Helsinki Criteria update 2014: asbestos continues to be a challenge for disease prevention and attribution

Aggiornamento dei Criteri di Helsinki 2014: l'amianto continua a essere una sfida per la prevenzione e l'attribuzione delle patologie

Harri Vainio,[1,2] Panu Oksa,[1] Timo Tuomi,[1] Tapio Vehmas,[1,3] Henrik Wolff[1]
[1] Finnish Institute of Occupational Health, Helsinki
[2] College of Public Health, Kuwait University, Kuwait
[3] Clinicum, Helsinki University, Helsinki

Corresponding author: Harri Vainio, harri.vainio@ttl.fi / harri.vainio@hsc.edu.kw

VERSIONE ITALIANA DISPONIBILE ON-LINE
WWW.EPIPREV.IT

INTRODUCTION

Asbestos is in many ways an ideal construction material: tough, light, durable, fire-resistant, and very cheap. Asbestos, once known as the "magic mineral", has been widely used as a constituent in buildings and building materials, machines, transport vehicles, and consumer products. Asbestos has a known historic use going back at least 4,500 years. Asbestos is the collective term for naturally occurring silicate minerals with a crystalline structure and a fibrous character. Total bans on asbestos use have introduced in over 50 Countries, including those in European Union, Japan, Australia, and South-Africa. In spite of bans, the total global use of asbestos lies still at the level of about two million metric tons a year.

Asbestos is highly toxic when inhaled. The contemporary new use of asbestos involves almost exclusively chrysotile ("white") asbestos. However, all the asbestos types, both amphiboles (e.g., crocidolite, amosite) and chrysotile are fibrogenic and carcinogenic to humans. Several factors determine how asbestos exposure affects the exposed individual. The dose is important – how much asbestos fibers an individual has inhaled – and so is the duration, how long the individual worked in the exposing job.

Inhalation of asbestos fibers may cause several serious illnesses, malignant and non-malignant. Currently, about 125 million people in the world are estimated to be exposed to asbestos at work. According to the most recent WHO estimates, more than 107,000 people die each year from asbestos-related lung cancer, mesothelioma, and asbestosis resulting from exposure at work. Approximately half of the deaths from occupational cancer are estimated to be caused by asbestos in Finland.[1,2]

The asbestos epidemic is far from being over. While the use of asbestos has been banned in many industrialized Countries, and production has been stopped in some Countries, the global production and use of asbestos remains at a high level of over two million metric tons a year. Asbestos is still widely used in many newly industrialized, rapidly developing Countries.[3] Exposure to asbestos fibers may also still occur in Countries that have banned the new use of asbestos in, e.g., demolition and asbestos removal activities. The need to create and develop diagnostic procedures for asbestos diseases and to strengthen the knowledge of the attribution of asbestos exposure has been strong for decades now. The Helsinki process, started in 1997, is an important and successful approach to do this in international collaboration.[4] The report of this process summarizes the updates the state-of-the-art-criteria for diagnosis and attribution of asbestos-related diseases. In addition to mesothelioma and lung cancer, asbestos also causes cancers of the larynx and ovaries.[5,6] The updates have been published as a Consensus report entitled *Asbestos, Asbestosis and Cancer, Helsinki Criteria Update 2014*.[7]

HELSINKI CRITERIA DOCUMENTS

The "Asbestos, asbestosis, and cancer" expert meeting was convened in Helsinki in 1997[4,8] and consisted of 19 participants from 8 Countries. This meeting had the goal to «discuss disorders in association with asbestos and to agree upon state-of-the-art criteria for diagnosis and attribution with respect to asbestos». In addition, questions concerning the surveillance of asbestos-exposed workers were discussed. The resulting consensus report was titled *Asbestos, asbestosis, and cancer: the Helsinki Criteria for diagnosis and attribution* (in the current report a shorter name «Helsinki Criteria» or just «Criteria» will be used). A follow-up Expert Meeting

on new advances in radiology and screening of asbestos-related diseases was organized in 2000 in Helsinki.[9,10]
Since 1997, a considerable amount of new knowledge regarding diagnosing and screening of asbestos diseases has accumulated. The Finnish Institute of Occupational Health, therefore, decided to integrate this new data to the Helsinki Criteria. The updating of the Helsinki Criteria was done with the help of 35 international experts over a period of two years, with a final meeting in Espoo, Finland, on 10-13 February 2014.
The Consensus Report *Asbestos, Asbestosis and Cancer: Helsinki Criteria for Diagnosis and Attribution 2014: recommendation (2014)* summarizes the updates. The Helsinki Criteria with the new updates are recommended to be used in programmes and practices for detection, diagnosis and attribution of asbestos-related diseases.
Only a part of the original 1997 Helsinki Criteria recommendations has been affected by the updates. In order to put the updates in perspective, it is helpful to know the original criteria. It is not possible to reiterate here the rather detailed original criteria in its entirety. However, some of the more general considerations are mentioned below.

- «In general, reliable work histories provide the most practical and useful measure of occupational asbestos exposure».
- «Using structured questionnaires and checklists, trained interviewers can identify persons who have a work history compatible with significant asbestos exposure».
- «A cumulative fiber dose expressed as fiber-years per cubic centimetre is an important parameter of asbestos exposure».
- «Analysis of lung tissue for asbestos fibers and asbestos bodies can provide data to supplement the occupational history».

These passages emphasize the importance of work histories in evaluating asbestos exposure. Almost all of the estimated two million tons mined each year is now chrysotile ("white" asbestos) with very little extraction of crocidolite ("blue"), amosite ("brown"), and other types. The evaluation of chrysotile exposure by measuring asbestos fibers and bodies is problematic because of the faster clearance of chrysotile fibers and is therefore not recommended. A multidisciplinary approach is usually needed in diagnosing asbestos-related diseases (ARDs). The detection of diffuse lung fibrosis, pleural thickening or lung cancer do not provide sufficient information about the aetiology of the condition. In diagnosing an ARD we need, as is the case of any occupational disease:

1. knowledge of a disease with prior information on causation to asbestos;
2. knowledge of occupational exposure at work;
3. reliable differential diagnostics.

Hence, the requirement of multidisciplinarity typically including radiologists, pathologists, occupational physicians, and pulmonologists.
The updates of the Helsinki Criteria[11] are described in an abbreviated form in following chapters. The overall view of the 2014 updates is in table 1.

SCREENING FOR ASBESTOS-RELATED LUNG CANCER

The following study designs allow for the simultaneous enrollment of asbestos-exposed workers into a screening programme:

A. offer screening to high-risk workers with asbestos exposure with or without smoking history, if the lung cancer risk is similar to the risk in the NLST study, and compare their outcomes with screened individuals at high risk based only on smoking history;[12]

B. settings that will demand evidence from randomized control trial (RCT) of asbestos exposed workers: conduct national or international pooled RCTs;

C. in settings where LDCT screening is available for asbestos exposed workers: follow standardized protocols for asbestos-exposed workers who meet entry criteria based on asbestos exposure with or without tobacco exposure history (as defined in **A** and monitor process and disease outcomes in comparison with respective RCT data for adults at risk for lung cancer based on smoking history alone.

In each of the examples above, the benefits, harms, and economic issues of LCDT screening should be studied. We recommend the following groups for LDCT screening:

- workers with any asbestos exposure and a smoking history equal to the entry criteria of the NLST study;[12]
- workers with asbestos exposure with or without a smoking history which alone or together would yield an estimated risk level of lung cancer equal to that in the entry criteria of the NLST study.[12]

Much work remains to be done related to risk estimation for lung cancer screening eligibility, especially the interplay between age, smoking history, other exposures to tobacco smoke, other risk factors such as occupational history or genetic predisposition. Evidence may also be gained through modelling of existing materials, especially the NLST material.

FOLLOW-UP OF ASBESTOS EXPOSED WORKERS AND DIAGNOSIS OF NON-MALIGNANT ASBESTOS DISEASES

We still recommend that asbestos exposed workers should be offered a medico-legal surveillance according to national regulations or compensation rules. When possible, these activities should be organized as national programmes and used for research.
A general follow-up schema of asbestos-exposed workers should be stratified according to the intensity, latency, and duration of exposure. Reliable work histories provide the

ITEM	HELSINKI CRITERIA (1997)	UPDATE (2014)
GENERAL CONSIDERATIONS	• Guidelines for identifying asbestos exposed persons with structured interview and fibers from tissue and BAL specimen given. • Guidelines for the diagnostics of asbestosis, pleural disorders, mesothelioma and lung cancer given.	Update concentrates on: • screening screening for asbestos-related lung cancer; • follow-up of asbestos exposed workers and diagnosis of non-malignant asbestos diseases; • new asbestos related disease entities; • pathology and biomarkers
ASBESTOS-RELATED NON-MALIGNANT DISEASES	• Roggli-Pratt modification of the CAP NIOSH classification of asbestosis recommended. • Radiology: small opacities with ILO grade 1/0 in radiographs regarded as early stage asbestosis, HRCT in selected cases. • Development of standardized reporting of HRCT scans recommended.	• New histology classification of asbestosis[14] is adapted • Criteria for the use of CT imaging in the diagnostics of asbestos-related diseases presented. Recommendation to use the international ICOERD CT classification in international studies. • Retroperitoneal fibrosis described as a new entity due to asbestos exposure (under certain conditions).
ASBESTOS-RELATED MALIGNANT DISEASES		
Lung cancer	• 4 types of lung cancer associated with asbestos exposure defined • Cumulative exposure of 25 fiber-years increases the lung cancer risk 2-fold • Risk estimates also related to tissue fiber levels and asbestos bodies in BAL fluid.	• The current classification (WHO 1999) includes 2 additional types of lung cancer (sarcomatoid and adenosquamous). These are included as types of lung malignancies that may occur as a consequence of asbestos exposure.
Mesothelioma	• Histopathological diagnosis discussed	• Additional recommendations for histopathological diagnosis given for epithelioid and sarcomatoid mesotheliomas, separate recommendations for peritoneal mesotheliomas.
Other malignancies	• Discussed as research needs	• Laryngeal and ovarian cancers viewed as asbestos-caused diseases • Guidelines for attribution given
SURVEILLANCE AND SCRRENING	• Possibilities for primary and secondary prevention (screening) discussed. • Scientific studies on screening recommended. • Descritti requisiti tecnici per HRCT (Conferenza di Helsinki del 2000). • Technical requirements for HRCT described • Several research topics suggested.	• Medico-legal surveillance (incl. spirometry) recommended according to the national regulation stratified according to the intensity, latency, and duration of exposure. • Vaccination against influenza and pneumococcus recommended for asbestosis patients. • LDCT screening recommended for asbestos exposed-workers with sufficiently high risk for lung cancer (see text for details). • The importance of obtaining standardized data in an international setting is stressed.

Table 1. Comparison between Helsink Criteria of 1997 and its update 2014.

most practical and useful measure of occupational asbestos exposure. High priority should be given to the high risk groups, including retired workers.

We propose that the follow-up of highly asbestos-exposed workers should be continued for up to 30 years after the cessation of exposure.

We still recommend the use of spirometry together with questionnaires on past or current exposure, and current symptoms as a reference check-up for all asbestos-exposed workers.

For clinical and medico-legal purposes, regular follow-up with spirometry is useful with intervals of 3-5 years, dependent on past exposure level, time since cessation of exposure, and age. Measurements of diffusion capacity might be used at baseline and in patients with documented asbestosis, but not for repeated screening purposes.

We recommend influenza and pneumococcal vaccination to patients with asbestosis.

THE USE OF CT IN DIAGNOSIS OF ASBESTOS-RELATED DISEASES

CT imaging may be useful when:

- a borderline finding of lung fibrosis (ILO 0/1-1/0) is detected;
- there is a discrepancy between lung function finding of restriction and radiographs interpreted as normal;
- widespread pleural changes severely hamper the radiographic visibility of lung parenchyma.

CT imaging should be done by using state-of-the-art multislice scanner technology and high resolution reconstruction algorithms. Exposure to ionizing radiation should be kept as low as possible. For international comparison of studies, we recommend the use of the ICOERD classification.[13]

Fibrosis sufficient for asbestosis with the ICOERD system could represent the sum grade of ≥2-3 bilateral irregular opacities in lower zones or bilateral honeycombing (sum grade ≥2).

NEW ASBESTOS-RELATED DISEASE ENTITIES

Asbestos-related cancers

In the report, the evidence for the attributability to asbestos exposure of laryngeal cancer, ovarian cancer, colorectal cancer, and stomach cancer was evaluated. The legal standard of «more likely than not», equivalent to a relative risk (RR) of 2, has been used in many Countries as a threshold for attribution of causation of disease in individuals by hazardous exposures and was used as a threshold in the 1997 Helsinki Criteria. The Consensus report 2014 recommends that the threshold RR used for individual attribution should be no greater than 2 and can be set at lower levels. To provide flexible guidance for setting threshold levels for individual causation, the consensus report determined the relationship between RR for each reviewed new cancer entity and RR for lung cancer, using data from cohort studies that evaluated RRs for both. The results of the evaluation and, in case the malignancy should be viewed as an asbestos related disease, the RR of lung cancer, at which the malignancy in question would reach an RR of 2, are indicated below.

Laryngeal cancer. The Working Group concluded that laryngeal cancer should be viewed as a disease that can be caused by asbestos.

The relative risk (RR) based on cohort studies for laryngeal cancer was estimated to reach 2 under conditions where the RR for lung cancer in an exposed population was 2.8.

Ovarian cancer. The Working Group concluded that ovarian cancer should be viewed as a disease caused by asbestos. The estimated RR for ovarian cancer would reach 2 under conditions where the RR for lung cancer in an exposed population was about 1.7.

Colorectal cancer. The Working Group considered that colorectal cancer cannot currently be viewed with certainty as a disease caused by asbestos.

Stomach cancer. The Working Group considered that stomach cancer cannot currently be viewed with certainty as a disease caused by asbestos.

Non-malignant asbestos related diseases

In the report, the attributability to asbestos exposure for two non-malignant entities was evaluated.

Ventilatory impairment and Chronic airway obstruction. Restrictive or mixed obstructive/restrictive patterns of ventilatory impairment associated with reduction of FEV1 below the lower limit of normal can be considered asbestos-caused if there has been asbestos exposure and radiographic pleural or parenchymal findings consistent with asbestos exposure are present. Ventilatory impairment of this type in the absence of asbestos-related radiographic changes cannot be viewed as asbestos-caused. Purely obstructive ventilatory impairment associated with reduction of FEV1 below the lower limit of normal cannot be viewed as caused by asbestos.

Retroperitoneal fibrosis. Retroperitoneal fibrosis (RPF) occurring in an individual with asbestos-related pleural and/or parenchymal radiographic findings should be viewed as caused by asbestos. RPF occurring in an individual with evidence of asbestos exposure but without asbestos-related radiologic findings can be viewed as caused by asbestos if other risk factors are not identified. All RPF patients are to be evaluated for a history of asbestos exposure along with other risk factors.

PATHOLOGY AND BIOMARKERS

Lung cancer types attributed to asbestos exposure

The Helsinki Criteria from 1997 mentions four major types of lung cancer that are associated with asbestos exposure (squamous cell, adeno-, large cell, and small cell carcinoma); the current classification from 2004 lists two additional types: sarcomatoid and adenosquamous carcinoma. Any of the six major histological categories mentioned above may be considered to occur as a consequence of asbestos exposure.

Asbestosis: histological criteria

In the original Helsinki Criteria from 1997, the Roggli-Pratt modification of the CAP NIOSH classification for asbestosis was used. A new classification has appeared in 2010. In the new classification, bronchial fibrosis is designated «asbestos airways disease». The updated Helsinki Criteria concerning the attributability of fibrotic conditions of the lungs to asbestos are applicable to both asbestosis as defined by the new classification and «asbestos airways disease». The report also provides guidance to pathologists for the use of asbestos fiber analysis in the differential diagnosis between asbestosis and other types of pulmonary fibrosis.

Biomarkers for the histopathological diagnosis of malignant mesothelioma

The Consensus Report of 2014 provides a detailed recommendation for the use of biomarkers in the histopathological diagnosis of mesothelioma. The Consensus report also notes that clinical correlation with the gross distribution of the tumour is critical for diagnosis of malignant mesothelioma, and that none of the immunohistochemical markers is entirely specific for that diagnosis. The report further notes that are no generally accepted immunohistochemical markers for distinction between benign and malignant mesothelial proliferations.

Biomarkers for screening and early diagnosis of mesothelioma

Some of biomarkers reviewed in the report may be useful in the treatment of malignancies as a follow-up tool and might help in early clinical diagnosis. A major unresolved question

is whether early detection will improve treatment outcome. At this point, no specific recommendations can be made regarding these biomarkers for screening or other purposes.

Markers for attribution to asbestos exposure in lung cancer

The Consensus report notes that the observed asbestos-related molecular alterations in lung cancer are consistent with the ability of asbestos fibers to induce DNA damage and chromosomal abnormalities. It was also noted that in one report a combination of three chromosomal abnormalities (2p16, 9p33.1, and 19p13) gave a clear dose response between pulmonary fiber count and either allelic imbalance or copy number alteration or both in at least two of the regions, with a very high specificity when the three regions were combined. Additional international multicentre studies with standardized methodology for molecular assays and exposure assessment are considered necessary before these biomarkers can be applied to support causal attribution in individual cases.

CONCLUSION

If we have learnt anything from the past, it is that the impact of hazardous asbestos exposures continually exceed predictions. As mentioned in the beginning of the text, most of the original criteria remain unchanged, there is a constant accumulation of new asbestos associated research, and it seems evident that regular update of the criteria are needed in future.

Conflict of interest: the author declares no conflict of interest.

REFERENCES

1. Santonen T, Oksa P (eds). *Memorandum from the Occupational Cancer Working Group*. Helsinki, Finnish Institute of Occupational Health, 2013. Available at: http://www.ttl.fi/en/publications/Electronic_publications/Documents/Memorandum_Cancer_2013.pdf
2. Finnish Institute of Occupational Health. Prevention and Management of Asbestos- Related Diseases in Finland. Helsinki 2014. Available at: http://www.ttl.fi/en/publications/Electronic_publications/Documents/Asbestos.pdf
3. Kameda T, Takahashi K, Kim R et al. Asbestos: use, bans and disease burden in Europe. *Bull World Health Organ* 2014;92(11):790-7. Available at: http://www.who.int/bulletin/volumes/92/11/13-132118.pdf
4. Asbestos, asbestosis, and cancer: the Helsinki criteria for diagnosis and attribution. Consensus Report. *Scand J Work Environ Health* 1997;23(4):311-6.
5. IARC (International Agency for Research on Cancer). *Arsenic, metals, fibres, and dusts*. Volume 100C, A Review on human carcinogens. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. 2012; vol 100C. Lyon, IARC, 2012. Available at: http://monographs.iarc.fr/ENG/Monographs/vol100C/mono100C.pdf
6. FIOH (Finnish Institute of Occupational Health) and IARC (International Agency for Research on Cancer). *The Helsinki Declaration on Management and Elimination of Asbestos-Related Disesases*. 2014. Available at: ttp://www.ttl.fi/en/international/conferences/helsinki_asbestos_2014/Documents/20%20March%202014%20Final%20Signed%20Declaration%20for%20website.pdf
7. Wolff H, Vehmas T, Oksa P, Rantanen J, Vainio H. Asbestos, asbestosis, and cancer, the Helsinki criteria for diagnosis and attribution 2014: recommendations. *Scand J Work Environ Health* 2015;41(1):5-15.
8. Tossavainen A, Huuskonen MS, Rantanen J, Lehtinen S (eds). Asbestos, asbestosis, and cancer. Proceedings of the International Expert Group Meeting, Helsinki FIOH. *People and Work,* Research Reports No. 14, 1997.
9. Tossavainen A. International expert meeting on new advances in the radiology and screening of asbestos-related diseases. *Scand J Work Environ Health* 2000;26(5):449-54.
10. Tossavainen A, Lehtinen S, Huuskonen MS, Rantanen J (eds). New advances in radiology and screening of asbestos-related diseases. Proceedings of the International Expert Meeting, FIOH, Helsinki 2000. *People and Work*, Research Reports No. 36, 2000.
11. Oksa P, Wolff H, Vehmas T, Pallasaho P, Frilander H. *Asbestos, Asbestosis and Cancer. Helsinki Criteria for Diagnosis and Attribution 2014*. Helsinki, Finnish institute of Occupational Health, 2014. Available at: http://www.ttl.fi/en/publications/Electronic_publications/Documents/Asbestos_web.pdf
12. National Lung Screening Trial Research Team, Aberle DR, Adams AM et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365(5):395-409.
13. Suganuma N, Kusaka Y, Hering KG et al. Reliability of the proposed international classification of high-resolution computed tomography for occupational and environmental respiratory diseases. *J Occup Health* 2009;51(3):210-22. Available at: http://dx.doi.org/10.1539/ joh.L8030
14. Roggli VL, Gibbs AR, Attanoos R et al. 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* 2010;134(3):462-80.