki Workshop participants incorporated the threshold figure for asbestosis as 25 fiber-years, at which the relative risk of lung cancer doubled. Proponents of the 25 fiber-year figure for a causal role for lung cancer often refer to the Pohlabeln[16] study, which shows a relative risk of 1.94 at the Helsinki trigger dose level. The 25 fiber-year model is used in Germany for adjudication purposes, and the German authors had specifically designed a study to test the validity of the cumulative dose. By use of the BIA (BK1/97) database of hygiene measurements provided at the 90th percentile dust measurements, there exists a recognized bias in favor of the claimant, and this is different from the hygiene standards used in epidemiological studies (50th percentile = mean weighted average level). A conversion of the 90th to 50th percentile dust levels for most activities requires a conversion factor of 0.3 to 0.5; that is, the German 25 fiber-year adjudication system is being applied at between 12 and 16 fiber-years exposure.

ASBESTOS BODIES/AMPHIBOLE FIBER LEVELS

A point made in the article, frequently ignored, is that ''each laboratory should establish its own reference values'' because there is interlaboratory variation due to methodology, which includes preparation techniques, analytical tools (scanning electron microscopy [SEM] or TEM at different magnifications), and counting procedures.[17] Unfortunately, there has been a tendency to translate a value obtained by one laboratory (using TEM) to the figures given in the Helsinki Criteria, which were obtained in one study by a Finnish laboratory using different methodologies (SEM) and counting rules. Data from the Finnish laboratory indicates that this should not be done. In a study comparing SEM and TEM values for asbestos fibers in the lungs of 29 mesothelioma patients, it was found that on average there was a 3 times higher level obtained by TEM compared to SEM.[18]

The Helsinki proponents do not define what is meant by the asbestosis range. The Cardiff laboratory has carried out mineral fiber analyses of lung tissues from several different industrial cohorts that have very different risks of developing lung cancer. The median amphibole asbestos fiber counts for all subjects irrespective of fibrosis were 16 million fibers per gram of dry lung tissue for a naval dockyard cohort and 106 million fibers per gram of dry lung tissue for an asbestos product factory cohort[19,20]; their respective standardized mortality ratios were 84 (not elevated) and 210 (more than doubling of risk).[11,21] Therefore, it is inappropriate to take levels of 2 million amphibole fibers (>5 μm) per gram of dry lung tissue or 5 million amphibole fibers (>1 μm) per gram of dry lung tissue as indicative of a doubling of risk for lung cancer when the procedure has been performed in a laboratory different from that in Finland.

There has been only one article that compared fiber burden measurements in lung tissue with ''expert'' estimates (not measurements) of cumulative asbestos exposure, and there was a very poor correlation.[22]

CONCLUSION

Clearly, many consider that the issue of ascribing lung cancer risk to asbestos exposure in the absence of asbestosis is not settled. In a recent review,[23] the authors came to an indeterminate conclusion, suggesting that epidemiology can probably not fully settle the issue and that the answer may be critically dependent on fiber type (see previous comments on the Reid study). Epidemiologic evidence has been advanced that favors either the position that asbestos exposure per se is causative *or* that the pathogenesis of asbestos-related lung cancer depends on the biologically plausible sequence of inflammation, fibrosis, and carcinogenesis. The writers believe that the weight of the evidence favors the latter alternative.

The Helsinki Criteria appear flawed. Assessment of exposure to asbestos anecdotally is a very imprecise science, and estimates of fiber-years of exposure in individual cases are mere ''guesstimates'' in the absence of measurements from reasonably comparable situations. Lung cancer risk related to asbestos exposure varies widely with industry. A lung asbestos fiber level obtained in one laboratory should not be compared with the levels recommended in the Helsinki Criteria, which were determined by a different laboratory using different analytical protocols. Although it may not be perfect, the presence of asbestosis remains the most reasonable criterion for causal attribution purposes.

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