and identifiable ABs in histological sections.\textsuperscript{233} In a series of 924 cases of lung cancer, Mollo \textit{et al.}\textsuperscript{32} diagnosed asbestosis by histological examination in 54 of 116 (46.6\%) ‘surgical’ cases with an AB concentration >1000 ABs/g dry lung.

In a case-referent study on AB concentrations in autopsy lung tissue with allowance for smoking, Mollo \textit{et al.}\textsuperscript{234} found a 4-fold increase in the RR for pulmonary adenocarcinoma at a lower cut-off count of 1000 ABs/g dry lung. In a stratified analysis from multiple comparisons, the RR was 5.59 for all lung cancers versus referents and 17.75 for adenocarcinomas versus referents (i.e., RR \~4 for 1000–9999 ABs/g dry lung, with evidence of a dose–response effect, with higher RR s for counts in excess of 10000 ABs/g dry). This study did not detect an association between asbestos exposure and lung cancer phenotypes other than adenocarcinoma.

\textbf{THE AWARD CRITERIA}

The AWARD (Adelaide Workshop on Asbestos-Related Diseases) Criteria\textsuperscript{225,235} were formulated in October 2000 by a group of 15 Australasian experts in asbestos-related disorders—including epidemiologists, an industrial hygienist and a medical scientist, occupational and respiratory physicians, pathologists, and radiologists—to address the applicability of The Helsinki Criteria to Australasia. The AWARD Criteria basically endorsed The Helsinki Criteria as ‘fair and reasonable’ for the attribution of lung cancer to asbestosis, with certain modifications for Australia:

1. Like The Helsinki Criteria, The AWARD Criteria also accept either clinical or histological asbestosis as a criterion for attribution of lung cancer to asbestosis.

2. The AWARD document\textsuperscript{225,235} acknowledged that the risks of lung cancer for the cohort of Quebec chrysotile miners/millers and for asbestos textile production (such as the South Carolina cohort) are not applicable to Australia, where the majority of asbestos exposures have been mixed amphibole-chrysotile exposures, or crocidolite-only exposure (the Wittenoom cohort).

3. The AWARD meeting also recognised that the counts of uncoated amphibole fibres in lung tissue as specified in The Helsinki Criteria apply to mixed amphibole-chrysotile exposures only. For amphibole-only exposures (such as ‘virtually pure crocidolite exposure’ for the Wittenoom cohort), higher lung tissue fibre counts are required to equate to 25 fibres/mL-years of exposure. For the Wittenoom cohort, about 220 million crocidolite fibres longer than 0.4 \textmu m of dry lung or, in the AWARD document itself,\textsuperscript{225,235} a figure of at least 100 million crocidolite fibres longer than 1 \textmu m dry lung are necessary to equate to 25 fibres/mL-years as an average or approximation.

In 2003, the Australasian Faculty of Occupational Medicine (AFOM) of The Royal Australasian College of Physicians addressed this issue independently of the AWARD group and commented that ‘it is unlikely that consensus will be reached in the near future on whether asbestos exposure can cause lung cancer in the absence of asbestosis.’\textsuperscript{6} However, ‘if asbestosis is held not to be a precondition’, the AFOM document\textsuperscript{6} suggested that an asbestos-related doubling of risk for lung cancer occurs at about 21 fibre-years for amphibole-only and mixed exposures, at 1667 fibre-years for chrysotile mining, and at 43 fibre-years for ‘pure chrysotile other than mining’.

\textbf{CRITERIA FOR ATTRIBUTION OF LUNG CANCER TO ASBESTOS IN GERMANY}

In the German prescription on occupational diseases (\textit{Berufskrankheitenverordnung}), existing criteria for ascribing lung cancer to asbestos were supplemented in 1992 by an estimated cumulative workplace asbestos exposure of at least 25 fibre-years.\textsuperscript{25,236} As shown in Fig. 1, a cumulative exposure of about 25 fibre-years was related to a 2-fold increased risk of lung cancer mortality in comparison to the general population, for the three areas of asbestosis—cement, asbestos textile and asbestos insulation work,\textsuperscript{177–182} representing the most important patterns of occupational exposure in Germany. The delimiting value of 25 fibre-years for compensation of lung cancer was obtained from the highest \(K_s\) for each of these three patterns of exposure,\textsuperscript{177,181,229} because random errors in general would depress the slope of the dose-response line.\textsuperscript{38,237}

Introduction of this new criterion was enabled by a convention on the magnitude of asbestos exposures at various workplaces, proposed by the German \textit{Berufsge- nossenschaften}.\textsuperscript{64} For certain work situations, a catalogue of fibre concentrations corresponding to the 90\textsuperscript{th} percentile (about twice the arithmetic mean value) of the measuring results was compiled,\textsuperscript{1} based on 9974 fibre counts with the membrane filter method, 1600 koinometer counts and 15 316 gravimetric measurements of the asbestos mass concentration.

These values are used throughout Germany to calculate cumulative workplace asbestos exposures relative to the delimiting value of 25 fibre-years. Following introduction of these regulations, the number of patients with compensated lung cancer increased from 223 in 1992 to

\begin{itemize}
\item There have been some criticisms over use of the 90\textsuperscript{th} percentile as opposed to the arithmetic mean (AM)—which corresponds roughly to the 70\textsuperscript{th} percentile and not the 50\textsuperscript{th}—with an argument that the German system tends to overestimate exposures (but see discussion in section ‘Latency intervals between asbestos exposure and lung cancer’). The factor between the AM and the 90\textsuperscript{th} percentile value is about 2 overall: it depends upon the geometric standard deviation (GS) of the logarithmic normal frequency distribution of the measured values. It is only 1.91 for GS = 2, and it increases from 1.55 for GS = 1.5 to 2.24 for GS = 3. This difference is thought to be small in comparison to the uncertainties that surround exposure estimates based on historical measurements, related to conversion factors used to translate particle counts and mass measurements into fibre concentrations. In comparison, if the 50\textsuperscript{th} percentile is used for GS = 3, the figure would be only about half of the AM because it would not adequately consider high concentration values. It is also worth emphasising that the database for the BK-Report\textsuperscript{5} does not deal with a random sample of workplace situations but a selection where there is routine supervision, and airborne fibre concentra-
\end{itemize}
ASBESTOS FIBRE CONCENTRATIONS IN LUNG TISSUE, ESTIMATED CUMULATIVE EXPOSURE, AND THE RISK OF LUNG CANCER

In The Helsinki Criteria, the following lung tissue concentrations were delineated to identify workers with a high probability of exposure to asbestos in the workplace:

(a) > 1000 ABs/g dry lung (equivalent to > 100 ABs/g wet lung);
(b) > 100 000 amphibole fibres > 5 μm in length/g dry lung;
(c) > 1 000 000 amphibole fibres > 1 μm in length/g dry lung;
(d) > 1 AB/mL BAL fluid.

Each laboratory should establish its own reference values, and the median values of those exposed occupationally should be substantially above the reference values. Besides other criteria (discussed also in The Helsinki Criteria), a lung fibre count exceeding this background range should be sufficient for probabilistic attribution of mesothelioma to asbestos exposure.

The basis for these concentrations of ABs and asbestos and amphibole fibres is tabulated in a review by Tossavainen, for lung tissue samples and BAL fluid from the general population or from patients not exposed in the workplace. Different fibre definitions, different measuring methods and different statistical parameters complicate comparison of these data. In Fig. 2A–C (data for BAL fluid not shown), the data are presented as the percentage of measurements below a certain concentration value according to the following rules:

(i) Geometric mean and median values: < 50%
(ii) Arithmetic mean values: < 70%
(iii) Upper limit of the range: < 100%

If several of these parameters were given for a series of measurements, they are presented side by side.

With the exception of two series of mesothelioma patients, the median values of the concentrations of short and long amphibole fibres and ABs ranged below the limit values given by The Helsinki Criteria. In most of the studies, less than 20% of the measured values exceed these limits. An increased percentage of counts exceeding the limits is observed for short amphibole fibres among Australian and, probably, Japanese patients. For ABs, an increased percentage is observed for one of the French and the Belgian series, as well as for Canadian patients living near the Quebec mines.

In a German mesothelioma case-referent study, 15% of 66 hospital referents who underwent lung resections mainly for lung cancer exceeded the limit value for long amphibole fibres (length > 5 μm), in comparison to about 70% of the cases. The same percentages of measurements above the delimiting value were obtained for short fibres (length > 1 μm). AB counts were also available for 147 referents and 66 cases: the limit value of 100 ABs/g wet lung (= 1000 ABs/g dry) was exceeded for 18% of the referents in comparison to 73% of the cases, and this percentage for referents diminished to 8.7% when evaluation was restricted to 69 unexposed referents. In a mesothelioma case-referent study on patients from Yorkshire, the concentration of total amphibole fibres longer than 0.5 μm was measured. Twenty-two per cent of 122 referents exceeded the limit value in comparison to 80% of 147 cases; when evaluation is restricted to referents not exposed occupationally to asbestos according to the judgement of surviving relatives (n = 61; Table 4 in Howel et al.), the percentage is slightly less than 20% (Fig. 1 in Howel et al.). For controls and workers from the textile factory in South Carolina, fibres were counted at a magnification of ×20 000 without specification of a minimum fibre length. Among 31 controls, the delimiting value for amphibole fibres > 1 μm in length was exceeded for 9.7% of the tremolite counts, 6.4% of the anthophyllite counts and 12.9% of the amosite and crocidolite counts. It may be assumed that some of these counts were obtained from the same patients.

In a study of 33 patients from Texas with no history of occupational exposure to asbestos, Dodson et al. found that all had no more than 20 ABs/g wet lung and 26 had no detectable ABs; chrysotile was undetectable in 19 cases, and 10 of the 33 had no asbestos fibres within the detection limits of the study (the total uncoated asbestos fibre burden was in the range of 0–290 000 fibres/g dry, for fibres > 0.5 μm with an aspect ratio of ≥ 3:1). Although amosite and crocidolite fibres were found occasionally,
they were few in number: anthophyllite (12 of 33 cases) was almost as likely.

It is also notable that in mesothelioma case-referent studies, increased ORs are found at fibre concentrations immediately above the delimiting values for occupational exposure given in The Helsinki Criteria. In comparison to a reference group for whom the tissue concentration was less than 50 000 fibres/g dry lung, Rödelsperger et al. found that the OR for mesothelioma (ORMESO) increased in an almost linear fashion according to the relationship:

\[
\text{ORMESO} \sim \frac{\text{Concentration of amphibole fibres longer than 5\,\mu m}}{25000 \text{ fibres/g dry lung}}
\]

In this study, a significantly increased ORMESO of 4.5 (95%CI 1.1–17.9) was observed, even at the low fibre concentration range between 100 000 and 200 000 fibres longer than 5\,\mu m dry lung.

Roggli and Sanders studied 234 cases of lung cancer with some history of asbestos exposure, but with no quantitation of exposure as fibre-years. For 70 patients with asbestosis they recorded a median total asbestos fibre concentration of 2.53 million fibres/g dry for fibres 5\,\mu m in length or more (converted from wet weight figures), which included a median count of 2.53 million commercial amphiboles (crocidolite/amosite) and 220 000 non-commercial amphiboles, and a median count of 270 000 ABs/g dry, although this AB count is well above (18 times) the upper limit of 5000–15 000 ABs specified in The Helsinki Criteria.

In 1994, Karjalainen et al. reported a case-referent study that examined the relationship between lung fibre burden and the risk of lung cancer based on 113 surgically treated lung cancer patients in comparison to 297 autopsy referents from the Finnish population. Lung tissue fibre analysis was carried out for fibres longer than 1\,\mu m by scanning electron microscopy (SEM) at a magnification of \times 5000 and included mainly amphibole fibres. In comparison to a reference group with a tissue concentration of...
less than 1 million fibres/g dry, the ORLCA increased to 1.7 for concentrations in the range 1.0–4.99 million fibres/g dry and to 5.3 for concentrations of 5.0 million or more fibres/g dry. Karjalainen et al.\textsuperscript{109} stated that when two cases of asbestosis and seven cases of minor ‘histological fibrosis compatible with asbestosis’ were excluded, an elevated ORLCA was still associated with asbestos fibre concentrations of 5.0 million or more fibres/g dry lung (age-adjusted ORLCA = 2.8; 95%CI = 0.9–8.7; \( P = 0.07 \)) and for asbestos fibre counts in the range 1.0–4.99 million fibres/g dry (ORLCA = 1.5; 95%CI = 0.8–2.9; \( P = 0.19 \)). One criticism directed at this study is that the results fail to achieve significance in terms of \( P \) values, thereby proving that ‘significance’ lies only with the cases of fibrosis.\textsuperscript{115} This objection overlooks the fact that the limit \( P \leq 0.05 \) is an arbitrary statistical convention and that reality lacks sharp boundaries of this type: what is possible in this study is the trend from a low to a higher ORLCA with transition from an intermediate fibre count (1.0–4.99 million) to the higher value (≥ 5.0 million). If one excludes the nine cases of fibrosis and assumes that seven were in the high fibre group (≥ 5.0 million fibres/g dry) and two were in the intermediate fibre group (1.0–4.99 million fibres/g dry),\textsuperscript{**} one can calculate the crude lung cancer ORs to be 2.85 and 1.8, respectively, as consistent as possible with the age-adjusted ORs of 2.8 and 1.5 in the original paper; trend testing then yields \( \chi^2 \) (trend) = 7.2 (\( P < 0.01 \)). In addition, it is possible from the published data to recalculate the OR for adenocarcinoma only, after exclusion of all cases with any fibrosis; assuming that all were in the high fibre group, the OR is still significantly elevated for a count > 1.0 million compared with < 1.0 million (ORLCA = 2.65; 95%CI = 1.1–6.26; \( P < 0.001 \)).\textsuperscript{1}

Much steeper dose–response relationships were obtained from mesothelioma case-referent studies.\textsuperscript{86,245,249,251} e.g., Rödelsperger \textit{et al.}\textsuperscript{244} calculate the mesothelioma OR to be about 100 when patients with a burden of 2.5 million amphibole fibres/g dry (for fibres longer than 5 \( \mu \)m) are compared with the reference group.

In assessing the significance of asbestos lung fibre burdens for attribution of lung cancer, it should be emphasised that the ‘controls’ for case-referent studies represent individuals without the disease in question, sampled randomly and independently of exposure.\textsuperscript{29,31} This is a critical necessity for the validity of a case-referent study. Thus, the ‘control’ group will generally comprise both exposed and unexposed individuals. In using data from ‘control’ groups in case-referent studies for assessing likely lung fibre levels in the unexposed in comparison to those exposed, only data from the unexposed fraction of the ‘controls’ should be used.

Estimates of cumulative exposure as fibre-years apply equally to all types and mixtures of asbestos. In contrast, fibre analysis of lung tissue applies mainly to amphiboles because of the lower biopersistence of chrysotile in lung tissue.\textsuperscript{54,252,253} Therefore, the concentrations of asbestos and amphibole fibres that correspond to 25 fibre-years of exposure are largely dependent on the proportion of amphiboles in the relevant asbestos-containing materials.

\textsuperscript{**}Based upon an assumption that the clinical asbestosis cases were in the heaviest exposure group and that the mild histological fibrosis cases were in the intermediate exposure group.

From historical national data on the consumption of the different types of asbestos and the known composition of various products (e.g., asbestos-cement products), there is abundant evidence that chrysotile comprised about 94.95% or more of asbestos consumption, and amphiboles about 5% or less.\textsuperscript{54,254,255} However, in some industries—e.g., workers at the Nottingham gas mask factory\textsuperscript{256} and the Wittenoom crocidolite miners/millers in Western Australia—\textsuperscript{257}—the exposures involved a far higher proportion of amphiboles (notably crocidolite for both of these industries, so that exposure at Wittenoom unaffected by other exposures was to virtually 100% crocidolite). It follows that for these workers, much higher tissue concentrations of amphibole fibres are equivalent to an exposure of 25 fibre-years than for those exposed to a small percentage of amphibole fibres during their lives.

Table 6 gives summary estimates of lung tissue concentrations of amphibole fibres and ABs that may be related to a cumulative exposure of 25 fibre-years. As expected, the concentrations increase according to the percentage of the amphibole used, so that the smallest amount is encountered among 38 workers from the South Carolina textile plant.\textsuperscript{86}

In the South Carolina textile industry, chrysotile contaminated with less than 1% tremolite was the only type of asbestos processed as raw material, besides a small amount of crocidolite yarn. The concentrations of asbestos fibres of all lengths (without a specified minimum length) per gram dry lung were compared with individual fibre-years, which were available for the same patients from an extensive industrial hygiene survey.\textsuperscript{256} Roughly 40 million asbestos fibres/g dry lung correspond to an exposure of 25 fibre-years, but this result is influenced by a high number of small chrysotile fibres; nevertheless, the quantity of amphibole fibres may be estimated to be 4.5 million fibres/g dry lung using geometrical mean values given for the single types of asbestos (Table 3 in Green \textit{et al.}\textsuperscript{86}). Figure 3 in this paper represents the relationship between tremolite as the main type of amphibole fibre and estimated fibre-years of exposure, and shows concordance with The Helsinki Criteria.

Somewhat greater amounts of amphiboles may be expected for the cases and controls in Rödelsperger \textit{et al.}\textsuperscript{194,244} and for the cohort reported by Albin \textit{et al.}\textsuperscript{258,259} However, Rödelsperger\textsuperscript{244} reported that: ‘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/\( \mu \)g’ (in other words, 2 million amphibole fibres/g dry lung for fibres longer than 5 \( \mu \)m; abstract and p. 307).

In Rödelsperger’s study on mesothelioma patients,\textsuperscript{244} 25 fibre-years and the count of 2 million uncoated fibres/g dry lung corresponded roughly to an AB count of 15 000/g dry lung given in The Helsinki Criteria (see also Thumb and De Vuyser\textsuperscript{235}); for obvious reasons, these values could not be derived for the control patients.

By far the largest amount of amphibole is expected for 90 crocidolite miners/millers from Wittenoom. A strong correlation between analysis of the lung burden and the estimate of fibre-years was observed.\textsuperscript{257,261} For these workers, concentrations of 21 000 ABs/g wet lung and...
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ABs, asbestos bodies; Ref, reference; TEM, transmission electron microscopy.

*ABs only counted by light microscopy, per gram wet lung.
220 million crocidolite fibres longer than 0.4 μm/g dry lung (≈ 100 million fibres longer than 1.0 μm) correspond to an exposure of 25 fibre-years. These concentrations are respectively 20- and 45-fold greater than the AB and fibre concentrations specified by The Helsinki Criteria. They support the proposition that the percentage of amphiboles used in the workplace is crucial if the concentration of asbestos fibres in the lung tissue forms the basis for estimation of fibre-years of cumulative exposure.

**LUNG CANCER AND THE CLASTOGENICITY AND MUTAGENICITY OF ASBESTOS**

Detailed discussion of the molecular and genetic aberrations inducible by asbestos in experimental animals and cultured cell lines lies outside the scope of this review (see references 1, 96, 167, 263–266). However, asbestos is known to be genotoxic and clastogenic, with the capacity to induce DNA strand breaks, anaphase–telophase abnormalities and sister chromatid exchanges in cell lines in vitro—where fibrosis cannot be implicated—and free radicals generated from the surface of asbestos fibres or macrophages are implicated in these aberrations. Both crocidolite and chrysotile have been shown to disturb cell division, producing binucleated cells, which may lead to aneuploidy or polyploidy. Asbestos fibres can also induce oncogene expression—such as c-fos and c-jun proto-oncogenes—in cultured rodent mesothelial cells. Asbestos-related adenocarcinoma of lung is also associated with p53 and k-ras mutations.

In a study of 84 male patients with a histological diagnosis of adenocarcinoma of lung, Nelson et al. found a higher prevalence of k-ras mutations in those with a history of asbestos exposure than in those without, after adjustment for age and pack-years smoked, and that the estimated intensity of exposure was greater for the patients with k-ras mutations than those without. There was no detectable association with the duration of exposure, but the time since first exposure was associated with mutation status; in addition, the association was not dependent on radiographic evidence of asbestos-related disease. Nelson et al. concluded that their data were suggestive of an increased likelihood of k-ras codon 12 mutations as a consequence of asbestos exposure and that ‘this process occurs independently of the induction of interstitial fibrosis’.

Wang et al. have also reported that chrysotile and cigarette smoke in solution act synergistically to produce DNA damage in a dose-dependent fashion and to activate c-ras in human embryo lung cells as assessed by p21 expression. Jung et al. found that amosite and cigarette smoke each produced an increase in DNA strand breaks and necrosis in rat bronchiolar epithelial cells in vivo, both alone and in additive fashion when in combination.

Using a papillomavirus-immortalised human bronchial epithelial cell line, Hei et al. found that a single 7-day treatment of the cells with chrysotile induced stepwise transformation, with altered growth kinetics, resistance to terminal differentiation and anchorage-independent growth, to produce progressive tumorigenic growth in nude mice. Hei et al. also found that treatment of the same cell line with α-particles to simulate the effects of radon, induced a similar pattern of apparent neoplastic transformation in the same cell line. The same group of researchers had shown earlier that chrysotile is
mutagenic for cultured mammalian cells—with the production of large deletions—and comparable with the mutagenicity of γ-rays.

The fragile histidine triad (FHIT) tumour suppressor gene located at 3p14.2\(^{279-283}\) appears to represent a site of genomic fragility relevant to carcinogenesis: FHIT protein is expressed in most non-neoplastic tissues, and the highest levels of expression occur in epithelial cells. FHIT appears to be subject to deletion or loss of heterozygosity (LOH) by cigarette smoke and asbestos.\(^{279,280,282,283}\) Diminished expression of FHIT has been recorded in up to 80% of cigarette smoke-associated lung cancers,\(^{279}\) and in both asbestos-associated lung cancers (~69%) and non-exposed cases (~59%) in one study,\(^{282}\) and in ~54% of mesotheliomas\(^{283}\) (Pylkänen et al.\(^{283}\) suggest that LOH affecting FHIT can be concealed by normal cells present in mesotheliomas). Genomic instability affecting FHIT has also been identified in cases of idiopathic pulmonary fibrosis.\(^{284}\)

**GENETIC SUSCEPTIBILITY TO LUNG CANCER**

It is well known that genetic factors play a major causal role in the genesis of some cancers, notably those related to mutations in tumour suppressor genes or DNA repair genes, with high penetrance of the mutated gene(s).\(^{285,286}\) Such cancers include gastrointestinal cancers in families with familial adenomatous polyposis (APC gene), and cancers related to mutations affecting DNA repair genes, such as hereditary non-polyposis colon cancer (HNPCC) and xeroderma pigmentosum (XP[,A-D] genes),\(^{286}\) and it has been estimated that genetic abnormalities of this type may account for about 1–4% of all cancers.\(^{286,287}\)

It is also known that in some circumstances there is an interplay between genetic predisposition to cancer and environmental factors.\(^{286,288}\) One classical example is xeroderma pigmentosum (XP), where the mutated DNA repair genes XPA-D) produce extreme susceptibility (>1000-fold above 'normal'\(^{288}\)) to skin cancers (basal and squamous cell carcinomas and melanoma),\(^{286}\) because of an impaired capacity to repair DNA damage induced in the skin by ultraviolet radiation in sunlight; management of patients with XP includes isolating them from sunlight to minimise the DNA damage and hence to reduce the otherwise virtually certain risk of skin cancer.

Delineation of the genetic component for cancers related to multiple gene variants of low penetrance poses far greater difficulties than for high-penetration single-gene disorders, and familial aggregation of some cancers is complicated by the fact, that apart from some shared genes, family members frequently share environmental factors, including diet, lifestyle, recreations and occupations. Although lung cancer risk is highly dependent on environmental factors such as cigarette smoke (and less commonly asbestos and other occupational/environmental factors), it is a truism that only a minority of tobacco smokers ever develop lung cancer during their lifetimes (about one in 10\(^{287,290}\)), and only a minority of those exposed to asbestos ever develops lung cancer. Chance alone might be invoked as the explanation for cancer/not-cancer—for example the ‘correct’ combination of mutational events may not occur at all or in the ‘correct’ order, or a mutational event may be lethal to the cell—however, there is evolving evidence for modulation of cancer risk by genetic susceptibility/resistance (G\(_S\) and G\(_R\)) factors.\(^{287,290-295}\)

In studies based on the Swedish Family-Cancer Database,\(^{296-298}\) the ‘proportion of cancer susceptibility, accounted for by genetic effects’ was estimated at 14%\(^{285}\) and later at 8%\(^{299}\) for lung cancer, with shared and childhood environmental components of 9 and 4%, respectively, and 79% for non-shared environmental factors.\(^{299}\) A further study on the same database gave an estimated familial population attributable fraction (PAF) of ~3% for lung cancer, with a familial percentage proportion of ~6% (defined as the percentage of affected offspring with affected parents).\(^{300}\) A further study on the Swedish Database also yielded a higher familial risk for large cell carcinoma and adenocarcinoma of lung (SIR\(_{S}=2.29\) and 2.18, respectively) than for other histological types (small cell carcinoma =1.74 and squamous cell carcinoma = 1.78).\(^{296}\)

Apart from gatekeeper genes such as p53 and k-ras, a number of studies have focused on polymorphisms for caretaker genes\(^{301}\)—for example, those encoding the cytochrome p450 superfamily,\(^{288,302,303}\) such as CYP1A1,\(^{302,303}\) as well as N-acetyltransferase, glutathione S-transferase M1 (GSTM1), microsomal epoxide hydrolase (mEH),\(^{290,304}\) NAD(P)H:quinone oxidoreductase (09,C→T polymorphism)\(^{290,305}\) and myeloperoxidase (MPO)\(^{306}\)—which are involved in the activation or detoxification of carcinogens,\(^{290,307}\) and on DNA repair genes\(^{290,308}\) (about 130 DNA repair genes have been recorded, divisible into base excision repair, nucleotide excision repair and mismatch repair genes).\(^{309}\) For example, in relation to DNA repair genes it has also been reported that polymorphisms affecting exons 10 and 23 of XPD module risks for lung cancer among never-smokers, so that the presence of one or two variant alleles was associated with an OR\(_{S,C}\) of 2.6 for exon 10 (95%CI = 1.1–6.5) and 3.2 for exon 23 (95%CI = 1.3–8.0)\(^{289}\) in addition, current or recent smokers had higher aromatic DNA adduct levels than former/never smokers, and the same study\(^{289}\) found that subjects with exon 10 AA and exon 23 CC had significantly higher aromatic DNA adduct levels than subjects with any other genotype, with an increased risk of lung cancer.

In all probability, many potential G\(_S\)/G\(_R\) genes have yet to be identified,\(^{290}\) and analysis of the interplay between multiple G\(_S\) and G\(_R\) genes and environmental carcinogens constitutes a problem of great complexity; nonetheless, it seems likely that ‘everyone may have a unique combination of polymorphic traits that modify genetic susceptibility and response to ... carcinogens’\(^{300}\) especially for multifactorial diseases such as lung cancer.\(^{290}\) To simplify matters, the following discussion concentrates mainly on the MPO gene.

MPO is a lysosomal enzyme found in both neutrophils \(^{\dagger\dagger}\)The largest database of its type in the World, the Swedish Family-Cancer Database contains data on people born in Sweden after 1931, including their parents; by 2002, the Database comprised information on 10.2 million individuals across 3.2 million families, with data on more than 1 million tumours.\(^{296-298}\)}
and macrophages, and it catalyses the reaction between H$_2$O$_2$ and Cl$^-$, generating hypochlorous acid (HOCl)$^{310}$ and other reactive oxygen species (ROS); MPO is involved in the metabolism of several DNA-damaging intermediary factors that include tobacco smoke mutagens, and MPO appears to contribute to lung carcinogenesis by activation of procarcinogens such as benzo[a]pyrene intermediates, 4-aminobiphenyl and arylamines.$^{311}$ The MPO gene is localised to the long arm of chromosome 17 and comprises 11 introns and 12 exons.

Multiple investigations have evaluated the potential protective effect of the variant A allele for MPO in comparison to the wild-type genotype G/G ($^{\rightarrow}$MPO G$\rightarrow$A) on the risk of lung cancer.$^{311-321}$ Although two studies$^{316,319}$ did not detect any significant association between the A allele in comparison to G/G, most found that the A allele was associated with up to a 70% reduced RR$^{\text{LCA/OCR}}$ at equivalent levels of smoking; in one study$^{314}$ the reduced risk was confined to the homozygous AA polymorphism and not to the heterozygous G/A form, and others detected a reduced risk for G/A$^{311,313,317,318,320}$ and one$^{315}$ reported the findings as the risk for G/A + A/A only. Most studies reported the protective effect of the A allele in terms of RR$^{\text{LCA/OR}}$ relative to G/G, but Lu et al.$^{321}$ and Schabath et al.$^{322}$ reported their results as an increased OR$^{\text{LCA}}$ for G/G relative to G/A + A/A. The proportions of G/G versus G/A and A/A appear not to differ greatly from lung cancer cases in comparison to controls: across all studies cited above, G/G was found in 62% of controls versus 65% of cases; for G/A and A/A for controls versus cases, the percentage proportions were 33 vs 31% and 5 vs 4%; when the two studies that found no effect of MPO polymorphisms on lung cancer risk$^{316,319}$ are removed, the proportions for controls versus cases become 61 vs 68% for G/G, 29 vs 33% for G/A and 3 vs 6% for A/A.

Evidence for a component of genetic susceptibility for asbestos-related mesothelioma$^{323-325}$ and for lung cancer is much less extensive than the evidence for cigarette smoke-related lung cancer. Nonetheless, this notion has biological plausibility,$^{326}$ and is supported by the following observations: (i) only a minority of asbestos-exposed individuals, even those exposed heavily to crocidolite, develop mesothelioma during their lifetimes$^{327,328}$ (see preceding discussion); (ii) familial clusters of asbestos-associated mesothelioma are well documented,$^{329-341}$ (iii) one study$^{323}$ found that patients with mesothelioma have a greater frequency of non-mesothelioma cancers among their parents than non-mesothelioma cases; and (iv) genomic variants have been described in mesothelioma, such as inactivating mutations of the neurofibromatosis type 2 (NF2) gene$^{342}$ and simian virus 40 (SV40) transcripts incorporated into the genome (although the evidence for a contributory causal role of SV40 in the development of asbestos-related mesothelioma remains unproven$^{343,344}$).

So far as we are aware, there are only two reports on G/Gs for asbestos-associated lung cancer, relative to polymorphisms for the GSTM1$^{345}$ and MPO genes.$^{322}$ Stucker et al.$^{345}$ found no evidence that the risk of lung cancer after asbestos exposure differed according to the GSTM1 genotype, although this study had ‘low statistical power’.$^{345}$ Conversely, in a molecular case-referent study, Schabath et al.$^{322}$ found that subjects with self-reported asbestos exposure and with the MPO genotype G/G had an OR$^{\text{LCA}}$ of 1.72 for asbestos exposure compared with no exposure after controlling for age, gender and smoking, whereas subjects with a G/A + A/A genotype had a lower OR$^{\text{LCA}}$ of 0.89. Subjects with G/G had an OR$^{\text{LCA}}$ of 1.69 for $\geq$45 pack-years of smoking (heavy) compared with <45 (light), whereas the OR$^{\text{LCA}}$ for those with G/A + A/A was <1.0. For GG, the joint effect of asbestos and heavy smoking in comparison to no asbestos and light smoking was 2.19, and the analogous OR$^{\text{LCA}}$ for G/A + A/A was 1.18.

Given the emerging evidence on G/Gs for lung cancer, for both cigarette smoke and (to a far lesser extent) asbestos, and taking into account the complexity of the multiple genes and polymorphisms implicated so far, it seems that individuals comprising any population will vary in their susceptibility to (and risk from) these carcinogens. Therefore, one can deduce that the risk derived as an average or mean across entire cohorts/populations will tend to underestimate the risk for those with a Gs profile (RR$^{\text{GS}}$) and to overestimate risk for those with GR (RR$^{\text{GR}}$). It also follows that those with the disease in question are more likely to have GS for that disease and therefore to be at greater risk than either: (i) those who are resistant (Gs); or (ii) the average/mean risk (i.e., RR$^{\text{GS}}$-[RR$^{\text{GS}}$+RR$^{\text{GR}}$]/2), even if the variation in risk from the mean is only very small.

Assessing the significance of interaction between genetic and environmental factors in disease causation involves a new type of epidemiological study, the case-only study,$^{345,346}$ in which departure from a purely multiplicative model of joint effect can be assessed by computing the case-only OR (OR$^{\text{C-O}}$), derived for cases with and without the susceptibility gene and with and without exposure from a 2 x 2 table; if OR$^{\text{CS}}$ represents the OR among control subjects related to exposure and susceptibility genotype, then:

$$\text{OR}_{\text{C-O}} = \frac{[\text{OR}_{\text{GE}}/(\text{OR}_{\text{F}} \cdot \text{OR}_{\text{G}})] \cdot \text{OR}_{\text{CS}}}{\text{OR}_{\text{GE}} \cdot \text{OR}_{\text{F}}}$$

where OR$^{\text{GE}}$, OR$^{\text{F}}$, and OR$^{\text{E}}$ are conventional case-control ORs for combined genetic susceptibility plus exposure, genetic susceptibility, and exposure separately.$^{346}$ Because the genotype and the exposure are generally independent variables in the source population from which the cases arise, the expected value of OR$^{\text{CS}}$ is unity; if the joint effect is more than multiplicative, OR$^{\text{C-O}}$ is greater than 1.0, and it is less than 1.0 if the joint effect is less than multiplicative.$^{346}$ Applied to the data in Table III of Schabath et al.$^{322}$ (asbestos and genotype), the above analysis gives an OR$^{\text{C-O}}$ of 0.96, indicating near-multiplicativity.

If such findings$^{322}$ are validated in other analogous investigations, they would suggest that the asbestos-related lung cancer risk derived as an average across groups might be revised upwards for those with a susceptibility genotype, so that cumulative exposures lower than the average (e.g., <25 fibres/mL-years) could be accepted as imposing an OR $\geq$2.0, and the risk would be correspondingly revised downward for those with a genetic resistance profile, with the requirement for a greater cumulative exposure to impose the same risk. We consider that this approach to carcinogenesis by environmental factors in general has a sound theoretical and, to a lesser extent,
empirical basis, and we expect that molecular epidemiological studies that address these issues will lead to further refinement of approaches to causation by cigarette smoke, asbestos, and other environmental carcinogens. Nonetheless, we consider that at present it is not possible to apply existing data on Gs/GR for the attribution of lung cancer to asbestos in the individual patient, or to modify existing cumulative exposure approaches to causation, because of: (i) contradictory and inadequate Gs/GR data, even for single gene polymorphisms; (ii) uncertainties surrounding Gs/GR profile effects overall; (iii) inadequate data on net Gs/GR interactivity with asbestos; and, as a consequence, (iv) unquantifiability of any such effects. We also emphasise that these theorisings do not detract from the critical role of the exogenous carcinogens in causation of the disease: in the absence of the carcinogen, it would be less likely that genetic susceptibility (Gs/no-exposure) would be expressed as a particular cancer at the time of occurrence of the cancer, than for a Gs/exposure situation (in other words, the carcinogens produce an increment in risk above ‘background’ Gs).

We emphasise that although ‘traditional’ epidemiology has been highly effective for the detection and quantitation of the net or average causal effects of various carcinogens across populations or groups as reflected in cohort or case-referent studies, it becomes less precise for the quantitation of causal effects when applied to assessment of causation in an individual, because of the following factors among many others:

1. Differential exposures to the carcinogen within the cohort or within the cases group for case-referent studies (unless the exposure estimates are individualised or stratified for different patterns of work and exposure). (See discussion of the study by Carel et al., p. 529.)

2. Changes over time in exposures and smoking habits across the cohort/group unless the parameters of exposure/ smoking are evaluated longitudinally over time.

3. Differential clearance of asbestos fibres from bronchopulmonary tissues, related to differences in the proportions of asbestos fibre types for mixed asbestos exposures and fibre dimensions, and the efficacy of host clearance mechanisms as influenced by a variety of factors that include innate and acquired differences in the capacity for fibre clearance.

4. Differential genetic susceptibility to the carcinogen(s).

In general, these factors will tend to depress unquantifiably the slope of the dose-response line in comparison to the real effects for those who have asbestos-associated lung cancer, and thereby underestimate probability of causation.

EXPOSURE ASSESSMENT: NATIONAL APPROACHES AND FUTURE DIRECTIONS

The cumulative exposure standard of 25 fibre-years or more for lung cancer attribution is also applied in Denmark, and equivalent job histories elsewhere in Scandinavia, with no requirement for asbestos. Occupational histories similar to those delineated by The Helsinki Criteria also form the basis for attribution in France and Belgium. In Australia, the courts have ruled in favour of the cumulative exposure model as a basis for attribution, and similar criteria were also endorsed by the AWARD Workshop.

Because decision-making on compensation now appears to favour The Helsinki Criteria approach, construction of databases such as those described by Burdorf and Swuste or Faserjahre will be essential for equitable compensation of lung cancer due to asbestos, when evidence of quantified exposure must be based on history. The approach in The Netherlands is more qualitative than the German system, with probabilistic assessments of the likelihood of different exposure levels. Without such systems, boards and tribunals will continue to spend inordinate time evaluating uncertainties over past exposures and conflicting opinions from expert witnesses. The aim of databased systems of these types is to create a matrix that defines asbestos exposure by industry, occupation and time. In association with each value, one can then assign 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 can be reached.

In practice, when there are no direct measurements of airborne fibre levels in a particular workplace, as is often the case in nations such as Australia, experts often express estimated cumulative exposure as a low/high range in fibre-years, based on: (i) the number and duration of work shifts which together comprise about 20% of calendar time; and (ii) published low and high values for airborne fibre concentrations generated by the same or similar types of work in other workplaces, and with derivation of a likely mean estimate.

On the basis of prevailing evidence, the cumulative exposure model for lung cancer induction by asbestos appears to conform to modern approaches to assessment of causality, with coherence of data across multiple different types of investigation that include dose-response data from epidemiological studies and case-referent studies based on lung tissue fibre measurements; the evidence also encompasses a variety of pathological observations that include the separate and combined clastogenic and mutagenic effects of asbestos and tobacco smoke on cell lines in vitro and on bronchiolar epithelium in vivo. In terms of generalisability, the cumulative exposure model appears to have explanatory-predictive value: after the 25 fibres/mL-year standard was introduced in Germany—where attribution is primarily an administrative exercise, so that decision-making is less likely to be skewed than by adversarial court-based systems of compensation—the excess lung cancer to mesothelioma ratio has shown close agreement with the same ratio obtained from multiple epidemiological investigations.

Finally, we emphasise that estimates of cumulative exposure (25 fibre-years or an equivalent job history) set forth in The Helsinki Criteria are applicable to amphibole and asbestos textile exposures and, we believe, mixed exposures (notably exposures to asbestos-cement and insulation materials that contained chrysotile and amphiboles).
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Acknowledgements

We are grateful to Dr Per Gustavsson of Stockholm for his comments on the Swedish case-referent analyses,94,164,190 and to Dr XiFeng Wu of the MD Anderson Cancer Center, Houston, USA, for information on myeloperoxidase polymorphism as a risk factor for lung cancer.311,315,322
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