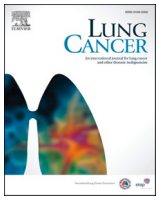
Lung Cancer 195 (2024) 107849

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan



Invited Review

Lung cancer caused by asbestos: What a reporting pathologist needs to know

S. Klebe [a,b,*], Vivek Rathi [c], P.A. Russell [c]

[a] Department of Surgical Pathology, SA Pathology at Flinders Medical Centre, Bedford Park, SA 5042, Australia
[b] Department of Anatomical Pathology, Flinders University, Bedford Park, SA 5042, Australia
[c] LifeStrands Genomics and TissuPath Pathology, Mount Waverley, Victoria, Australia

ARTICLE INFO

Keywords:
Lung cancer
Asbestos
Attribution
Causation
Helsinki criteria

ABSTRACT

Asbestos is a carcinogen that can cause lung cancer. The suspicion that a lung cancer diagnosis may be associated with exposure to asbestos has no bearing on treatment. However, attributing an individual's lung cancer to asbestos exposure has important medicolegal implications and may impact public health measures and policy. Simultaneous exposure(s) to other carcinogens (such as tobacco smoke, silica and many others) adds complexity while trying to answer the causation question. The Helsinki criteria were formulated to assist attributing lung cancer to previous asbestos exposure. Surrogate markers can be used and include signs of asbestosis and pleural plaques. The most widely used criterion for the presence of asbestosis is interstitial fibrosis in conjunction with 2 or more asbestos bodies/1 cm^2 tissue section by light microscopy. Identification of asbestos bodies ty light pr electron microscopy provides an important element for asbestos diagnosis. However, fibrosis may be subtle, and the distribution of asbestos bodies is not uniform throughout the lungs, some types of asbestos fibres have low biopersistence, and not all types of asbestos readily form asbestos bodies. Additional criteria require knowledge of exposure history, which is often unknown to pathologists, but reliance on morphology in isolation may lead to mis-classification of interstitial lung disease as idiopathic. While a smoking-related lung cancer signature has emerged, an asbestos-related lung cancer signature has not yet been identified. In this review we will discuss practice points for the surgical pathologist.

1. Introduction

The recognition of a single or multiple causes of malignancy may have major implications for public health. Causal relations may also provide a basis for financial compensation. Identification of asbestos as the main cause for mesothelioma development has led to a ban of these carcinogenic minerals in many developed countries, and since there is no threshold identified below which asbestos does not induce mesothelioma patients can readily apply for compensation once a pathologist definitively diagnoses mesothelioma. The situation for lung cancer caused by asbestos is more complicated, since the morphology of an asbestos-induced lung cancer (ARLC) is identical to a lung cancer induced by one of many other causes, including smoking. Surrogate criteria are used to support the conclusion that a lung cancer is 'asbestos-related', and statements such as 'no evidence of asbestosis' maybe subject to misinterpretation and lead to inadvertent misclassification of lung disease.

Asbestos is the term used for two groups of naturally occurring minerals, amphiboles (actinolite, amosite, anthophyllite, crocidolite, and tremolite) and serpentines (chrysotile). Chrysotile or white asbestos, is the most widely used form of asbestos, that continues to be mined commercially until today. The International Agency for Research on Cancer (IARC) recognises all forms of asbestos as capable of causing lung cancer [1] but tobacco smoking remains the most dominant causative factor for lung cancer and complicates any judgment about the role of asbestos or other inhalational carcinogens.

Many countries have banned asbestos and its use is noticeably declining in many regions including Western Europe, Australia, Japan and Korea, but in 2016, lung cancer still accounted for 86 % of all occupational deaths, and asbestos was responsible for 63 % of the 349,000 (95 % uncertainty interval 269,000 to 427,000) deaths that were due to occupational carcinogens [2]. There remains a significant and ongoing social and economic burden of ARLC.

There is no demonstrated difference in prognosis or treatment

* Corresponding author at: Department of Surgical Pathology, SA Pathology at Flinders Medical Centre, Bedford Park, SA 5042, Australia.
E-mail address: Sonja.klebe@sa.gov.au (S. Klebe).

https://doi.org/10.1016/j.lungcan.2024.107849
Received 17 October 2023; Received in revised form 4 June 2024; Accepted 6 June 2024
Available online 21 June 2024

response for patients with ARLC, so the implications for an individual case are largely medicolegal, and criteria to determine eligibility for compensation maybe retrospectively applied to a routine pathology report where these factors were never considered. The endemic under-recognition of ARLC has wider implications on public health [3]. The expertise often concentrates with those pathologists who have a dedicated interest, which typically involves some medicolegal work. Publications that define criteria for, say, asbestosis, may have immediate medicolegal impact, which will only be apparent to those with a special interest. Understanding these difficulties and the limitations of the routine pathology assessment performed in isolation is important for any pathologist reporting lung specimens. We here provide some practice points.

2. History

The German literature contains autopsy reports of lung cancer in patients with asbestosis in the mid-1930 s [4–7]. The link between lung cancer and asbestosis was more explicitly recognized in 1938 [8,9], and Wedler stated in 1939 that there was 'no doubt that asbestos was able to cause lung cancer' [8]. As a result, in 1943, lung cancer in association with any degree of asbestosis was designated a compensable disease in Germany [8,10]. This ruling in the midst of WWII might not have attracted much attention of the medical fraternity in rest of the world. Despite animal models of chrysotile-induced lung tumours in mice [11], there was a reluctance by some English and American scientists to acknowledge the link, which remains reflected in compensation schemes [12].

3. The Helsinki criteria

The *Helsinki Criteria* [13,14] and their various modifications [15–17] estimate an increase 0.5–4 % for each fiber per cubic centimeter per year (fiber-years) of cumulative exposure. Using the upper boundary of this range, a cumulative exposure of 25 fiber-years is calculated to double risk of lung cancer, with the RR of 2 arbitrarily regarded as significant. Much lower RRs have been translated into public health measures. As an example, the pooled RR for never-smoking women exposed to passive smoking from spouses for development of lung cancer is 1.27 (95 % CI 1.17–1.37), as assessed in a large *meta*-analysis [18] that includes studies from North America (RR 1.15 (95 % CI 1.03–1.28)), Asia, (RR 1.31 (95 % CI 1.16–1.48)) and Europe (RR 1.31 (1.24–1.52)).

When dealing with a singular causal factor and a rare disease outcome (such as *asbestos-induced mesothelioma*), the 'risk' collapses into a singular event (mesothelioma). As noted earlier, the confounding effects of other (non-asbestos) carcinogens seriously complicate the risk assessment in lung cancer [1] The prevailing evidence indicates that the relationship between cumulative asbestos exposure and lung cancer is governed by a no-threshold linear dose–response model (for an example see Hodgson and Darnton [19]) with some evidence that the gradient of the dose–response line is steeper at low exposures, with some plateauing of the gradient at higher exposures [3,20–22] *with no requirement for asbestosis* [23]. The evidence for such a cumulative exposure model is set forth in some detail in several reviews [3,15,22]. Therefore, a critical review of what defines 'significance' in a particular setting is necessary.

The Helsinki criteria also provide histological indicators that may be used to diagnose ARLC, but they have not been updated for many years and some of the most disputed issues relate to pathology reporting [24–26]. In particular, a reliance on histopathological diagnosis of asbestosis coupled with restrictive criteria for diagnosis of asbestosis is problematic. A lack of recognition and under-representation of asbestos-related cancers has been reported [3].

4. Asbestos bodies and asbestosis

Asbestosis has long been strongly linked to lung cancer, and *whilst asbestosis it not a conditio sine qua* its presence remains a very important factor for attribution while a positive history of asbestos exposure remains paramount [23,27]. By definition, asbestosis represents diffuse, usually lower-zone, pulmonary interstitial fibrosis as a consequence of inhalation of asbestos fibres. However, while the dose–response effect for both asbestos-related cancers and fibrosis is well recognised, there is no proven sequential or obligatory biological linkage between fibrosis and carcinogenesis [3]. Curiously, this is not disputed for other occupational carcinogens, such as silica. The histological criteria for asbestosis have changed over time, and are not universally agreed upon [28–31], but despite this, the Helsinki Criteria are based on the 2010 criteria by Roggli et al. [28]. They seem to be outdated, unsuitable for our time, where most relevant exposures were to chrysotile. According to those criteria, a histological diagnosis of asbestosis requires the identification of diffuse interstitial fibrosis in technically sound lung samples plus the presence of 2 or more asbestos bodies per section area of 1 cm^2 ***or*** a count of uncoated asbestos fibres (by electron microscopy) that falls in the range recorded for asbestosis by the same laboratory. Many lung cancer diagnoses today are made on core or endobronchial biopsies in which there is insufficient non-neoplastic lung tissue present to reliably comment on the presence or absence of asbestosis. Furthermore, fibre counts are variable throughout the lungs, with higher counts found in the lower lobes [32]. Multiple sections may be required and Molle et al. [32] reported that in 12 out of 56 cases asbestosis was demonstrated only after repeated examination of additional sections, conducted after finding more than 1,000 asbestos bodies per gram of dry weight (gdw) indicating occupational asbestos exposure. In these 56 cases, the median fibre concentration was 3,281/gdw. The authors also found 5 additional cases without asbestos bodies on histology, but concentrations higher than this median and interstitial fibrosis. Most routine pathology laboratories do not have access to Electron Microscopy as a means of fibre count, methods for counting are flawed [25], and in the case of chrysotile, this is likely not going to be helpful, due to the low biopersistency [33]. Hammar et al. at the time highlighted many of the issues with that definition of asbestosis (which, amongst others, did not specify how many sections should be searched to arrive at an average per cm^2- should the pathologist search 1 section? 20? 50?) [31], but in the absence of updated definitions pathologists continue to rely on those criteria. The *absence* of asbestos bodies does not exclude a diagnosis of asbestosis. Because of the rapid clearance of chrysotile asbestos fibres from lung tissue, fibre analysis is not appropriate for chrysotile-only asbestos exposure [13] and chrysotile fibres do not readily form asbestos bodies, so that ~ 98 % of asbestos bodies have an amphibole asbestos core. The Helsinki Criteria recognise this possibility of chrysotile-induced asbestosis without increased asbestos body count or increased fibre burden but do not provide guidance on how to diagnose this [27]. Finally, significant numbers of asbestos bodies can occasionally be seen in tissue sections from patients without interstitial fibrosis, and the presence of one or even a few asbestos bodies does not equal a histological diagnosis of asbestosis- but it should be reported since it may help to establish exposure in a patient [34]. Exposure information is rarely available to the reporting pathologist, but if available such information should always be shared.

Clinical diagnostic criteria for asbestosis [35] include a compatible exposure history, along with clinical and radiographic features. Radiologists recognise that it can be very difficult to distinguish idiopathic pulmonary fibrosis from asbestosis, and often erroneously defer to histopathology as definitive test.

The Helsinki criteria indicate that a history of exposure, rather than tissue burden can be used (Histological diagnosis of asbestosis is just *one* potential criterion), and this becomes important for practising pathologists who may not be aware of this. Many a so-called idiopathic pulmonary fibrosis diagnosis may, in fact, be asbestosis, which could not diagnosed as such because exposure information and histology were never linked, and because pathologists have not questioned the validity of the histopathological diagnostic criteria.

Sometimes an autopsy is requested to further evaluate the possibility of ARLC, typically for medicolegal reasons. In those instances, due to the up to 10-fold of variation of the asbestos load among different sites, three samples of 2 cm^3 (preferably peripheral) lung tissue from different anatomic sites have been recommended for an optimal fiber analysis [28], but we prefer a minimum of two paraffin blocks from each lobe, and retain a 1 cm^3 block of fixed (not embedded) tissue from each lobe for fibre analysis since paraffin-embedding can negatively affect the yield [36]. The limitation of this approach with possibility of obtaining misleading results for contemporary patients with chrysotile exposure should be communicated.

A statement in a routine histopathology report such as 'no asbestos bodies identified' may be inappropriately given significance in determining the cause of an individual's lung cancer, and ultimately access to compensation. This would best be qualified by a comment suggesting correlation with exposure history.

Are there other histopathological features that can diagnose ARLC as such? These are questions often asked when a patient with asbestos exposure was a cigarette smoker as well.

5. Histological subtype

Asbestos exposure increases the risk for lung carcinoma of all histological types [37,38], despite a number studies suggesting adenocarcinoma is the most frequent subtype of ARLC [39,40]. When the histological types of lung carcinoma were examined in a case series of workers exposed to asbestos cement dust (n = 29) and matched controls (n = 87), the proportion of adenocarcinomas was 31 % among exposed subjects and 15 % among controls (mid-p = 0005) and the proportion of adenocarcinoma was even higher (45 %, 5/11; mid-p = 0003) among workers with high exposure. A population-based study on the risk of lung cancer by histological category based on incident cancer cases in Denmark also supported the association between adenocarcinoma and asbestos exposure [41], with an RR of 3.31 for adenocarcinoma, and 1.67 for squamous cell carcinoma. To address smoking as a potential confounding factor, former Wittenoom asbestos workers received a smoking-history questionnaire. Between 1979 and 1990, 71 cases of lung cancer occurred among men in this cohort: 27 % had squamous cell carcinoma, 31 % adenocarcinoma, 18 % small cell carcinoma, 11 % large cell carcinoma, and 13 % unclassified or indeterminate. After adjusting for smoking, the authors concluded that squamous cell carcinomas coincided with increasing crocidolite exposure. At the same time increasing crocidolite exposure was also associated with larger numbers of adenocarcinomas [42]. It has been noted that it is difficult to accurately classify and quantify smoking status as a confounding factor [40].

In conclusion, **a particular histological type neither establishes nor excludes ARLC, regardless of smoking status.**

6. Anatomical location

Attempts have also been made to associate tumour location and cause. In the general population, lung cancer originates frequently in the upper lobes and many adenocarcinomas seem to occur in the upper lobes [43]. Workers with asbestosis presented with high numbers of lung cancer in the lower lobes [44]. Data on lobar distribution of lung cancers have also been used to estimate if a lung cancer could be attributed to asbestos exposure. Critical values of the relative risk at which attribution of lung cancer to asbestos equalled its attribution to other causes, mainly smoking, were calculated, and the relative critical risks were compared with standardised mortality ratios reported from cohorts of workers with asbestosis. The ratios ranged from 6.3 to 9.1, and the authors concluded that it was highly improbable that the asbestos-related lung cancer coincided with a specific anatomical (lobar) region [45]. In line with these findings, the Helsinki Criteria indicate that location of the tumour does not determine attributability [27]. **Anatomical location does not determine causation** [38].

7. Plaques

The presence of visceral pleural plaques in a lung cancer surgical resection specimen is unusual since plaques are typically found on the parietal pleura, and should be reported. The association of pleural plaques with the cumulative dose of asbestos and time since first exposure has been demonstrated [46]. Some authors suggest that in the setting of lower zone interstitial disease, the presence of pleural plaques favors a diagnosis of asbestosis [47–49]. Plaques may be best regarded as an indicator of significant exposure to asbestos. However, **a *lack* of plaques does not exclude that a lung cancer was caused by asbestos.**

8. Rounded atelectasis

Rounded atelectasis is mostly a radiological diagnosis but can sometimes be diagnosed in resection specimens [50]. It can result from any type of pleural inflammatory reaction, with asbestos being the most common cause. It should be mentioned when it is encountered in a resection specimen [51,52].

9. Molecular signature of asbestos-related lung cancer

As multiple causal factors for lung cancer have emerged it may be difficult or even impossible to find a unique molecular marker for one typical carcinogen such as asbestos. As Banks et al. noted as early as 1999 a molecular marker may represent an ideal tool to link an individual's lung cancer to asbestos exposure [53]. Since that time the concept of a "mutational signature" has evolved, consisting of a particular combination of mutations caused by DNA replication infidelity, exogenous or endogenous carcinogen exposures, defective DNA repair pathways and enzymatic DNA editing. The identification of mutational signatures has been aided by large-scale analyses which have identified recurrent mutational events in a large range of cancer types [54]. A comprehensive list of mutational signatures is available on the COSMIC website (cancer.sanger.ac.uk/signatures/), with an updated version (version 3.3) available since June 2022. Over time the concept of a "tumour signature" has merged with that of a mutational signature. This is because in some cancer types the pattern of mutations may reflect a particular mutagen, to the extent that it is valid to deduce that exposure to the mutagen must have occurred at some stage in the patient's past. For example, a mutational signature has been identified associated with smoking, and due to mutagens in tobacco [55]. This'smoking signature' has been identified in most of the common lung cancer histological subtypes including adenocarcinoma and squamous cell carcinoma (46,47). Along the same lines, it would be of enormous benefit to conclude to an "asbestos exposure signature". Early work in this area in the late 1990's focused on the presence of codon 12 KRAS mutations in asbestos-related lung cancers (48.49) but may not be specific [56–59]. The selection of lung cancer cases- and the methodology used to separate ARLC from non-ARLC will eventually determine the validity of this work. One study found that lung cancers of never-smokers (defined by less than 100 cigarettes/lifetime) who had been exposed to asbestos had a lower frequency of EGFR mutations than patients who had not been exposed [60].

Identification of the molecular pathways by which asbestos exposure causes invasive mesothelioma may help uncover an asbestos exposure mutational signature. To this end, the genetic landscape of mesothelioma is now being more fully elucidated with several recent studies published in which recurrent alterations in BAP1, CDKN2A, NF2, MTAP, TP53 and SETD2, have been identified, with alterations in these genes occurring with a prevalence of at least 10 % in one study [61,62]. Much more work is needed in this area, but it may well be that a molecular marker or perhaps mutational signature will be uncovered which in the near future to accurately attribute lung cancer to asbestos exposure [62].

10. Discussion & practice points

Morphological assessment in isolation has limited to no utility to diagnose ARLC. Asbestosis is used a as a surrogate for asbestos exposure but has limitations and must be used critically. To be clear, an absence of asbestos bodies does not exclude asbestosis. Absence of fibrosis does not exclude significant exposure to asbestos. Asbestos bodies without fibrosis are a significant finding, since it is not fibrosis that causes the lung cancer [3]. A diagnosis of idiopathic pulmonary fibrosis can only be made if relevant exposures have been excluded.

Routine pathology reporting can affect individuals in their medico-legal pursuits, and impact health policy, as asbestos-related lung cancers and interstitial lung disease alike remain under-recognised. Better definitions are urgently needed to define pulmonary fibrosis – what constitutes idiopathic pulmonary fibrosis, and what significance should be assigned to historical histological criteria for asbestosis when the bulk of asbestos in use today does not readily form asbestos bodies. Whilst pathologists should comment on the presence or absence of fibrosis, asbestos bodies, plaques and round atelectasis they must note the limitations of these assessments which may be used inappropriately to assign or dismiss a causative effect. There is no molecular signature available to date that can clearly identify ARLC however work in this area may hold promise.

Credit authorship contribution statement

S. Klebe: Writing – review & editing, Writing – original draft, Conceptualization. **Vivek Rathi:** Writing – review & editing, Writing – original draft. **P.A. Russell:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: SK provides reports on diagnosis and causation of lung diseases to courts and tribunals of Australia.

Acknowledgement

No funding was received for this work.

References

[1] IARC, A Review of Human Carcinogens: Arsenic, Metals, Fibres, and Dusts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, in: IARC (Ed.) pp. 219-309.
[2] G.B.D.O.C. Collaborators, Global and regional burden of cancer in 2016 arising from occupational exposure to selected carcinogens: a systematic analysis for the Global Burden of Disease Study 2016, Occup. Environ. Med. 77 (3) (2020) 151.
[3] D.W. Henderson, K. Rodelsperger, H.J. Woitowitz, J. Leigh, After Helsinki: a multidisciplinary review of the relationship between asbestos exposure and lung cancer, with emphasis on studies published during 1997–2004, Pathology 36 (6) (2004) 517–550.
[4] K.M. Lynch, W.A. Smith, Pulmonary asbestosis III: Carcinoma of lung in asbesto-silicosis, American Journal of Cancer 24 (1935) 56–64.
[5] S.R. Gloyne, Two cases of squamous carcinoma of the lung occurring in asbestosis, Tubercle 17 (1935–1936) 5–10.
[6] D.S. Egbert, A.J. Geiger, Pulmonary asbestosis and carcinoma. Report of a case with necropsy findings, Am. Rev. Tuberc. 34 (1936) 143–150.
[7] S.R. Gloyne, A case of oat cell carcinoma of the lung occurring in asbestosis, Tubercle 18 (1936–1937) 100–101.
[8] R.N. Proctor, The Nazi War on Cancer, Princeton University Press, Princeton, 1999.
[9] M. Nordmann, Der Berufskrebs der Asbestarbeiter, Z. Krebsforsch. 47 (1938) 288–302.
[10] P.E. Enterline, Changing attitudes and opinions regarding asbestos and cancer 1934–1965, Am. J. Ind. Med. 20 (1991) 685–700.
[11] M. Nordmann, A. Sorge, Lungenkrebs durch Asbestsatub im Tierversuch, Z Krebsforsch 51 (1941) 170.
[12] H. Woitowitz, A.L. Frank, X. Baur, The German experience with asbestos-related diseases: a failure of compensation due to the manipulation of science., JoSPI November 1 (2023).
[13] Multiple authors, Asbestos, asbestosis, and cancer: the Helsinki criteria for diagnosis and attribution, Scand J Work Environ Health 23(4) (1997) 311-6.
[14] P. Oksa, H. Vaino, Asbestos, Asbestosis, and Cancer: Helsinki Criteria for Diagnosis and Attribution 2014, in: F.I.o.O. Health (Ed.) Juvenes Print, Helsinki, 2014.
[15] S. Klebe, J. Leigh, D.W. Henderson, M. Nurminen, Asbestos, smoking and lung cancer: an update, Int. J. Environ. Res. Public Health 17 (1) (2019).
[16] M. authors, Asbestos-Related Diseases: Report by the Industrial Injuries Advisory Council in Accordance with Section 171 of the Social Security Administration Act 1992 Reviewing the Prescription of the Asbestos-Related Diseases, HMSO, London, 2005.
[17] D.E. Banks, R. Shi, J. McLarty, C.T. Cowl, D. Smith, S.M. Tarlo, F. Daroowalla, J. Balmes, M. Baumann, American College of Chest Physicians consensus statement on the respiratory health effects of asbestos, Results of a Delphi Study, Chest 135 (6) (2009) 1619–1627.
[18] R. Taylor, F. Najafi, A. Dobson, Meta-analysis of studies of passive smoking and lung cancer: effects of study type and continent, Int. J. Epidemiol. 36 (5) (2007) 1048–1059.
[19] J.T. Hodgson, A. Darnton, The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure, Ann. Occup. Hyg. 44 (8) (2000) 565–601.
[20] P. Gustavsson, R. Jakobsson, F. Nyberg, G. Pershagen, L. Järup, P. Schéele, Occupational exposure and lung cancer risk: a population-based case-referent study in Sweden, Am. J. Epidemiol. 152 (1) (2000) 32–40.
[21] P. Gustavsson, F. Nyberg, G. Pershagen, P. Scheele, R. Jakobsson, N. Plato, Low-dose exposure to asbestos and lung cancer: dose-response relations and interaction with smoking in a population-based case-referent study in Stockholm, Sweden, Am. J. Epidemiol. 155 (11) (2002) 1016–1022.
[22] D.W. Henderson, J. Leigh, Asbestos and carcinoma of the lung, in: R.F. Dodson, S. P. Hammar (Eds.), Asbestos: Risk Assessment, Epidemiology and Health Effects, 2nd edition, CRC Press/Taylor & Francis, Boca Raton Fl, 2011, pp. 269–306.
[23] D. Egilman, A. Reinert, Lung cancer and asbestos exposure: asbestosis is not necessary, Am. J. Ind. Med. 30 (4) (1996) 398–406 [Review] [55 refs],.
[24] Collegium Ramazzini response to 'Asbestos, asbestosis, and cancer, the Helsinki criteria for diagnosis and attribution 2014: recommendations', Scand. J. Work Environ. Health. 42 (1) (2016) 91–94.
[25] X. Baur, H.J. Woitowitz, L.T. Budnik, D. Egilman, C. Oliver, A. Frank, C. L. Soskolne, P.J. Landrigan, R.A. Lemen, Asbestos, asbestosis, and cancer: The Helsinki criteria for diagnosis and attribution. Critical need for revision of the 2014 update, Am. J. Ind. Med. 60 (5) (2017) 411–421.
[26] P.J. Landrigan, Comments on the 2014 Helsinki Consensus Report on Asbestos, Ann. Glob. Health. 82 (1) (2016) 217–220.
[27] H. Wolff, T. Vehmas, P. Oksa, J. Rantanen, H. Vainio, Asbestos, asbestosis, and cancer, the Helsinki criteria for diagnosis and attribution 2014: recommendations, Scand. J. Work Environ. Health 41 (1) (2015) 5–15.
[28] V.L. Roggli, A.R. Gibbs, R. Attanoos, A. Churg, H. Popper, P. Cagle, B. Corrin, T. J. Franks, F. Galateau-Salle, J. Galvin, P.S. Hasleton, D.W. Henderson, K. Honma, Pathology of asbestosis - an update of the diagnostic criteria, Report of the Asbestosis Committee of the College of American Pathologists and Pulmonary Pathology Society Arch Pathol Lab Med 134 (2010) 462–480.
[29] S.P. Hammar, Asbestosis, in: R.F. Dodson, S.P. Hammar (Eds.), Asbestos: Risk Assessment, Epidemiology, and Health Effects, 2nd editon.,, CRC Press/Taylor & Francis, Noca Raton, Fl, 2011, pp. 447–479.
[30] M. Akira, K. Morinaga, M. Akira, S. Yamamoto, Y. Inoue, M. Sakatani, The comparison of high-resolution computed tomography findings in asbestosis and idiopathic pulmonary fibrosis High-resolution CT of asbestosis and idiopathic pulmonary fibrosis, Am. J. Ind. Med. 59 (4) (2016) 301–306.
[31] S.P. Hammar, J.L. Abraham, Commentary on pathologic diagnosis of asbestosis and critique of the 2010 Asbestosis Committee of the College of American Pathologists (CAP) and Pulmonary Pathology Society's (PPS) update on the diagnostic criteria for pathologic asbestosis Am J Ind Med 58(10) (2015) 1034-9.
[32] F. Mollo, C. Magnani, P. Bo, P. Burlo, M. Cravello, The attribution of lung cancers to asbestos exposure: a pathologic study of 924 unselected cases, Am. J. Clin. Pathol. 117 (1) (2002) 90–95.
[33] X. Baur, A.L. Frank, Ongoing downplaying of the carcinogenicity of chrysotile asbestos by vested interests, J. Occup. Med. Toxicol. 16 (1) (2021) 6.
[34] A. Churg, Asbestos, asbestosis, and lung cancer, Mod. Pathol. 6 (1993) 509–510.
[35] Diagnosis and initial management of nonmalignant diseases related to asbestos, Am J Respir Crit Care Med 170(6) (2004) 691-715.
[36] B.K. Kuhn, F. Barresi, H. Dressel, B. Vrugt, Discrepancies of asbestos body and fiber content between formalin-fixed and corresponding paraffin embedded lung tissue, Inhal. Toxicol. 33 (1) (2021) 18–24.
[37] A. Churg, Neoplastic asbestos-induced disease, in: A. Churg, F.H.Y. Green (Eds.), Pathology of Occupational Lung Disease, 2nd edn, Williams & Wilkins, Baltimore, 1998, pp. 339–391.
[38] L.S. Nielsen, J. Bælum, J. Rasmussen, S. Dahl, K.E. Olsen, M. Albin, N.C. Hansen, D. Sherson, Occupational asbestos exposure and lung cancer–a systematic review of the literature, Arch Environ. Occup. Health 69 (4) (2014) 191–206.
[39] A. Karjalainen, S. Anttila, E. Vanhala, H. Vainio, Asbestos exposure and the risk of lung cancer in a general urban population, Scand. J. Work Environ. Health 20 (1994) 243–250.
[40] O. Auerbach, L. Garfinkel, V.R. Parks, et al., Histologic type of lung cancer and asbestos exposure, Cancer 54 (1984) 3017–3021.
[41] E. Raffn, E. Lynge, B. Korsgaard, Incidence of lung cancer by histological type among asbestos cement workers in Denmark, Br. J. Ind. Med. 50 (1993) 85–89.
[42] N.H.D. Klerk, A.W. Musk, J.L. Eccles, J. Hansen, M.S. Hobbs, Exposure to crocidolite and the incidence of different histological types of lung cancer, Occup. Environ. Med. 53 (3) (1996) 157.

[43] C.M. Kinsey, R.S. Estepar, Y. Zhao, X. Yu, N. Diao, R.S. Heist, J.C. Wain, E.J. Mark, G. Washko, D.C. Christiani, Invasive adenocarcinoma of the lung is associated with the upper lung regions, Lung Cancer 84 (2) (2014) 145–150.
[44] W. Weiss, Lobe of origin in the attribution of lung cancer to asbestos, Br. J. Ind. Med. 45 (8) (1988) 544–547.
[45] W. Weiss, Asbestosis and lobar site of lung cancer. [Review] [26 refs], Occup. Environ. Med. 57 (5) (2000) 358–360.
[46] C. Paris, S. Thierry, P. Brochard, M. Letourneux, E. Schorle, A. Stoufflet, J. Ameille, F. Conso, J.C. Pairon, A.M. National, Pleural plaques and asbestosis: dose- and time-response relationships based on HRCT data, Eur. Respir. J. 34 (1) (2009) 72–79.
[47] T.A. Sporn, V.L. Roggli, Asbestosis, in: T.D. Oury, T.A. Sporn, V.L. Roggli (Eds.), Pathology of Asbestos-Associated Diseases, 3rd edition, Springer, New York, 2014, pp. 53–80.
[48] K.B. Baumgartner, J.M. Samet, D.B. Coultas, C.A. Stidley, W.C. Hunt, T.V. Colby, J. A. Waldron, Occupational and environmental risk factors for idiopathic pulmonary fibrosis: a multicenter case-control study. Collaborating Centers, Am. J. Epidemiol. 152 (4) (2000) 307–315.
[49] M. Gulati, C.A. Redlich, Asbestosis and environmental causes of usual interstitial pneumonia, Curr. Opin. Pulm. Med. 21 (2) (2015) 193–200.
[50] R. Menzies, R. Fraser, Round atelectasis. Pathologic and pathogenetic features, Am. J. Surg. Pathol. 11 (9) (1987) 674–681.
[51] H.D. Roach, G.J. Davies, R. Attanoos, M. Crane, H. Adams, S. Phillips, Asbestos: when the dust settles an imaging review of asbestos-related disease, Radiographics 22 Spec No (2002) S167-84.
[52] A. Thompson, M. Wills, R. House, Rounded atelectasis in an asbestos exposed worker, Occup. Med. (lond) 54 (7) (2004) 494–496.
[53] D.E. Banks, M.L. Wang, J.E. Parker, Asbestos exposure, asbestosis, and lung cancer [editorial; comment], Chest 115 (2) (1999) 320–322.
[54] L.B. Alexandrov, S. Nik-Zainal, D.C. Wedge, P.J. Campbell, M.R. Stratton, Deciphering signatures of mutational processes operative in human cancer, Cell Rep. 3 (1) (2013) 246–259.
[55] L.B. Alexandrov, S. Nik-Zainal, D.C. Wedge, S.A.J.R. Aparicio, S. Behjati, A.V. Biankin, G.R. Bignell, N. Bolli, A. Borg, A.-L. Børresen-Dale, S. Boyault, B. Burkhardt, A.P. Butler, C. Caldas, H.R. Davies, C. Desmedt, R. Eils, J.E. Eyfjörd, J. A. Foekens, M. Greaves, F. Hosoda, B. Hutter, T. Ilicic, S. Imbeaud, M. Imielinski, N. Jäger, D.T.W. Jones, D. Jones, S. Knappskog, M. Kool, S.R. Lakhani, C. López-Otín, S. Martin, N.C. Munshi, H. Nakamura, P.A. Northcott, M. Pajic, E. Papaemmanuil, A. Paradiso, J.V. Pearson, X.S. Puente, K. Raine, M. Ramakrishna, A.L. Richardson, J. Richter, P. Rosenstiel, M. Schlesner, T.N. Schumacher, P.N. Span, J.W. Teague, Y. Totoki, A.N.J. Tutt, R. Valdés-Mas, M.M. van Buuren, L. van 't Veer, A. Vincent-Salomon, N. Waddell, L.R. Yates, J. Zucman-Rossi, P. Andrew Futreal, U. McDermott, P. Lichter, M. Meyerson, S.M. Grimmond, R. Siebert, E. Campo, T. Shibata, S.M. Pfister, P.J. Campbell, M.R. Stratton, I. Australian Pancreatic Cancer Genome, I.B.C. Consortium, I.M.-S. Consortium, I. PedBrain, Signatures of mutational processes in human cancer, Nature 500(7463) (2013) 415-421.
[56] T.K. Hei, L.J. Wu, C.Q. Piao, Malignant transformation of immortalized human bronchial epithelial cells by asbestos fibers, Environ. Health Perspect. 105 (Suppl 5) (1997) 1085–1088.
[57] K. Husgafvel-Pursiainen, A. Karjalainen, A. Kannio, S. Anttila, T. Partanen, A. Ojajarvi, H. Vainio, Lung cancer and past occupational exposure to asbestos. Role of p53 and K-ras mutations, Am. J. Respir. Cell. Mol. Biol. 20 (4) (1999) 667–674.
[58] H. Vainio, K. Husgafvel-Pursiainen, S. Anttila, A. Karjalainen, P. Hackman, T. Partanen, Interaction between smoking and asbestos in human lung adenocarcinoma: role of K-ras mutations, Environ. Health Perspect. 101 (Suppl 3) (1993) 189–192.
[59] K. Husgafvel-Pursiainen, P. Hackman, M. Ridanpaa, S. Anttila, A. Karjalainen, T. Partanen, O. Taikina-Aho, L. Heikkila, H. Vainio, K-ras mutations in human adenocarcinoma of the lung: association with smoking and occupational exposure to asbestos, Int. J. Cancer. 53 (2) (1993) 250–256.
[60] S. Couraud, P.J. Souquet, C. Paris, P. Dò, H. Doubre, E. Pichon, A. Dixmier, I. Monnet, B. Etienne-Mastroianni, M. Vincent, J. Trédaniel, M. Perrichon, P. Foucher, B. Coudert, D. Moro-Sibilot, E. Dansin, S. Labonne, P. Missy, F. Morin, H. Blanché, G. Zalcman, BioCAST/IFCT-1002: epidemiological and molecular features of lung cancer in never-smokers, Eur. Respir. J. 45 (5) (2015) 1403–1414.
[61] M. Pagano, L.G. Ceresoli, P.A. Zucali, G. Pasello, M. Garassino, F. Grosso, M. Tiseo, H. Soto Parra, F. Zanelli, F. Cappuzzo, F. Grossi, F. De Marinis, P. Pedrazzoli, R. Gnoni, C. Bonelli, F. Torricelli, A. Ciarrocchi, N. Normanno, C. Pinto, Mutational Profile of Malignant Pleural Mesothelioma (MPM) in the Phase II RAMES Study, Cancers (basel) 12 (10) (2020).
[62] S. Hiltbrunner, Z. Fleischmann, E.S. Sokol, M. Zoche, E. Felley-Bosco, A. Curioni-Fontecedro, Genomic landscape of pleural and peritoneal mesothelioma tumours, Br. J. Cancer 127 (11) (2022) 1997–2005.