

Asbestos, Asbestosis, and Cancer

Helsinki Criteria for Diagnosis and Attribution 2014

Finnish Institute of Occupational Health
Helsinki 2014

Finnish Institute of Occupational Health
Topeliuksenkatu 41 a A
00250 Helsinki
www.ttl.fi

Editors: Panu Oksa, Henrik Wolff, Tapio Vehmas, Paula Pallasaho and Heikki Frilander
Technical editors: Kaisa Into and Alice Lehtinen
Design: Arja Tarvainen/Tuula Solasaari

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PREFACE

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. Asbestos is still widely used in many newly industrialized, rapidly developing countries. Exposure to asbestos fibres (fibers) may also still occur in countries that have banned the new use of asbestos in, e.g., demolition and asbestos removal activities. According to the most recent WHO estimate, more than 107 000 people die each year from asbestos-related lung cancer, mesothelioma and asbestosis resulting from exposure at work (1).

The first 'Asbestos, asbestosis, and cancer' symposium convened in Helsinki in 1997 and included 19 participants from eight countries. The purpose of the meeting was to "discuss disorders in association with asbestos and to agree upon state-of-the-art criteria for diagnosis and attribution with respect to asbestos (2, 3), in addition to questions concerning the surveillance of asbestos-exposed workers." The resulting document was named the Helsinki Criteria. A follow-up Expert Meeting on new advances in radiology and the screening of asbestos-related diseases was held in 2000 in Helsinki (4, 5).

Since 1997, a considerable amount of new knowledge regarding the diagnosis and screening of asbestos diseases has been accumulated. The Finnish Institute of Occupational Health therefore decided to integrate this new data into the Helsinki Criteria. The updating of the Helsinki Criteria was carried out with the help of international experts over a period of two years, with a final meeting in Espoo, Finland, on 10–13 February 2014. The conference was organized by the Finnish Institute of Occupational Health in collaboration with the International Commission on Occupational Health, ICOH.

The Consensus Report *Asbestos, Asbestosis, and Cancer: Helsinki Criteria update 2014* (6) summarizes up-to-date information on methods for the management and elimination of asbestos-related diseases. We recommend using the updates in programs and practices for the detection, diagnosis and attribution of asbestos-related diseases.

We wish to most cordially thank all the international and national experts for their important work, Ms. Solveig Borg for her technical assistance, the sponsors, The Finnish Work Environment Fund, the Federation of Finnish Learned Societies, the Federation of Accident Insurance Institutions, and the Finnish Cancer Society for their financial support.

Helsinki June 30th 2014

Harri Vainio and Panu Oksa

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UPDATING THE HELSINKI CRITERIA

The Finnish Institute of Occupational Health (FIOH) was contacted in 2011 about updating the Helsinki Criteria by incorporating new research findings and accommodating the changes in medical practices and classifications that had occurred during recent years.

To evaluate the need for this, we sent a questionnaire to selected international contacts. In the questionnaire, we inquired about various aspects of the Criteria, about policies regarding the surveillance of asbestos-exposed workers, and the opinion regarding the need for and focus on updates in the Criteria.

The answers indicated a considerable variation of opinions, although some general trends could be seen. The questionnaires, the possible updates and the question of the desirability of an updating process were discussed at an initial meeting of international experts and FIOH staff on December 2nd, 2011. As a result, preparations for a new meeting began.

The following subject areas were selected for updating:

1. CT screening for asbestos-related lung cancer
2. Diagnostics and follow-up of asbestos-related diseases
3. New asbestos-related disease entities
4. Pathology and biomarkers.

Subject area 1 is in response to recent research results suggesting that screening for lung cancer with CT may prevent cancer deaths.

Subject Area 2 is mostly a response to our findings from the questionnaires, i.e. that the follow-up of asbestos-related diseases differ substantially.

Subject Area 3 was inspired by the recent IARC review in which the classifications of some asbestos-related malignancies were upgraded.

Subject Area 4 was included because some classification pathology used in the old Criteria is now obsolete. In addition, there was an interest in staying abreast of the developments in biomarkers for asbestos-related diseases.

Most subject areas are additions to the old Criteria. Most of the original Criteria remain unchanged. In its concept, this updating process is rather similar to the meeting in 2000. The selection of subject areas has thus been driven by the perceived need for updates, and this process is not a systematic re-evaluation of the criteria in its entirety.

For each area, a working group was assembled, with a chairman, one or two rapporteurs (members of FIOH staff with special expertise) and three to five members.

In the fall of 2012, it was decided that the updating process would be associated with an asbestos-related conference, the International Conference on Asbestos Monitoring and Health Surveillance in Individuals (Helsinki Asbestos 2014) on 11–13 February 2014 in Hanasaari Cultural Centre, Espoo, Finland. This provided an opportunity to hear views from a wider group of experts. The conference was organized by the Finnish Institute of Occupational Health in collaboration with the International Commission on Occupational Health, ICOH.

Each working group created an evidence-based review. The working groups first formulated two preliminary drafts, which were circulated among the entire HCU group for comments and then revised. Based on this review, a set of recommendations for each subject area was formulated. The recommendations were then processed at the HCU group pre-conference meeting and the ensuing versions of the drafts were discussed at the workshops of the conference. The modified drafts were presented and discussed in a plenary session on the last conference day.

Much of the original Criteria remain unchanged. In specific issues, some additions were made to the old Criteria by the Helsinki Criteria Update 2014 group. Table 1 summarizes the key points of the 1997 Helsinki criteria and its 2014 updates.

Table 1. Comparison of Helsinki Criteria 1997 and its 2014 update.

Item	Helsinki criteria 1997	2014 update
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 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 of 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 (2) 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	<ul style="list-style-type: none"> <li data-bbox="165 997 311 1028">• Lung cancer <li data-bbox="165 1232 336 1263">• Mesothelioma <li data-bbox="165 1467 384 1498">• Other malignancies 	<p data-bbox="816 997 1329 1150">Four types of lung cancer associated with asbestos exposure defined. Cumulative exposure of 25 fiber-years increases lung cancer risk two-fold. Risk estimates also related to tissue fiber levels and asbestos bodies in BAL fluid.</p> <p data-bbox="816 1232 1329 1293">Histopathological diagnosis discussed</p> <p data-bbox="816 1467 1329 1498">Discussed as research needs</p> <p data-bbox="816 997 1329 1150">The current classification (WHO 1999) includes two 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.</p> <p data-bbox="816 1171 1329 1293">Additional recommendations for histopathological diagnosis given for epithelioid and sarcomatoid mesotheliomas, separate recommendations for peritoneal mesotheliomas.</p> <p data-bbox="816 1344 1329 1436">Laryngeal and ovarian cancers viewed as asbestos-caused diseases. Guidelines for attribution given.</p>
Surveillance and screening	Possibilities for primary and secondary prevention (screening) discussed. Scientific studies on screening recommended. Technical requirements for HRCT described (Helsinki conference in 2000). 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 of lung cancer (see text for details). The importance of obtaining standardized data in an international setting is stressed.

PARTICIPANTS OF THE HELSINKI CRITERIA UPDATE 2014

Harri Vainio*, Finnish Institute of Occupational Health, Finland, *Chairman, HCU 2014*
Panu Oksa*, Finnish Institute of Occupational Health, Finland, *Vice Chairman, HCU 2014, Rapporteur Area 2*
Sisko Anttila*, HUSLAB, Finland
Murray Finkelstein, Canada
Heikki Frilander*, Finnish Institute of Occupational Health, Finland, *Rapporteur Area 2*
Per Gustavsson, Karolinska Institutet, Sweden
Gunnar Hillerdal*, Karolinska University hospital, Sweden
Sergio Iavicoli*, INAIL, Italy
Kouki Inai*, Institute of Support Center of Remote Medicine, Japan
Agnes Kane*, Brown University, USA
Seong-Kyu Kang, Korea Occupational Safety and Health Agency, Republic of Korea
Takumi Kishimoto*, Okayama Rosai Hospital, Japan
Helge Kjuus*, National Institute of Occupational Health, Norway, *Chairman, Area 2*
Thomas Kraus*, Aachen University, Germany
Yukinori Kusaka*, University of Fukui School of Medicine, Japan
Sverre Langård, Oslo University Hospital Ullevål, Norway
Nea Malila*, Finnish Cancer Register, Finland
Steven Markowitz*, City University of New York, USA
Anthony B. Miller*, Canada
Aubrey Miller*, National Institute of Environmental Health Sciences, USA
Paula Pallasaho*, Finnish Institute of Occupational Health, Finland, *Rapporteur Area 3*
John Parker, West Virginia University, USA
Jorma Rantanen*, Finland
Victor L. Roggli*, Duke University Medical Center, USA, *Chairman, Area 4*
Lesley Rushton, Imperial College London, GB
Riitta Sauni*, Ministry of Social Affairs and Health, Finland, *Rapporteur Area 1*
Robert A. Smith*, American Cancer Society, USA, *Chairman, Area 1*
Leslie Stayner, University of Illinois at Chicago, USA
Kurt Straif*, International Agency for Research on Cancer (IARC),
France Ken Takahashi*, University of Occupational & Environmental Health, Japan
Timo Tuomi*, Finnish Institute of Occupational Health, Finland
Axel Wannag*, Arbeidstilsynet (Dammen), Norway
Tapio Vehmas*, Finnish Institute of Occupational Health, Finland, *Rapporteur Area 1*
David N. Weissman*, National Institute for Occupational Safety and Health, USA, *Chairman, Area 3*
Henrik Wolff*, Finnish Institute of Occupational Health, Finland, *Rapporteur Area 3 and 4*

**Present at update meeting in Helsinki 10–13 February 2014*

1

Screening for asbestos-related lung cancer

Tapio Vehmas, *Finnish Institute of Occupational Health, Finland*

Riitta Sauni, *Ministry of Social Affairs and Health, Finland*

Anthony B. Miller, *Dalla Lana School of Public Health, University of Toronto, Canada*

Kurt Straif, *International Agency for Research on Cancer (IARC), France*

Nea Malila, *Finnish Cancer Register, Finland*

Robert A. Smith, *Cancer Control Department, American Cancer Society, Atlanta, GA, USA*

Objectives: Review the existing literature on the efficacy of lung cancer screening with low-dose computed tomography (LDCT) in asbestos-exposed workers in order to update the 1997 and 2000 Helsinki Criteria during the International Conference of Monitoring and Surveillance of Asbestos-Related Diseases, 10–13 February, Espoo, Finland

Methods: Two separate literature searches were conducted; the first focused on the evidence related to the effects of LDCT screening on lung cancer, and the second focused on original studies on screening for lung cancer in asbestos-exposed workers.

Results: Three recent systematic reviews of screening for lung cancer with LDCT conclude that screening is associated with a reduced risk of lung cancer mortality, and that benefits outweigh harms. There is no evidence of benefit from screening with chest x-ray. Twelve studies of LDCT screening for lung cancer in asbestos-exposed workers principally were case series with a limited number of subjects, no control groups and little follow-up data on mortality, providing only weak if any inferential evidence about the efficacy of lung cancer screening specifically targeted to adults with a history of asbestos exposure.

Conclusions: Adults with a history of exposure to asbestos who meet absolute lung risk criteria set by randomized trials and existing lung cancer screening guidelines should be offered screening. Study designs that allow for simultaneous enrollment of asbestos-exposed workers into a screening program while also collecting minimum but essential data are a high priority as are international data pooling projects.

Introduction

Lung cancer is one of the most common and fatal cancers worldwide. While long-term exposure to tobacco smoke is the underlying cause of most lung cancer, lung cancer accounts for more than half of all occupational cancers, and it is estimated that between 5% and 7% of newly diagnosed cases are attributable to exposure to asbestos, which is by far the single most important occupational carcinogen. A greater than additive effect modification describes the association between asbestos and cigarette smoke in causing lung cancer (1, 2). The World Health Organization estimates 107 000 people die each year from occupational exposure to asbestos, and more than 125 million still are exposed to asbestos in the workplace (3).

Lung cancer is most often diagnosed at an advanced stage, which makes the prognosis poor. Despite observations of more favorable survival when lung cancer was diagnosed at an early stage, early randomized controlled trials (RCT) of lung cancer screening with chest X-rays (CXR) failed to demonstrate that screening reduced lung cancer mortality (4). The considerable methodological limitations of the CXR RCTs conducted in the 1970s were among the reasons that CXR screening was included in the Prostate Lung Colorectal and Ovarian Cancer Screening Trial (PLCO), which enrolled adults during 1993–2001 (5). Still, in the PLCO, the risk ratio for lung cancer mortality among average risk adults invited to receive four rounds of CXR screening was 0.99 (0.81-1.10) compared with the control group, again providing no evidence of a benefit from screening for lung cancer with CXR (6). A recent update of the Cochrane Collaboration review of lung screening concluded there was no evidence to justify screening with CXR or sputum cytology (7).

Interest in screening for lung cancer with low dose computed tomography (LDCT) began to increase during the mid-late 1990s, especially following the baseline results of the Early Lung Cancer Action Project (ELCAP), which demonstrated substantially better performance in the detection of small, favorable stage lung cancers with LDCT compared with CXR (8). Given the significantly better prognosis associated with the detection of lung cancers early in their natural history, and the superior performance of LDCT compared with CXR, the accumulation of favorable observational evidence led to the initiation of RCTs in the U.S. and Europe. The largest RCT of LDCT screening conducted to date is the National Lung Screening Trial (NLST) (9), which recruited a high risk group of men and women who were current or former smokers (quit \leq 15 years) ages 55–74 who had at least a 30 pack-year smoking history. The NLST randomized approximately 57 000 study subjects to a LDCT arm vs. CXR arm for three rounds of annual screening.

At a median of 6.5 years of follow-up, there was a 20% reduction in lung cancer mortality in the LDCT arm compared to the CXR arm (95% CI 6.8%–26.7%) (9). Further, there also was a significant reduction in mortality from all causes of 6.7%, of which deaths from lung cancer accounted for about half of the difference. RCTs also have been conducted or still are underway in Europe. When the three good- or fair-quality trials (1 U.S. trial & 2 European trials) were combined in a random effects meta-analysis, the relative risk of lung cancer mortality was 0.81 (95% CI, 0.72–0.91) (10).

While the new data on LDCT screening of smokers is promising, there is a need to clarify whether the same principles of LDCT screening could be applied to other groups at high risk for lung cancer, and in this context, specifically those with prior exposure to asbestos. This paper includes a systematic review on CT screening for asbestos-related lung cancer. It also reviews the current knowledge on lung cancer screening based on previous and recent systematic reviews, compares lung cancer risk-estimation calculators that include asbestos exposure, and provides background data for recommendations accepted at the International Conference on Monitoring and Surveillance of Asbestos-Related Diseases at Hanasaari, Espoo, Finland in February 2014.

Methods

Two separate literature searches were conducted. First, we searched for evidence on the effects of lung cancer screening with LDCT from systematic reviews (SR) and second, we searched for original studies on screening for lung cancer in asbestos-exposed workers.

PubMed database was searched for SRs on lung cancer screening between November 1, 2010 and March 7, 2014 using the following terms: “lung neoplasms”[Mesh] AND screening* [tw] AND “Tomography”[Mesh] OR tomograph*[tw] OR CT[tw] OR LDCT[tw] AND systematic review [tw] or evidence review [tw]. The Cochrane database also was searched using the term “lung cancer screening.” Other criteria included English language, inclusion of both CXR and LDCT studies, and reviews that met Institute of Medicine criteria (11). A total of 67 articles were identified, and three recent SRs met the inclusion criteria (7, 10, 12).

In order to retrieve papers on CT screening for lung cancer among asbestos-exposed workers, PubMed database was searched until Mar 3, 2014 using terms “Tomography”[Mesh] OR tomograph*[tw] OR CT[tw] OR LDCT[tw] OR CECT[tw] AND asbest* AND (“Lung Neoplasms”[Mesh] OR “lung cancer”[tw]). This search strategy yielded 158 articles. Original papers in English language describing primary lung cancer screening studies, whether case series or comparative studies, were accepted.

Review articles and case reports were excluded. Articles were first evaluated by title, then by abstract and if not clear whether to include or not, by full text. The evaluation was carried out by two reviewers (RS and TV) in consensus. Twelve papers fulfilling the inclusion criteria were accepted.

Results

Three recent SRs of lung cancer screening that included LDCT studies and the recent U.S. NLST were identified. Two of the SRs were updates of prior SRs of lung cancer screening conducted for the Cochrane Collaboration (13) and the United States Preventive Services Task Force (USPSTF),(14), while the third was conducted principally by the American Society of Clinical Oncology (ASCO) for a consortium of U.S. organizations preparing to issue lung cancer screening guidelines (12). The description of SRs is given in Table 1. One SR focused exclusively on RCTs of LDCT screening in adults at high risk of lung cancer due to smoking history (12), while the other SRs included RCTs and cohort studies of imaging exams (LDCT and CXR) as well as sputum cytology in average risk adults and adults at high risk based on smoking history (7, 10). None of the SRs addressed asbestos exposure as a risk factor for lung cancer, or screening outcomes in the context of asbestos exposure. The primary outcome in each SR was lung cancer specific mortality, although two SRs also included all-cause mortality (10, 12). The SRs also focused on secondary outcomes including cancer detection rate (CDR), nodule detection rate (NDR), recall rate, stage at diagnosis, survival, harms of screening (interval imaging, invasive procedures, complications, post-operative deaths, incidental findings), costs, quality of life, and the effect of screening on smoking cessation.

Table 1: Systematic Reviews of Lung Cancer Screening with LDCT

Comparison	Systematic Reviews of Lung Cancer Screening		
	ACS, ACCP, ASCO, NCCN (2012) ¹²	Cochrane (2013) ⁷	USPSTF (2013) ¹⁰
Update of previous review?	No	Yes (1999, 2004, ¹³ 2010 ⁷)	Yes (2004 ¹⁴)
Literature period	1996–4/2012	1996–5/2012	2000–2012
Literature sources	Ovid, EMBASE, Cochrane, reference lists; published data only.	EMBASE, MEDLINE, PREMEDLINE, Cochrane, Lung Cancer (up to 2000); Contact with experts to identify other data sources	MEDLINE, Cochrane, Scopus, reference lists
Target population	Individuals at elevated risk of developing lung cancer because of age and smoking history	Not specified	Asymptomatic men and women at average risk or current and former smokers at high risk
Intervention(s)	LDCT screening	Alone or in combination--CXR, CT, sputum examinations	Alone or in combination--LDCT, CXR, sputum cytology
Target audience for the review	Physicians, allied professionals, and policy makers.	Not specified	Not specified
Inclusion criteria	RCTs and cohort studies of LDCT screening for lung cancer (English only)	RCTs of screening for lung cancer using sputum examinations, chest radiography or chest CT	RCTs and cohort studies that evaluated screening or treatment interventions for lung cancer and reported health outcome (English only)
Exclusion criteria	Studies that only assessed screening among participants with risk factors other than smoking (eg, asbestos), meta-analysis or case series reports of outcomes only among patients diagnosed with lung cancer	Non-controlled trials, Studies, trials without disease specific mortality as an outcome, and trials with < 5 years follow-up.	By Key Question: children, symptomatic, prior lung cancer, no screening, cost effectiveness, editorials, case reports, studies without comparison group, sample sizes < 1000, or < 500, < 5 years of follow-up
Asbestos addressed	No	Some literature evident, but no focus on asbestos exposure	Described as a risk factor, and evident in excluded literature
Primary outcome	Lung cancer mortality All-cause mortality	Lung cancer mortality	Lung cancer mortality All-cause mortality Lung cancer incidence
Other outcomes	Nodule detection rate; Frequency of additional imaging; Frequency of invasive diagnostic procedures (e.g., needle or bronchoscopic biopsy, surgical biopsy, surgical resection); Complications from the evaluation of suspected lung cancer; Rate of smoking cessation or re-initiation.	Compliance with screening and follow up; Incidence of lung cancer; Five-year survival; Stage at diagnosis; Resection rate; Postoperative deaths; Harms of screening, including adverse outcomes from further diagnostic testing in those who have a positive result on initial screening; Costs; Quality of life	Reduction in lung cancer morbidity; five-year and ten-year survival rates; Impact on smoking cessation; Detection of other abnormalities; Quality of life; Direct harms from screening and/or treatment interventions

Table 1: Systematic Reviews of Lung Cancer Screening with LDCT

Comparison	Systematic Reviews of Lung Cancer Screening		
	ACS, ACCP, ASCO, NCCN (2012) ¹²	Cochrane (2013) ⁷	USPSTF (2013) ¹⁰
CONCLUSIONS—BENEFITS & HARMS			
Disease specific mortality	“Low-dose computed tomography screening may benefit individuals at an increased risk for lung cancer, but uncertainty exists about the potential harms of screening and the generalizability of results.”	“Annual low-dose CT screening is associated with a reduction in lung cancer mortality in high-risk smokers but further data are required on the cost effectiveness of screening and the relative harms and benefits of screening across a range of different risk groups and settings.”	“Strong evidence shows that LDCT screening can reduce lung cancer and all-cause mortality.”
Cost effectiveness	Cost-effectiveness of LDCT screening for lung cancer was not addressed in any of the systematic reviews		
False positives	The review notes that the rate of harms associated with LDCT is high, although considerable variation was observed within and between study designs. The review notes that false positive rates based on nodule categorization or screening protocols often are inconsistent—sometimes unclear if FP rates are based on newly identified nodules, or are assigned to the current round or to an earlier round if they can be seen retrospectively. Also, size thresholds for workup vary and are inconsistently reported, as are the potential denominators for estimating false-positive rates, such as per screening round or per person-year.	The review notes that the rate of false positive examinations associated with LDCT screening is high.	Range from 9.2% to 51%; (PPV ranging from 2.2% to 36%); Most FP resolved with additional imaging.
Biopsy	Rates described	The biopsy rate associated with positive findings is relatively low	Rates described, along with PPV. The majority of biopsies performed were for cancer, not benign disease, with positive predictive values for invasive procedures or biopsy ranging from 50 to 92 percent.
Harms due to interventions, including death	Described as low. The review notes that the only study describing complications from LDCT screening was the NLST	Described, but conclusion is that benefits likely exceed harms	Clear description of the balance of benefits and harms, concludes that benefits outweigh harms
Radiation risk	Addressed, noting that benefit of screening exceeds possible incidence/mortality association with radiation exposure	Described in discussion in context of follow-up for positive findings, relies on Brenner’s estimates from 2004	Described in the discussion as a theoretical harm
Incidental findings	Not noted	Not noted	Noted as a harm, most commonly reported findings were emphysema and coronary artery calcifications

Table 1: Systematic Reviews of Lung Cancer Screening with LDCT

Comparison	Systematic Reviews of Lung Cancer Screening		
	ACS, ACCP, ASCO, NCCN (2012) ¹²	Cochrane (2013) ⁷	USPSTF (2013) ¹⁰
Anxiety	Uncertain	Not assessed	Individuals with positive or indeterminate exams showed some short-term increases in anxiety and distress, but not long-term; patients with negative scans had a reduction in distress.
Smoking behavior	Insufficient evidence to conclude that screening contributes to higher quit rates	Insufficient evidence from literature to assess the impact of screening on smoking behavior	Individuals with positive or indeterminate screens showed a trend toward reduced smoking or sustained abstinence
Quality of life	The effect of LDCT on quality of life is uncertain	None of the studies included in the review assessed the impact of screening on quality of life.	Overall, LDCT screening did not appear to significantly impact overall health-related quality of life
Overdiagnosis	<p>The overdiagnosis rate for LDCT screening cannot yet be estimated; NLST data show a persistent gap of about 120 excess lung cancers in the LDCT group vs. the chest radiographs group, but further follow-up is needed.</p> <p>Note...inappropriate to conclude that the gap is persistent, since this would imply that the entirety of the overdiagnosis was attributable to the prevalent screen.</p>	Acknowledges possibility of overdiagnosis. Counsels against drawing conclusions from Mayo. Notes excess incidence in NLST 5 years after cessation of screening (119 cases), and further notes the excess number of BACs (adenocarcinoma in situ) in the CT arm (95 vs. 13), speculating that excess incidence may be mostly attributable to BAC lesions, which have very good survival, but also longer lead time. Also concludes NLST is not a good source of overdiagnosis estimates due to inclusion of CXR arm.	Magnitude is uncertain.
MAIN CONCLUSIONS	LDCT screening may benefit individuals at an increased risk for lung cancer, but uncertainty exists about the potential harms of screening and the generalizability of results.	<p>Conclusions from previous systematic reviews altered by new data from NLST and PLCO. Annual LDCT is associated with a reduction in lung cancer death in high risk smokers and former smokers.</p> <p>Further data are required on the cost effectiveness of screening, and the relative harms and benefits of screening across a range of different risk groups and settings.</p>	Good evidence shows LDCT can significantly reduce mortality from lung cancer. However, there are significant harms associated with screening that must be balanced with the benefits.

Abbreviations: ACS, American Cancer Society; ACCP, American College of Chest Physicians; ASCO, American Society of Clinical Oncology; NCCN, National Comprehensive Cancer Network; USPSTF, United States Preventive Services Task Force; LDCT, low dose computed tomography; CXR, chest x-ray; NLST, National Lung Screening Trial; PLCO, Prostate, Lung, Colorectal, and Ovarian Trial

The SRs all resulted in the conclusion that an invitation to annual lung cancer screening with LDCT in adults at high risk for lung cancer was associated with a reduction in lung cancer mortality (7, 10, 12), and all-cause mortality (10, 12). The SRs that assessed the benefit of an invitation to CXR or sputum cytology found no evidence of benefit of either test (7, 10). The SRs also noted that the rate of harms associated with lung cancer screening with LDCT was high, although the predominant harm was being recalled for further evaluation and short-term follow-up, and most abnormal findings were resolved with additional imaging. By comparison, false positive biopsy rates were fairly low, and positive predictive values associated with biopsy were high (10). While the SRs noted other harms (radiation exposure, incidental findings, anxiety associated with false positives, overdiagnosis), none were judged to alter the favorable balance of benefits to harms. Perhaps the harm that is the greatest concern is that screening for lung cancer with LDCT results in overdiagnosis, defined as the detection of lung cancers that never would have become apparent or life threatening if the patient had not undergone screening. Each SR concluded that the occurrence of overdiagnosis is possible, but that presently the magnitude was uncertain. Recently, NLST investigators estimated that LDCT screening in the NLST resulted in 18% of screen-detected cancers being over-diagnosed (15); however, the magnitude of this estimate has been challenged on the basis of inadequate follow-up of the NLST cohort and several other factors (16,17).

In the 12 published papers on lung cancer screening in asbestos-exposed workers included in this review, the description of asbestos exposure commonly was vague and divergent (such as “definite” or “in contact with asbestos”) (Table 2). Only one paper makes fiber calculations (18). Only a single paper provided a clear lower limit for asbestos exposure as an inclusion criterion (19). Only four studies described set inclusion criteria based on smoking history, which varied from any smoking history to minimum pack-year thresholds (20–23) and three studies set pack-year thresholds at ten or 20 years based on asbestos exposure/non-exposure (20–22). Ten papers provided participants’ smoking data, i.e. pack-years or smoking category (non-smoker or never-smoker, ex-smoker, current smoker). The mean/median age of study subjects was provided in 11 papers, with only five providing clear inclusion criteria based on the minimum age of study subjects, which typically was age 40 or 50 years, while upper age limits were described in four papers ranging from age 70–80 years. One paper provided no age data. Inclusion/exclusion criteria other than asbestos exposure, smoking, or age was provided in seven papers. Three papers required good physical condition or capability for surgery of the subjects, while five papers required no previous cancer or symptoms of cancer being present. The number of workers participating in the included baseline screenings varied from 169 to 5662.

Ten papers gave at least some technical detail on the CT procedure (Table 3). Single slice technology was used in six studies with slice thickness of 5 mm in two studies (19, 24) and 10 mm in four studies (20, 22, 23, 25). Multislice/multidetector technology (MSCT) was used in four studies (21, 26–28) and in two studies there was no description of the imaging parameters (18, 29). The milliampers (mA) varied from 10 to 125. Only the study by Das and colleagues (26) calculated effective dose (average 1.1. mSv). This study had the lowest mA values compared to other papers when mA values were noted, suggesting that higher radiation doses may apply to the rest of the studies.

There was a great variation in the definition of positive findings in screening. The ELCAP protocol (8) was referred to in two papers (18, 28); 5 papers gave their own nodule millimeter criteria for a positive finding, ranging from 2 to 6 mm in non-calcified solid nodules, one defined positive lesions as those under 20 mm, and the remainder were non-specific. Eight papers reported the results of baseline (prevalence) screening, while there were at least elements of repeat (incidence) screening in four papers.

None of the studies had a control group, but one compared the lung cancer incidence to that of the regional register of residents and found no significant difference (18). In two studies CT was compared to the performance of chest radiographs with the same patients (19, 24).

In the included asbestos screening studies, the proportion of subjects with suspicious lung lesions varied from 6.1% to 57% (Table 4). Other incidental findings varied from 1.9% to 69.2%, with the wide range attributable to variable criteria for noting incidental findings. The number of lung cancers detected varied from 0.2% to 4.8% in the baseline (prevalence) screenings. One study found as many screen-detected mesotheliomas as lung cancers (28), and in two studies only 1 out of 5 screen-detected lung cancers was operated (18, 22).

Table 2. Patient characteristics in CT screening projects among asbestos-exposed workers

Author (Yr.)	Number screened	Age, yrs.	Asbestos exposure	Smoking history*
Callol (2007) ²⁰	466 1 st round; 406 2 nd round	50–73 mean 60.5	In contact with asbestos at work	> 20 P-Y > 10 P-Y (+ asbestos)
Clin (2009) ¹⁹	719	50–75 mean 61.3	High continued exposure > 1 y High discontinued exposure ≥ 10 y	NR**
Clin (2011) ²⁹	5662	mean 63.02	Low - High	Not required Smoking category given for subjects with and without lung nodules
Das (2007) ²⁶	187	45–75 mean 66.6	16-45 y; = 30 High risk power-plant workers	NS=01% FS=10% CS=89%
Fasola (2007) ²⁴	1045	40–75 mean 58	Definite, median 30 yrs.	Not required Median 18.5 P-Y
Greenberg (2012) ²⁰¹²	1182	> 50 mean 63.0	307 (26%) with asbestos exposure	>20 P-Y; = 42
Loewen (2007) ²⁷	169	37–83	70 (39.3%) with asbestos exposure	P-Y = 58
Lynch (1988) ²⁵	260	NR	Latency from initial asbestos exposure > 10 y	NR
Mastrangelo (2008) ¹⁸	1119 (58% of invited)	mean 57.1	All asbestos-exposed = 17.7yrs. =123 fiber/ml x y	NS=35% FS=47.2% CS=17.8%
Roberts (2009) ²⁸	516	32–83 mean 60.0	Asbestos exposure > 20 y ago or pleural plaques	NS=23.4% FS=56.4% CS=20.2%
Tiitola (2002) ²²	602	38–81 mean 63.0	Asbestosis Pleural plaques and smoking > 10 p-y	>10 P-Y, if no asbestosis diagnosis P-Y = 24 yrs.
Vierikko (2007) ²³	633 had HRCT; 180 also spiral CT	45–86 mean 64.0 Spiral CT: < 70 y	Asbestosis Pleural plaques	Current or ex- smoker required for spiral CT NS=22.0% FS=58.0% CS=19.9% P-Y = 17.2 yrs.

* NS=Non-smoker; FS=Former smoker; CS=Current smoker; P-Y = pack-years (years of smoking multiplied by average number of packs, or fraction thereof, per day); ** NR=Not reported

	Other inclusion/exclusion criteria
	Incl: good physical condition, absence of neoplastic antecedents Excl: Not amenable to surgery, other cancer, pregnancy
	Asymptomatic for cancer No contraindication for surgery
	Register based volunteers
	Not reported
	No prior cancer No suspicion on lung cancer No chest CT during previous 2 years
	High-risk urban cohort No prior cancer or chemotherapy
	High risk cohorts from several sources: asbestos-exposed anamnestic aerodigestive cancer with no evidence of disease for > 2 y COPD patients 2 of 4 risk factors present, one of which could be asbestos-related lung disease on chest radiograph
	CT performed due to a mismatch of b-readers interpretation on the presence of asbestosis or pleural disease
	Retired asbestos workers from companies' registers
	Volunteers from occupational health clinics and from workers' unions etc. Good health, no prior cancer
	Volunteers recognized from previous (non-CT) screening programs, occupational wards and trade union registers
	Volunteers recognized from previous screening programs, occupational wards Spiral CT exclusion: non-operable

Table 3: Intervention and control characteristics in CT screening projects among asbestos-exposed workers

Author, year	CT methodology (slice thickness, mA etc.)	Definition of positive finding*	Screening type: Baseline/repeat interval/duration	Control group
Callol (2007) ²⁰	10 mm, 50 mA	No lower limit	two rounds/two-year interval	No
Clin (2009) ¹⁹	5 mm, 50 mA	1-6 nodules > 2 mm diameter	1–3 rounds	CT compared to chest X-ray among the same patients
Clin (2011) ²⁹	NR	Lesion > 5 mm or “requiring surveillance” or “suspicious”	Baseline	No
Das (2007) ²⁶	MSCT, 10–20 mA	Nodule > 6 mm	Baseline analyzed (annual screening on-going)	No
Fasola (2007) ²⁴	5 mm, 40 mA	NCNs, or CNs >20 mm with malignant pattern	Baseline	CT compared to chest X-ray among the same patients
Greenberg (2012) ²⁰¹²	MSCT, 40–80 mA, various scanners	Nodule ≥ 4 mm	Baseline	No
Loewen (2007) ²⁷	MSCT, mA?	“Clinically significant parenchymal abnormality”	Baseline	No
Lynch (1988) ²⁵	10 mm, mA?	NR	Baseline	No
Mastrangelo (2008) ¹⁸	Not reported	ELCAP protocol	Baseline	Cancer incidence compared to that in the population
Roberts (2009) ²⁸	MSCT, 50–60 mA	ELCAP criteria SNs ≥ 5 mm NSNs ≥ 8 mm	>1 round in 356/516 (on-going), annual	No
Tiitola (2002) ²²	10 mm, 125 mA	NCNs > 5 mm	Baseline	No
Vierikko (2007) ²³	Spiral CT: 10 mm, 36–110 mA	NCNs, non-fatty nodules	Baseline	No

* NCNs=Noncalcified nodules; CNs=Calcified nodules; NSNs = Non-solid nodules; SNs=Solid nodules

Table 4: Outcome in CT screening projects among asbestos-exposed workers*

Author, year	Patients with suspicious lung lesions	Patients with other incidental findings	# False negatives/ interval cancers	# Lung cancers	Complications, radiation dose	Behavioral aspects, smoking, anxiety etc.	Other comments
Callol (2007) ²⁰	1 st round =98 (21%) 2 nd round = + 9 (2.2%)	9 (1.9%)	NR	1 st round = 1/466 (0.2%); 2 nd round = 4/406 (1%)	NR	NR	NR
Clin (2009) ¹⁹	23%	NR	NR	2.16%	NR	NR	NR
Clin (2011) ²⁹	933 (16.5%)	NR	NR	50/5662 (0.9%)	NR	NR	NR
Das (2007) ²⁶	Total 163/187 (87.7%) 6–10 mm nodules 57/187 (30.5%)	13/187 (7.0%)	NR	9/187 (4.8%)	Mean effective dose 1.1 mSv		Thin slices associated with increased positive findings
Fasola (2007) ²⁴	44%	Pleural abnormalities (44%) 1 thymic carcinoma	NR	9/1045 (0.86%)	NR	NR	NR
Greenberg (2012) ²⁰¹²	52%	Emphysema 35.6%	NR	30/1182 (2.5%)	NR	NR	NR
Loewen (2007) ²⁷	93/169 (57%)	NR	4/13 (31%)	All modalities 13/169 (7%) With CT 9/169 (5.3%)	NR	NR	NR
Lynch (1988) ²⁵	16/260 (6.2%)	Fissural plaque 6 Fibrotic bands 3 Rounded atelectasis 8	NR	2/260 (0.77%)	NR	NR	NR
Mastrangelo (2008) ¹⁸	242/1119 (21%)	Pleural plaques 32%	0% based on passive surveillance of hospital discharge registers	5/1119 (0.4%)	NR	Smoking cessation recommended	244 962 € cost/lung ca detected (only one was treatable)
Roberts (2009) ²⁸	All nodules 371/516 (71.9%) Screen positives 91/516 (17.6%)	two pleural and two peritoneal mesotheliomas, 69.2% pleural plaques	four interval cancers found	4/516 (0.8%) prevalence lung ca, 2/356 (0.6%) incidence lung ca	Rate of invasive procedures 1.1-1.9% of scans	NR	NR
Tiitola (2002) ²²	111/602(18.5%), recognized by at least 2/3 observers	one peritoneal mesothelioma	two additional lung cancers reported in cancer registry after three yrs: not retrospectively visible in scans	5/602 (0.8%)	NR	NR	3 cancers potentially operable; only 1 operated for various reasons
Vierikko (2007) ²³	86/633 (13.6%)	Patients with incidental findings, 277/633 (46.2%), 46 requiring further examinations	NR	5/633 (0.8%)	NR	NR	NR

* NR indicates no reported data in the paper; **NCNs=Noncalcified nodules; CNs=Calcified nodules; NSNs = Non-solid nodules; SNs=Solid nodules

Discussion

The SRs included in this review did not focus on asbestos-exposed individuals, but they offer high quality evidence on the methods, benefits and potential harms associated with LDCT screening for lung cancer in high-risk current and former smokers. The data provided by the NLST study persuaded a number of U.S. organizations to issue recommendations for LDCT lung cancer screening using the same, or nearly the same, criteria for the target population as were used as criteria for eligibility to participate in the NLST (30–34), while European countries are awaiting the results of their RCTs currently underway (35).

All three SRs resulted in the conclusion that LDCT screening in high-risk smokers and former smokers is associated with a reduction in mortality from lung cancer. However, all three SRs expressed concerns about the high initial rate of false positive findings, and stressed that many key aspects of LDCT screening for lung cancer remain uncertain. This latter is not unexpected soon after the demonstration of the efficacy of a screening test, since experience and evidence on the effectiveness of cancer screenings accumulates over time after implementation and as protocols evolve. For example, data are needed on the cost effectiveness of screening that takes into account the frequency of screening and costs associated with various management strategies for adults with positive test results. Lung cancer screening will be a work in progress for the foreseeable future.

We could find only 12 articles on LDCT lung cancer screening among asbestos-exposed subjects that met the inclusion criteria. This number is surprisingly low, because asbestos exposure is a well-known risk factor for lung cancer and many asbestos-exposed workers around the world have been and are regularly tested with CXR and high-resolution CT (HRCT) examinations, despite lack of supporting evidence for their effectiveness.

The number of lung lesions detected in these studies showed a wide range, which was most likely due to the different selection criteria of the subjects, the varying definitions of positive findings, observer factors and CT technology. The same also applies to secondary findings. Callol et al. (20) found suspicious lung lesions among 21% of the participants during their baseline screening, but only among 2.2% during their second screening round. This was likely due to the fact that they had previous images for comparison in the 2nd round. All studies of LDCT screening (in high-risk smokers and in asbestos-exposed workers) have shown a high rate of positive findings on baseline screening (of which the large majority are false positives), with a considerable decline in the recall rate in subsequent rounds. For example, in the review of Bach et al. (12), the average nodule detection rate per screening round was 20%. This rate varied from 3% to 30% in RCTs and 5% to 51% in the cohort studies. In NLST, the detection rate did not decrease

until the third round, but the persistence of an elevated rate of positive findings was largely due to the protocol, which defined a positive finding at screening automatically positive on the next examination (9).

The published articles of asbestos-exposed persons have been case series with a limited number of subjects, no control groups and little follow-up data on mortality, providing only weak if any inferential evidence about the efficacy of lung cancer screening specifically targeted to adults with a history of asbestos exposure. A recent systematic review of LDCT screening of adults with occupational exposure to asbestos by Ollier, et al. (36) reached the same conclusions that are reached here, i.e., there is little evidence to measure the efficacy of lung cancer screening in asbestos-exposed adults, but the available evidence indicates that LDCT screening in this population detects asymptomatic lung cancer at a favorable stage similar to the performance that has been observed in high risk former and current smokers. Therefore, at this time the assessment of how asbestos-exposed workers should be followed mainly must be based on risk assessment and the outcome of the RCTs of LDCT screening for lung cancer in high-risk smokers.

There are a limited number of tools for assessing absolute risk of lung cancer based on combined asbestos exposure and smoking history. With the exception of one study (26) in our review, there were no risk calculations to guide the identification of adults at high risk due to asbestos exposure or the combination of asbestos exposure and smoking. Das and colleagues (26) selected their subjects by using “an empiric lung cancer risk calculation” $[\text{age (years)/50}] \times 3 \times \text{asbestos exposure time (years)} \times \text{smoking habits (non-smoker} = 0.1, \text{ ex-smoker} = 0.3, \text{ smoker} = 1)$, although neither relative nor absolute risks were provided. At present, most lung cancer screening guidelines define risk-based eligibility for screening based on the same combination of age and smoking history that was used in the NLST (9), and several qualify adults for screening at a younger age and with fewer pack-years of smoking if one or more established risk factors (including asbestos exposure) are present (30, 31). Insofar as asbestos exposure, and the combination of asbestos exposure and smoking history, are associated with elevated risk for lung cancer, there is a need to identify the risk levels appropriate for screening among asbestos-exposed adults, and the degree to which the age/exposure indications that contribute to an absolute risk threshold in current and former smokers are appropriate for adults with a history of asbestos exposure. In the meantime, there are a number of lung cancer risk assessment models (37), and several lung cancer risk calculators that include both smoking history and asbestos exposure, in addition to other relevant patient history factors (37).

The Memorial Sloan Kettering lung cancer prediction model (MSK; also known as the Bach Model) was derived from subjects enrolled in the Carotene and Retinol Efficacy Trial (CARET) (38). The CARET study had enrolled

18 172 subjects from two populations, one of which was a cohort of 4060 men ages 45–69 years who were current or former smokers and had either radiographic evidence of asbestos exposure, or an employment history (minimum duration of 5 years) in an occupation at high risk for asbestos exposure. A history of asbestos exposure was independently associated with a 24% increase in the risk of lung cancer (HR=1.24, 95% CI 1.04–1.48; $P=.02$). The model is available on the internet as a decision tool that predicts the absolute risk of lung cancer death over a six-year period in a 1000 adults who do and do not undergo screening with LDCT (39).

The Liverpool Lung Project (LLP, www.MyLungRisk.org) model was developed using data from the LLP case control study and is distinct from the MSK model in that it calculates lung cancer risk among current, former, and never smokers, while also including other important risk factors including asbestos exposure. Asbestos exposure was determined by collecting an occupational history using specialized tools, after which an expert judged the likelihood of asbestos exposure, frequency, and intensity of exposure. Since an underlying priority for the development of the model was to use only variables easily assessed by clinicians, asbestos exposure was positive if an individual was exposed for at least 1 year of their working life (40, 41). As was the case in the MSK model, exposure to asbestos was an independent, statistically significant risk factor for lung cancer. After adjustment for occupational confounders, the overall risk of lung cancer based on asbestos exposure was 1.51 (95% CI: 1.02–2.04). The LLP model highlights the degree to which smoking history confers a substantial increased risk for lung cancer when combined with family history, asbestos exposure, etc., but also reveals that combinations of risk factors in never smokers also can elevate the absolute risk of lung cancer risk above the threshold presently used in guidelines for lung cancer screening. For example, Cassidy, et al. (40) observed that a male, never smoker, aged 67 with a personal history of cancer, a family history of lung cancer, and a history of exposure to asbestos had an absolute risk of lung cancer in the next five years of 3.16%.

The Institute of Cancer Policy (ICP) has an on-line lung cancer risk calculator that addresses some of the limitations described above by combining five risk calculators (38, 40, 42–44) into a single risk calculator that plots and displays the results of each (45). Since three of the models include asbestos exposure, it is possible for any given smoking history to observe how the addition of occupational asbestos exposure modifies the absolute risk estimate over time.

Table 5 shows absolute risks of lung cancer using the ICP calculator for combinations of smoking history and occupational asbestos exposure, with estimates of five, six, and ten-year absolute risks of lung cancer in current and former smokers with and without asbestos exposure using the Tammemagi

(smoking history only), LLP, and MSK models. The Tammemagi model is included for comparison because it was the basis for estimating absolute risk for the NLST (44, 46). In these examples, we vary age, smoking status and history, and asbestos exposure for white males with a body mass index (BMI) of 25, no coronary obstructive pulmonary disease (COPD), emphysema, chronic bronchitis, and no personal history of cancer or family history of lung cancer. All current and former smokers began smoking at age 18, smoked 20 cigarettes per day, and all former smokers quit ten years prior to their current age. As would be expected, there is a substantial increase in risk as years of smoking increases, and in all instances risk is higher for current smokers compared with former smokers with and without prior occupational exposure to asbestos. Likewise, in all instances, current and former smokers with prior asbestos exposure have higher absolute five- and ten-year risks compared with adults without asbestos exposure. These models also reveal the degree to which adults ages 55 years and older with a smoking history less than 30 pack-years still exceed the absolute risk threshold for the NLST (1.34% over 6 years) if asbestos exposure and other risk factors (family history, emphysema, exposure to dust, pneumonia, COPD, etc.) are present. Further refinement of risk estimation algorithms, absolute risk thresholds for screening eligibility, and provider access to simple, easy to use risk calculators is a high priority as lung cancer screening programs are implemented.

Table 5: Absolute Risk of Lung Cancer* Among Current and Former Smokers by Asbestos Exposure

Age	Tammemagi (6 yr. risk)		LLP (5 yr. risk)		LLP-A (5 yr. risk)		MSK** (10 yr. risk)		MSK-A (10 yr. risk)	
	CS	FS	CS	FS	CS	FS	CS	FS	CS	FS
55	1.5%	0.6%	0.7%	0.6%	1.1%	1.1%	2.4%	1.0%	5.0%	1.2%
60	2.6%	1.1%	3.2%	1.1%	5.8%	2.1%	6.6%	2.1%	8.0%	2.6%
65	4.5%	1.9%	4.6%	1.7%	8.4%	3.1%	9.3%	4.0%	11.4%	4.9%
70	7.5%	3.2%	6.0%	6.0%	10.7%	10.7%	12.3%	6.5%	14.8%	7.9%
75	12.3%	5.5%	9.0%	9.0%	15.8%	15.8%	-	8.8%	-	10.6%

* The hypothetical subjects are white males ages 55–75, high school graduates with BMI = 25, no COPD, emphysema, chronic bronchitis, and no personal or family history of lung cancer. Each initiated smoking at age 18, and smoked 20 cigarettes per day. CS= current smoker; FS=former smoker (quit ten years from current age, i.e., 55 yrs. old CS has 37 pack-years, FS has 27 pack-years); A = Asbestos exposure; MSK = Memorial Sloan Kettering model; LLP = Liverpool Lung Project model;

**The MSK model requires smoking duration of 25–55 years

Several important caveats about these risk calculators are worth noting. First, absolute risk estimations using these models are shown here simply to demonstrate the greater than additive effect of asbestos exposure to lung cancer risk in the context of the lung cancer risk levels used by current lung cancer screening guidelines. None of these models presently is endorsed by any organization as a basis for decisions about screening, and as with all risk calculators, each achieves only modest discriminatory power. Second, while the models produce similar absolute risks for some age, pack-year combinations, at other levels the estimates are dissimilar, which likely is due to the different populations and underlying exposures from which the risk estimates are generated, as well as different approaches to model inputs. For example, model inputs for exposures differ in that some are categorical, some are continuous, and some have minimum and maximum thresholds, resulting in the paradoxical appearance of similar absolute lung cancer risks for adults with very different exposure histories. Finally, it is not clear how the interplay between cumulative exposures of asbestos exposure and tobacco exposure modify the age-incidence curve, resulting in uncertainty about the interplay between absolute risk and the age to begin screening.

Recommendations

Current U.S. organization recommendations for lung cancer screening are presented in Table 6. Most of the recommendations have adapted the inclusion criteria of the NLST. At the moment there are no clear data for how these guidelines can be adapted to asbestos-exposed persons. While the NCCN and the American Association for Thoracic Surgery have endorsed screening between ages 50–74 for adults with a 20 pack-year history of smoking if they also have one additional risk factor for lung cancer (i.e., a family history, a history of occupational exposure to asbestos, etc.) this recommendation appears to be based on a general approximation of the greater than additive risk of multiple risk factors for lung cancer. However, no risk calculator reveals risk levels approaching the NLST criteria for a 50-year-old man with a 20 pack-year history with either a family history or occupational exposure to asbestos.

Table 6: Lung Cancer Screening Recommendations from U.S. Organizations

Society*	Year	Age range	Minimum pack-years (P-Y) **	Former Smokers- Years since cessation	Additional risk factors considered	Other Considerations***
ACS ³³	2013	55–74	≥30	≤ 15	No	Adults who are candidates for screening should engage in a process of shared decision making; Screening only should be done in an institution that supports multidisciplinary teams, and has experience with LDCT imaging. Recommend against chest radiograph for screening. Strong emphasis on smoking cessation for current smokers.
USPSTF ³²	2014	55–80	≥30	≤ 15	No	Adults who are candidates for screening should engage in a process of shared decision making; Once former smokers have reached > 15 years since smoking cessation, they should stop screening.
ACCP ³⁴	2013	55–74	≥30	≤ 15	No	Screening only should be done in an institution that supports multidisciplinary teams, and has experience with LDCT imaging.
ASCO ¹²	2013	55–74	≥30	≤ 15	No	Screening only should be done in an institution that supports multidisciplinary teams, and has experience with LDCT imaging.
ALA ⁴⁸	2012	55–74	≥30	≤ 15	No	No history of lung cancer; Screening only should be done in an institution that supports multidisciplinary teams, and has experience with LDCT imaging. Strong emphasis on smoking cessation for current smokers; Recommend against chest radiograph for screening; Screening centers should develop ethical practices for advertising and promotion;
NCCN ³⁰	2012	55–74	≥30	≤ 15	Yes	Adults with one or more risk factors in addition to smoking history (i.e., asbestos or other occupational hazards, radon exposure, family history, personal cancer history, COPD, pulmonary fibrosis) may begin screening if they are age 50 and have a ≥ 20 P-Y history of smoking.
AATS ³¹	2012	55–74	≥30	≤ 15	Yes	Adults with one or more risk factors in addition to smoking history (i.e., asbestos or other occupational hazards, radon exposure, family history, COPD with FEV1 < 70%, cancer/thoracic radiation, pulmonary fibrosis, and > 5% absolute risk of developing lung cancer within the next 5 years) may begin screening if they are age 50 and have a ≥ 20 P-Y history of smoking

* ACS=American Cancer Society; USPSTF=United States Preventive Services Task Force; ACCP= American College of Chest Physicians; ASCO=American Society of Clinical Oncology; ALA=American Lung Association; NCCN= National Comprehensive Cancer Network; AATS=American Association of Thoracic Surgeons.

** Pack-years is a unit for measuring smoking history, and is calculated by multiplying the number of packs of cigarettes smoked per day by years smoked, i.e. 1 pack-year = 1 pack per day for 1 year, or 2 pack years = 2 packs per day for 1 year.

*** All organizations recommend that candidates for screening should be in good health and not have any life-limiting co-morbidity that would preclude curative treatment.

However, according to the LLP model, a 60-year-old man with a ten-pack year history, asbestos exposure, and a family history of either early or late-onset lung cancer exceeds NLST absolute risk thresholds. Thus, there is an urgent need to further study asbestos-exposed adults to determine how to accurately estimate absolute risk of lung cancer based on actual or approximations of asbestos exposure alone or combined with smoking history and other risk factors, and to determine the benefits, adverse effects, and economic issues concerning their inclusion in LDCT screening for lung cancer. Ongoing studies, preferentially RCTs, with sufficient power may still provide an opportunity to identify study subjects with prior asbestos exposure, either in individual trials, or through data pooling projects. Well-designed cohort studies may also be useful, but in either case, it is critically important that there is adherence to a common methodology so that meta-analysis is possible going forward.

The optimal screening interval for lung cancer may not be dependent on the underlying risk factors, but more work on estimating risk-based sojourn times will need to be done before this statement can be made with greater confidence. Pastorino et al. (47) detected more cancer with annual vs. biennial screening, but did not observe a survival benefit with either interval compared to the control arm; in contrast, the NLST observed a mortality reduction associated with annual screening (9). Given the high costs associated with lung cancer screening, the question of whether wider screening intervals might be equally effective among all or some subgroups undergoing screening will likely be a focus of future investigations.

The responsibility for screening should be nationally or regionally organized so that preferably a single unit/institute would be in charge for the whole process. This includes the organization of screening, quality control, the collection and analysis of all data on benefits, complications and economic issues. The organizer should have sufficient expertise on epidemiology, pulmonology, radiology and other relevant sciences. The participating units should be included in the most feasible manner nationally and educated in a sufficient manner.

In conclusion, at this time there is limited evidence to guide risk estimation and LDCT screening in workers at high risk for lung cancer due to asbestos exposure with or without a history of smoking. However, based on the favorable outcome of the lung cancer LDCT screening studies, the dose-response risk of lung cancer in asbestos-exposed workers, and the well-established greater than additive contribution to risk in adults exposed to both asbestos and tobacco smoke, it is reasonable to recommend that adults with asbestos exposure be evaluated for eligibility for lung cancer screening. Those adults with prior exposure to asbestos who are in reason-

ably good health and who are at or above the risk threshold set for participation in the NLST, whether based on smoking history, the combination of asbestos exposure and smoking history, or asbestos exposure alone should be considered for screening for lung cancer.

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, and other risk factors such as occupational history or genetic predisposition. Going forward it is imperative that efforts are focused on answering these key questions about lung cancer risk, patient selection, and the benefits and harms of lung cancer screening in asbestos-exposed adults.

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2 Follow-up of asbestos-exposed workers and diagnosis of non-malignant asbestos diseases

Helge Kjuus, National Institute of Occupational Health, Norway

Tapio Vehmas, Finnish Institute of Occupational Health, Finland

Murray Finkelstein, Canada

Takumi Kishimoto, Okayama Rosai Hospital, Japan

Thomas Kraus, Aachen University, Germany

Heikki Frilander, Finnish Institute of Occupational Health, Finland

Panu Oksa, Finnish Institute of Occupational Health, Finland

Introduction

Based on the two International Expert Meetings in Helsinki: Asbestos, Asbestosis and Cancer, 1997 and New Advances in Radiology and Screening of Asbestos-Related Diseases, 2000 (1, 2), the Helsinki Criteria for the diagnosis and follow-up of asbestos-related diseases were developed. Now, 13–16 years later due to new knowledge in the field, together with the fast development of new imaging techniques for early diagnosis of pulmonary effects related to asbestos exposure, it seems it is time to discuss the need for updating these criteria. This paper will focus on criteria for the follow-up of asbestos-exposed workers and the diagnosis of non-malignant asbestos diseases. It will address recommendations for the follow-up of asbestos-exposed workers, related to non-malignant outcomes, such as asbestosis and pleura plaque, and also discuss diagnostic criteria and classification systems based on new imaging techniques, such as HRCT.

Follow-up of asbestos-exposed workers

What is the role of the imaging methods: plain radiograph, HRCT, spiral CT, others?

The traditional method for medical screening of asbestos-exposed workers has been the conventional chest radiograph, with standardized interpretation using the ILO system for classification of radiographs for pneumoconiosis (3).

The recommended follow-up routines for the radiological follow-up of asbestos-exposed workers differ between countries, as exemplified in Table 1, which is based on questionnaire information recently received from some of the participants of the Helsinki Criteria Conference in 2000, and the available literature.

Table 1. Recommended radiological follow-up schema of asbestos-exposed workers in some countries.

Country	Method	Interval	Comment	Reference
Italy	Chest x-ray or CT	Left to occupational physician's decision*	The occupational physician responsible for health surveillance should decide on further examinations.	Legislative Decree 81/08 and subsequent modifications and integrations; art. 259 Guidelines – Health surveillance of workers exposed to carcinogen and/or mutagenic substances at the workplace edited by Italian Society of Occupational Health and Industrial Hygiene (SIMLII), 2007, Latest update 2013
UK	“Specific examination of the chest”	At least two years	Health records are kept for at least 40 years from the date of last entry.	Health and Safety, 2012 No. 632. The Control of Asbestos Regulations 2012
U.S.	Chest X-ray	One to five years depending on age and latency	Only required of current workers	OSHA (U.S. Federal government) [https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=standards&p_id=9995]
Canada, Ontario			Occupational health is a provincial, not federal responsibility.	No regulations specifying follow-up of exposed workers
Japan	Chest X-ray	Twice a year	Subjects are present and past workers who handle asbestos as well as indirectly exposed workers.	Laws and ordinances under the framework of the Industrial Safety and Health Law http://www.mhlw.go.jp/new-info/kobetu/roudou/sekimen/iryo/
Finland	Chest X-ray	1 st before work, 2 nd after ten years, and thereafter every three years		Government Regulation 1485/2001; Nordman et al. 2006 (4)
Norway	Chest X-ray	Only the first x-ray is compulsory	There is no systematic national follow-up of previous asbestos-exposed workers for non-malignant asbestos diseases.	Employees allowed to remove asbestos at present are followed according to EU regulations.
Sweden	Chest X-ray	Biannually	It is recommended that examinations continue after cessation of exposure, but this is not mandatory.	Swedish Work Environment Authority: Provisions and general recommendations: 2006:6, Occupational medical supervision.
Korea	Chest X-ray	Annually	Retired workers included	Guideline for Health Examination (in Korean).
Germany	Chest X-ray	Every one to three years	Retired workers included, high risk workers** low dose CT yearly	DGUV 2010 (5) and Kraus 2014 (6)

* Italy: Health examination of workers should be carried out: a) at beginning of employment, b) in periodical checkups (at least once every three years or according to occupational physician's decision) and planned follow-ups on retirement. They should include at least the following measures: 1) keeping records of a worker's medical and occupational history, 2) a general clinical examination, with particular reference to the chest and 3) lung function tests.

** Definition of the high risk group in Germany: first exposure before 1985, at least ten years of exposure, more than 30 pack years tobacco smoking, age at least 55 years of age, fit for thoracic surgery, no previous lung cancer.

From this table, it seems that the chest X-ray still is the dominant method of radiological follow-up of asbestos-exposed workers. However, several countries have now introduced HRCT for the radiological follow-up of asbestos-exposed workers, either as a supplementary method to the chest X-ray, or as a substitute for the traditional chest X-ray. The national recommendations in this field, however, seem to be primarily related to the early detection of asbestos-related lung cancer, and not so much to non-malignant pulmonary effects. In addition, it seems that the current national follow-up regulations of asbestos workers are developed more for medico-legal and compensation purposes than based on pure, medical criteria.

HRCT is used if possible in the diagnosis of asbestosis. The poor sensitivity and specificity of radiographs to detect lung fibrosis have become well known in the use of CT/HRCT (7, 8, 9) (Figure 1). The correlation between the ILO score and the HRCT fibrosis score was 0.41, giving the coefficient of determination (r^2) of only 0.17, which indicates the proportion of variance in HRCT fibrosis explained by the ILO score. While lung tissue can be directly visualized with CT/HRCT, radiographs have poorer contrast resolution, are disturbed by superposing soft tissues, and are more liable to be affected by patients' positioning and varying degree of inspiration.

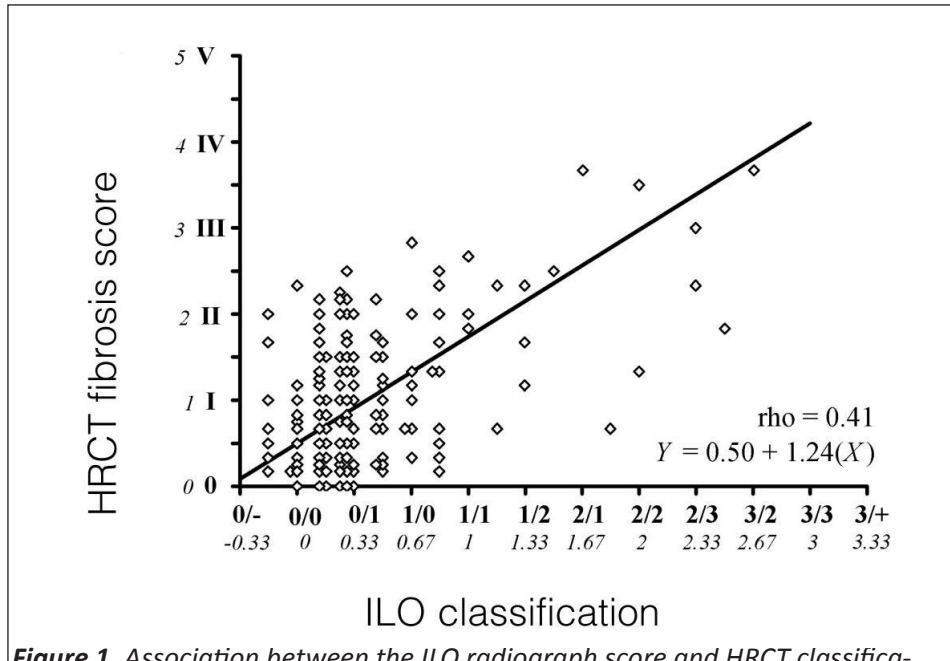


Figure 1. Association between the ILO radiograph score and HRCT classification of interstitial lung fibrosis according to the Finnish system (adapted from Huuskonen et al. 2001 (10)).

Therefore, chest radiographs should be supplemented with HRCT imaging at least when

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

HRCT imaging should be conducted in the prone position to guarantee the optimal aeration of dorsobasal lung parts, i.e. the area that is usually most affected by fibrotic changes. Radiation aspects should be taken into account and six or more slices (11) imaged. Modern multislice/detector CT (MSCT/MDCT) provides an easy method for imaging the whole lungs with thin slices thus virtually combining the information from conventional spiral imaging and HRCT. This technology blurs the boundary between HRCT imaging of special lung signs e.g. for finding or follow-up of fibrosis and screening for lung cancer.

During the last two decades, several classification or coding systems for the evaluation of pneumoconiosis in CT have been presented by Japan, Germany, France and Finland (12). The Helsinki meeting in 2000 recommended that a common, international classification scheme for pulmonary and pleural abnormalities detected on CT scans of asbestos-exposed workers should be established for the early identification of occupational and environmental respiratory diseases, comparable to the 1980 ILO International Classification of Radiographs for pneumoconiosis (2). Such a common classification system was described by Kusaka et al. (12) and by Hering et al. (13). This classification has now been further developed (ICOERD) (14, 15). Some countries, such as France, have developed a nationally-based classification system. For international comparison, we recommend the use of the ICOERD classification.

The role of other methods for follow up: spirometry, questionnaires, and others

In accordance with previous recommendations, based on the HCU criteria, 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. Reliable work histories provide the most practical and useful measure of occupational asbestos exposure. Using structured questionnaires and checklists, trained interviewers can identify workers who have a work history compatible with significant asbestos exposure. A cumulative fiber dose as expressed in fiber-years per cubic centimeter, is an important parameter of asbestos exposure. The questionnaire should provide detailed information on past (and current) asbestos exposure, and smoking habits, for

further classification into relevant risk groups for stratified follow-up, especially if the follow-up schema is stratified according to the quantity of exposure it is recommended to calculate or approximate worker's exposure as fiber years. The most comprehensive method for calculation of fiber-years has been created by Deutsche Gesetzliche Unfallversicherung, DGUV in Germany (17). To quantify the risk of smoking for lung cancer, calculation of pack-years for current and ex-smokers is recommended, and also years since cessation for ex-smokers.

The spirometry should include flow-volume curves. Measurements of diffusion capacity for CO are not recommended for screening purposes. Mild functional changes may be seen even in case of a normal radiograph, but these are not specific to asbestos diseases. To make a diagnosis, radiographic changes are needed. For clinical and medico-legal purposes, however, regular follow-up with spirometry might be useful, based on national practice and legal requirements. This might take place every three to five years, depending on exposure level, time since cessation of exposure and age. It is more important to advise all asbestos-exposed workers to contact their doctor if they develop symptoms or signs of respiratory disease.

Should the follow up schema be stratified according to the intensity and duration of exposure?

We recommend that a general follow-up schema of asbestos-exposed workers should be stratified according to the intensity and duration of exposure. High priority should be given to workers with high cumulative asbestos exposure who are current or past smokers. The rationale behind the stratified follow-up, however, will mainly be related to future lung cancer risk, rather than non-malignant effects. The question of whether there should be a minimum exposure requirement (e.g. fiber-years) for a life-long surveillance of the worker or if the follow-up should end, e.g. 30 years after the last exposure, will mainly depend on estimations of the individual worker's lung cancer risk.

Asbestos-related deterioration of lung function may progress over a long time, at least 15 years after cessation of the exposure (16). Short term exposure to amosite was followed by radiographic parenchymal and pleural progression, which were still detectable ≥ 20 years after the end of exposure (18). The risk of progression of radiographic fibrotic processes was higher among smokers, workers employed during earlier years, those with a longer latency period, blue-collar workers directly involved in the production processes, and employees in the asbestos cement and/or textile industries (19).

It is therefore evident that both radiographic and functional pulmonary deterioration may occur long after asbestos exposure. Follow-up is necessary, especially if it is relevant from the compensation point of view. Asbestos-exposed patients with pathological lung and pleural signs in HRCT (20) or lung functional deterioration (21) have increased mortality. We therefore recommend the follow-up of asbestos-exposed workers for at least 30 years after cessation of exposure.

Could biomarkers be of practical benefit for follow-up diagnostics?

The question has been raised as to whether some biomarkers could be of practical benefit for the follow-up diagnostics of asbestos-related disease. It has been shown that asbestosis patients have increased alveolar NO output and high levels of LTB4 and 8-isoprostane in exhaled breath condensate reflecting the chronic pulmonary inflammation and tissue damage (22; 23). Borderline parenchymal changes on HRCT in asbestos-exposed subjects are also associated with increased markers of pulmonary inflammation (24). Such borderline parenchymal changes are likely a mild or early form of the same pathological process that leads to asbestosis. More studies are needed to assess if the markers of inflammation could be used to predict the risk of developing diffuse pulmonary fibrosis and asbestosis among subjects with borderline parenchymal changes. For mesothelioma diagnosis, several new biomarkers, such as soluble mesothelin-related peptides/proteins, osteopontin etc. have been under consideration. See Pathology and biomarkers, page 123.

Immunization or vaccination of asbestosis patients

The last decades have seen reports related to a possible increased risk of pneumonia among workers exposed to gases and fumes. The question has now been raised as to whether asbestos-exposed workers also have an increased incidence of or mortality from pneumonia, and could thus benefit from Pneumococci vaccination.

A recent study reported an increased risk for pneumonia mortality (ICD-10 codes J10-J18) among asbestos-exposed workers with lung fibrosis in Finland. The hazard ratio (HR) was 2.26 (95% CI:0.98–5.19) among subjects with “some interstitial fibrosis”, and 3.30 (95%CI:1.22–11.23) among subjects with “definite interstitial fibrosis” (25). Based on these findings, the authors recommend that both current and former asbestos workers with lung fibrosis should be vaccinated against influenza and Pneumococcus. We are not aware of other studies that have examined this specific association among asbestos-exposed workers.

However, there are several reports on the relationship between welding exposure and mortality from pneumonia, and the British Health Authorities have recently recommended that welders exposed to metal fumes are offered the pneumococcal vaccine, paid by the employer (26). We recommend influenza and pneumococcus vaccination to patients with documented asbestosis. Further studies on the relationship between asbestos exposure, asbestosis and pleura plaque on the one hand, and incidence and mortality from pneumococci pneumonia on the other, are required before any recommendation can be given for extending this recommendation to asbestos-exposed workers in general. Cost benefit considerations must also be included in a further assessment of such recommendations.

Diagnosis of non-malignant asbestos diseases (asbestosis and pleural plaques)

Should there be a definition of minimum criteria for diagnosis of asbestosis in HRCT?

It is well known that ILO abnormalities occur in the general population without work-related asbestos exposure. According to a meta-analysis, the prevalence of small opacity profusion that is considered pathological (1/0 or greater) varies widely, from 0.21% to 11.7%, showing an average population prevalence of 5.3% (27).

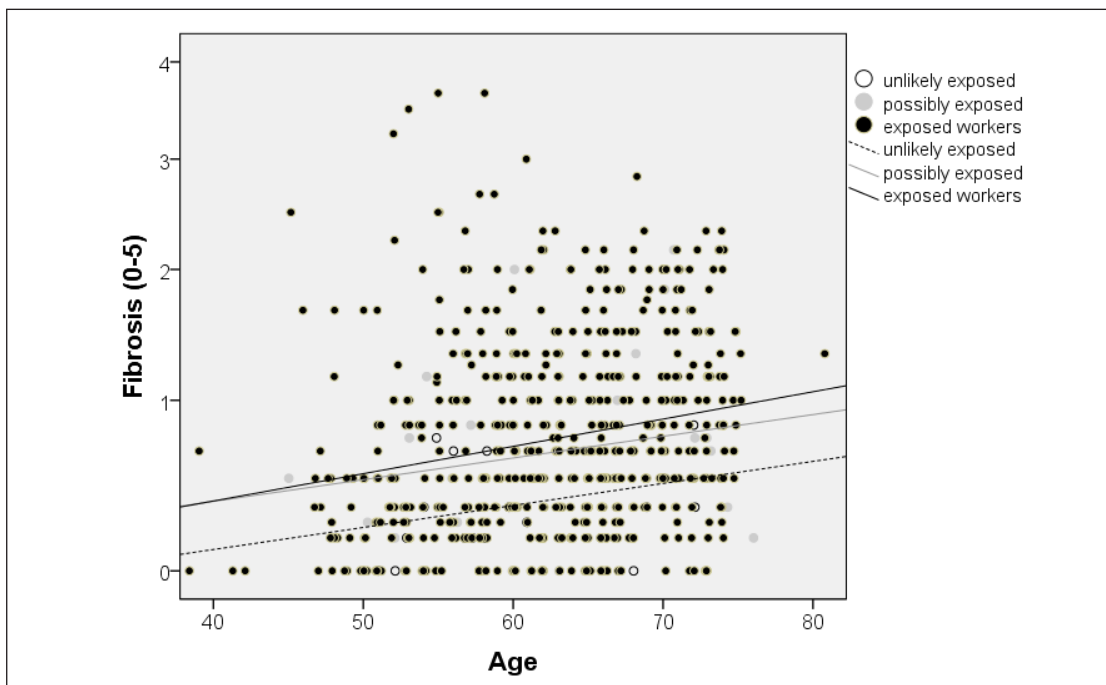


Figure 2. Relation between age and HRCT fibrosis among asbestos-exposed workers and age-matched hospital controls with unlikely or possible asbestos exposure.

Small lung opacities and pleural abnormalities were considerably more prevalent in the older age groups and in men (28). There is less data on HRCT abnormalities occurring in the general population, supposedly because of the study problems from radiation exposure. The previously unpublished plot below is based on Finnish 'ASBE' screening material (29, 30).

It is clear that HRCT lung fibrosis also exists among those with different asbestos exposure and shows a distinct, although limited increase with age. The occurrence of limited lung fibrosis among the general population makes the definition of a threshold value for asbestosis important. This depends on the fibrosis classification system used and the characteristics of the national general population. The Finnish threshold value is 2, using the classification system in Figure 2. This corresponds to the sum grade of irregular opacities of 2–3 on the ICOERD scale or finding of bilateral honeycombing. It is the authors' opinion that the ICOERD scale is somewhat rough considering very limited opacities. Subclasses (e.g. 1/0, 1/1, 1/2 mimicking the ILO system) could be used. We therefore recommend that fibrosis sufficient for asbestosis according to the ICOERD system could represent the sum grade of ≥ 2 –3 irregular opacities or bilateral honeycombing (sum grade ≥ 2).

Should there be minimum criteria for plaques to be accepted as occupational disease?

If yes, these criteria and the classification system to be used must be defined.

Very small plaques may be common but difficult to separate from naturally thicker than average pleura, intercostal muscles, subpleural scars, adhesions etc. in CT/HRCT. They possess little if any functional or other deleterious effects. Diagnosing them may thus be frustrating and even harmful to the patient. From 2000 onwards, even the ILO system for reporting radiographs records only plaques of ≥ 3 mm in thickness. In Finland, a considerable number of the general population harbors radiographic plaques (Zitting 1995).

When asbestos-exposed workers with pleural plaques were compared to hospital patients with no known asbestos exposure with CT (Tiitola et al. 2002b), the following differences emerged:

Plaque characteristics	Controls	Exposed workers
Greatest thickness	< 10 mm	> 5 mm
Calcification	none little	little considerable abundant
Plaque area in hemithorax*	< 45 cm ²	> 45 cm ²

* Best cut-off value determined by ROC-analysis

However, even the smaller plaques can be caused by asbestos exposure, thus it is difficult to recommend any minimum criteria for diagnosis. According to ICOERD, all visible pleural thickening is recorded: differential diagnosis of etiology depends upon disease and occupational history.

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3

New Asbestos-Related Disease Entities

David Weissman, National Institute for Occupational Safety and Health, USA

Per Gustavsson, Karolinska Institutet, Sweden

Aubrey Miller, National Institute of Environmental Health Sciences, USA

Lesley Rushton, Imperial College London, England

Leslie Stayner, University of Illinois at Chicago, USA

Paula Pallasaho, Finnish Institute of Occupational Health, Finland

Henrik Wolff, Finnish Institute of Occupational Health, Finland

Introduction

In 1997, The Helsinki Criteria document was developed by a group of 19 participants from eight countries. The group was charged to “discuss disorders in association with asbestos and...agree upon state of the art criteria...for diagnosis and attribution with respect to asbestos” (1). The 1997 Criteria provided a framework for determining attribution of asbestos-causation at the individual level for several conditions, including asbestosis, pleural disorders, mesothelioma, and lung cancer.

From the standpoint of determining asbestos-causation at the individual level, lung cancer was perhaps the greatest challenge. As noted in the Criteria, lung cancer occurs at a relatively high incidence in the general, non-asbestos-exposed population. Thus, it is not possible to determine with certainty whether an asbestos-exposed individual’s lung cancer developed because of asbestos exposure or from some other cause. Instead, attribution at the individual level requires a probabilistic approach, estimating the likelihood that asbestos has caused or contributed materially to disease development.

The model underlying the Criteria’s approach to lung cancer estimated a linear increase in the relative risk (RR) for lung cancer with increasing cumulative asbestos exposure (2). The Criteria considered a level of exposure associated with a 50% or greater chance of asbestos-causation as a threshold for determining individual attribution based on the often used “more likely than not” civil standard of proof. The RR associated with this attributable fraction among the exposed (AF) is 2. However, lower levels of RR are also associated with some probability of causation. This can be calculated using the following formula: $AF = (RR-1)/RR$ (3). Proceedings of the Criteria workgroup note that in some situations, a RR of 1.1 has been accepted as indication of a material

contribution to causation (2). Based on the formula above, this RR would be associated with a 9% chance of asbestos causation. The Criteria also addressed latency, requiring a minimum of ten years from the first asbestos exposure to attribute lung cancer to asbestos. Finally, although the Criteria acknowledged the importance of cigarette smoking as a cause of lung cancer, it did not attempt to apportion the relative contributions of asbestos exposure and tobacco smoking.

The Criteria and its associated proceedings document identify a cumulative asbestos exposure history of 25 fiber/mL-years as raising the RR of lung cancer to 2 and suggest practical ways to document exposure at or above that level in an individual. One approach is to document occupational history. Examples of sufficient occupational history included “1 year of heavy exposure (e.g. manufacture of asbestos products, asbestos spraying, insulation work with asbestos materials, and demolition of old buildings) or five to ten years of moderate exposure (e.g., construction, shipbuilding)...In some circumstances of extremely high asbestos exposure, a 2-fold risk of lung cancer can be achieved with exposure of less than 1 year.” The presence of asbestosis diagnosed radiologically (by plain chest film or computed tomography) or histologically also documents sufficient exposure.

The Criteria also addresses use of asbestos bodies and fiber counts in lung tissue and bronchoalveolar lavage (BAL) fluid as biomarkers of 25 fiber/mL-years of exposure. It recommends that fiber levels of “2 million amphibole fibers (>5 μm) per gram of dry lung tissue or 5 million amphibole fibers (> 1 μm) per gram of dry lung tissue” be used as thresholds and notes that “[t]his lung fiber concentration is approximately equal to 5,000 to 15 000 asbestos bodies per gram of dry tissue, or 5 to 15 asbestos bodies per milliliter” of BAL. It also recommends electron microscopic fiber analyses “[w]hen asbestos body concentrations are less than 10 000 asbestos bodies per gram of dry tissue.” It should be noted that recommendations for fiber analyses apply only to amphibole fibers, since chrysotile fibers are cleared more quickly from lung tissue. Thus, occupational history is “probably a better indicator of lung cancer risk from chrysotile than fiber burden analysis.”

The current review addresses selected conditions not addressed by the original Helsinki Criteria document where new evidence of asbestos-causation has since emerged. It provides information that will help those faced with the task of attributing causation to asbestos at the individual level. Although the risk of developing these conditions may increase with asbestos exposure, they also occur in the general population and are associated with other risk factors. Thus, the challenge in determining asbestos-causation of these conditions at the individual level parallels that faced by the original Criteria document in addressing lung cancer. Although complete information is not always available,

the review provides information to assist those who must determine individual causation, such as strength of evidence for asbestos-causation, magnitude of effect, exposure-response relationships, and other risk factors.

Methods

New entities to be evaluated were suggested by the Helsinki Criteria Update Group, and supplemented based on suggestions from the New Entities Workgroup. Entities addressed in the report include the following cancers: laryngeal, ovarian, stomach, and colorectal. In addition, the report addresses ventilatory impairment and chronic airway obstruction; and retroperitoneal fibrosis. An individual Workgroup member took the lead for each evaluated entity. Workgroup products were reviewed by the entire group and final conclusions were required to be based on group consensus.

When available, evaluations of the asbestos-related entities made use of one or more high-quality, structured, authoritative reviews that were available in English as foundations. For example, evaluations of asbestos-related cancers made use of a recent authoritative review by the International Agency for Research on Cancer (IARC) in March, 2009 (4). The IARC study concluded that “[a]sbestos causes mesothelioma and cancer of the lung, larynx, and ovary. Also positive associations have been observed between exposure to all forms of asbestos and cancer of the pharynx, stomach, and colorectum. For cancer of the colorectum, the Working Group was evenly divided as to whether the evidence was strong enough to warrant classification as sufficient.” The current review assesses whether literature published since IARC report provides information that might have affected its conclusions.

If past structured English-language reviews were not available, or to identify references published after the structured reviews, potential references for consideration were identified using searches of PubMed. At a minimum, searches included the disease entity name and the word “asbestos.” Abstracts were used to identify potentially relevant articles for further review. Potentially relevant articles were also identified from the reference lists of the fully reviewed articles and Workgroup members’ personal knowledge of the literature. The focus of the review was on human studies, although information from animal studies was also considered, as appropriate. Tables documenting references considered in foundational structured reviews and additional references identified by the workgroup are provided in an online supplement.

Evaluated entities were classified for strength of evidence for asbestos-causation using categories paralleling those that the US National Toxicology Program (NTP) uses to classify potential carcinogens (5). “Entity known to be

caused by asbestos” was defined by sufficient evidence in humans to indicate a causal relationship between exposure to asbestos and development of the entity. In the case of asbestos-related cancers reviewed here, it is equivalent to the IARC Group 1 classification, “sufficient evidence of carcinogenicity in humans.” “Entity reasonably anticipated to be caused by asbestos” was defined by limited evidence in humans which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded. In the case of asbestos-related cancers reviewed here, it is equivalent to the IARC Group 2A classification “probably carcinogenic in humans.” An additional category, “not classifiable” could also be used. In deciding whether new information had been published that might have affected the IARC classifications, the weight of evidence in light of conventional Bradford Hill Criteria (e.g. strength, consistency, specificity, temporality, biological gradient, plausibility) was considered.

In general, only limited exposure-response information is available for the new asbestos-related entities, including cancers, evaluated here. To provide an approximation of the RR for asbestos-causation of a new cancer entity relative to the RR for lung cancer in an exposed cohort, cohort studies that evaluated RRs for the both a new cancer entity and lung cancer were identified and the quantitative relationships between these RRs were assessed. For cohort studies that included men and women, lung cancer RRs based on data for both genders were used in the analyses. For stomach and colorectal cancer, linear regression analyses relating SMR values for these entities and for lung cancer were obtained from figures 2.1 and 2.2 respectively of the IARC review of asbestos (4). For laryngeal cancer and ovarian cancer, SIR and SMR values respectively for the new cancer entity were obtained from published cohort studies reporting at least 2 asbestos-exposed individuals with the entity and the values related to reported risks for lung cancer by linear regression. Based on these analyses, for each new entity, RR for the entity when lung cancer RR is 2; and RR for lung cancer when the new entity RR is 2 are reported. In general, SMR or SIR values from total cohorts are used in these analyses. However, in a few studies, two non-overlapping cohorts were reported in a single publication. In this situation, cohorts were evaluated separately.

Cancers for which IARC found sufficient evidence for asbestos-causation in humans

Laryngeal cancer

Laryngeal cancer (ICD-9 161; ICD-10 C32) accounts for approximately 1.2% of world cancer cases and 82,000 deaths a year (6). Most laryngeal cancers are squamous and most arise in the glottis (vocal cords). Supraglottic, and subglottic laryngeal cancers are relatively rare. This disease is markedly more frequent in males than in females; (male: female ratio of 12:1 and 6:1 in developing and developed countries, respectively) and there is a large geographic variability in disease frequency. Survival from cancer of the larynx in developed countries is moderately good. The main risk factors for cancer of the larynx are tobacco and alcohol, each of which has a multiplicative effect (7-9).

The role of asbestos in causing laryngeal cancer remains controversial (10) with differing results between cohort and case-control studies.

Cohort studies

IARC reviewed available cohort studies as part of its recent update (4); Table 1 in online supplement). As noted by IARC these studies cover a range of industries, some of which evaluated risk of laryngeal cancer in workers with asbestosis, who thus were heavily exposed. Many of the studies observed only small numbers of laryngeal cancers giving wide confidence intervals around the risk estimates. Larger studies include Reid (2004) (11), (RR=1.82, 95%CI 1.16, 2.85), Liddell (1997) (12) (SMR=1.11), Selikoff and Seidman (1991) (13) (RR=1.70), Raffn (1989) (14) (SIR=1.66, 95%CI 0.91,2.78), Finkelstein (2004) (15) (SMR=1.32, 95%CI 0.72, 2.21), Tola (1988) (16) (SIR=1.20, 95%CI 0.77, 1.79) and Puntoni (2001) (17) (RR=1.64, 95%CI 1.21, 2.32).

Cohort studies not reviewed in the IARC report include a cohort in the Swedish construction industry of 307 799 male workers followed during 1971–2000. Asbestos exposure was related to an increased laryngeal cancer incidence, with a RR of 1.9 (95% CI=1.2-3.1) for workers ever exposed to asbestos (adjustment for smoking) (18). This association was stronger for workers with a moderate exposure level (RR=2.3, 95% CI=1.4-3.8); however, there were only two laryngeal cancers in the high-exposure group.

Harding et al. (2009) (19) report an SMR of 1.48 (95%CI 1.09, 1.45) and a PMR of 1.01 (95%CI 0.76, 1.34) in an update of a large cohort of British asbestos-exposed workers. In a Poisson regression analysis adjusted for age and sex, laryngeal cancer was associated with age exposed, length of exposure and smoking status.

A study of asbestos cement workers in Italy found an SMR of 0.97 (95%CI 0.31, 2.26) based on only five cases of laryngeal cancer (20). A study of asbestos-related cancers among Norwegian Royal Navy personnel found no elevated risk of laryngeal cancer (21).

Some of the studies have attempted to investigate dose-response relationship using cumulative exposure and other proxy measures of dose such as duration of exposure to asbestos dust, although the numbers of laryngeal cancers are extremely small. There is a tendency for the highest categories to show greater risks than those found 'forever' exposed.

Risk of laryngeal cancer relative to lung cancer in the cohort studies reported by IARC, supplemented with the newer studies reported here, was evaluated. There was no relationship between laryngeal and lung cancer SMR reported in 20 cohort studies, perhaps because laryngeal cancer is less likely to result in mortality if appropriately treated and thus might be less frequently reported on death certificates than lung cancer. However, there was a strong relationship between laryngeal and lung cancer SIR, as shown based on data from seven non-overlapping cohorts reported in six publications that is plotted in Figure 1. The estimated laryngeal cancer SIR is 1.58 when the lung cancer SIR is 2. The estimated lung cancer SIR is 2.78 when the laryngeal cancer SIR is 2.

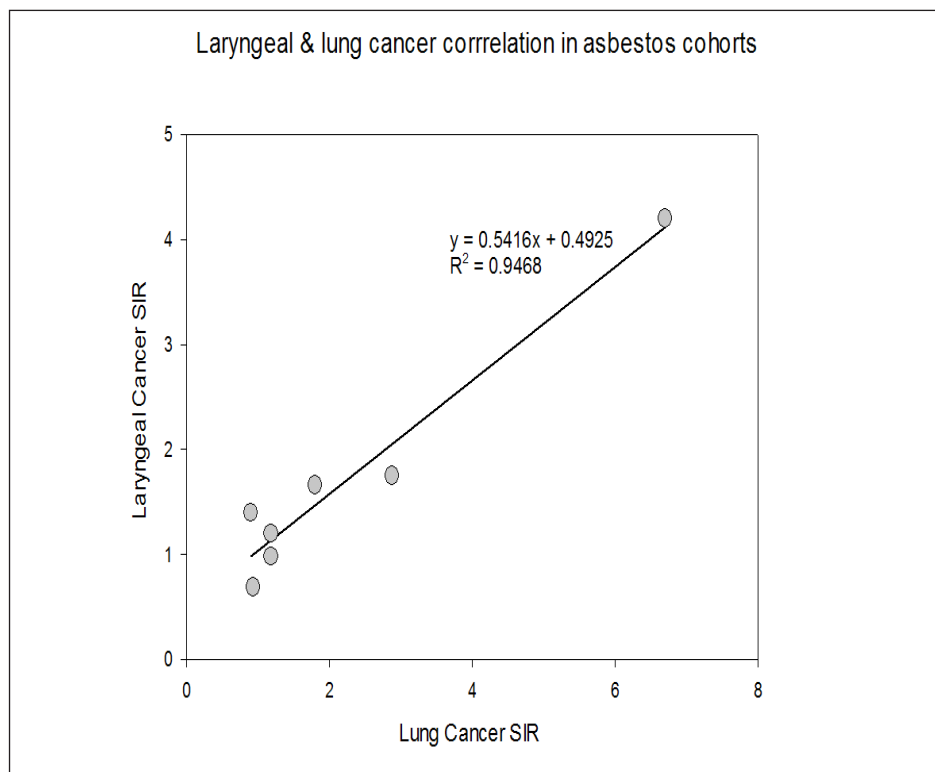


Figure 1. Laryngeal and lung cancer correlation in asbestos cohorts.

Case-control studies

There have also been a number of case-control studies. IARC reviewed 15 of these; all except one (22) showed a positive association. Fortunato et al. (2012) (23) carried out a review and meta-analysis of 14 case-control studies that controlled for alcohol and tobacco to inform selection of a suitable risk estimate for use in a laryngeal cancer burden estimate for Great Britain (GB). Nine of the 14 studies were thought to be relevant to exposure experience in GB and were included in a meta-analysis (see below and Table 2 in online supplement).

The studies vary in size with the odds ratios (OR) ranging from just below 1 to 1.8. Four studies also gave risk estimates without adjustment for tobacco and alcohol consumption. In Dietz et al. (2004) (24) and Muscat & Wynder (1992) (25), the association between asbestos exposure and laryngeal cancer was weakened by controlling for other covariates; in Brown et al. (1988) (26) and Olsen et al. (1984) (27), the estimates were the same with or without adjustment for tobacco and alcohol consumption.

Four of the case-control studies (Gustavsson et al. 1998 (28), Imbernon et al. 1995 (29), Marchand et al. 2000 (30), Wortley et al. 1992 (31)) presented results on the dose-response relationships with two (Gustavsson and Marchand) showing a trend for increasing risk as cumulative exposure increased, but the results were unclear in the other two studies.

Reviews and meta-analyses

There have been several reviews of laryngeal cancer and asbestos exposure with varying conclusions. Four reviews (Browne & Gee 2000 (32), Edelman 1989 (33), Griffiths & Molony 2003 (34), Wight et al. 2003 (35)) have concluded that, overall, the evidence does not indicate that asbestos exposure increases the risk of laryngeal cancer and that positive results are probably due to a missing or insufficient adjustment for alcohol and tobacco consumption. They found that associations were significant in case-control studies without adjustment for smoking and alcohol consumption, or borderline significant with these adjustments. Among cohort studies, no associations were found.

In contrast, other reviews have concluded that there is a positive association between laryngeal cancer and asbestos exposure. Goodman et al. (1999) (36) reviewed 69 asbestos-exposed occupational cohorts, 42 in Europe, 22 in North America and the remainder elsewhere. The earliest study was published in 1967 and the most recent in 1997. The studies covered a variety of occupations, including: asbestos products manufacture (22%); cement workers (20%); shipyard workers (12%); asbestos miners and millers (10%); and textile workers (10%).

The pooled analysis had 4 cohorts that provided results with latency and 27 without. Overall, the meta-SMR for laryngeal cancer from these four cohort studies, without taking into account latency and confounding factors (tobacco and alcohol), was 1.33 (95% CI=1.14–1.55), with a very high degree of homogeneity ($p=0.99$). In addition, a proxy of dosage exposure (using deaths from mesothelioma) showed no dose-response in laryngeal cancer. A weak association between laryngeal cancer and asbestos was concluded.

Browne and Gee (2000) reviewed 22 cohort studies including observed and expected numbers of laryngeal cancer deaths (32). The summary of all cohorts showed a mean SMR for laryngeal cancer of 1.08 ($O=114$, $E=105.8$); among these 22 studies, 17 are common with the meta-analysis by Goodman et al. (1999) (36). In addition, 17 case-control studies were also reviewed (9 with adjustment for smoking and alcohol, 4 with adjustment for only smoking and 4 without adjustment): of the 17 studies, 8 showed no increase in relative risk; of the remaining nine, the increase in seven was not significant and the significance was only borderline in the two remaining ($RR=1.8$, 95% CI=1.0–3.4 (Olsen et al., 1984) (27); $RR=2.4$, 95% CI=1.0–5.9 (Blot et al., 1980) (37). The mean RR for seven of the nine case-control studies with adjustment for smoking and alcohol was 1.25. Two studies were not included in the meta-analysis: Elwood et al., 1984 (38) did not give figures and mentioned that no indication of any substantial relationship was found; Zaganiski et al. (1986) (39) used two methods, one based on self-reported exposure and the other one based on occupations but only the last one was retained.

The British Institute of Medicine (IOM) carried out a review and meta-analysis of both cohort studies and case-control studies (40). For cohort studies the RR was 1.4 (95%CI 1.19, 1.64) for any versus no exposure. For 'high' versus no exposure the lower bound summary (using the smallest high versus no exposure metric in studies with multiple exposure gradient metrics) RR was 2.02 (95%CI 1.64, 2.47) and the upper bound (using the largest high versus no exposure metric) RR was 2.57 (95%CI 1.47, 4.49). A meta-analysis of case-control studies gave a summary RR of 1.43 (1.15, 1.78) before adjusting for tobacco and alcohol with an adjusted summary meta-RR of 1.18 (95% CI 1.01, 1.37).

The meta-analysis by Fortunato et al. (2012) included nine of the studies which were thought to be relevant to exposure experience in GB (23). Five studies were excluded (Ahrens et al. 1991 (41), asbestos exposure assessment based on self-report; Berrino et al. 2003 (42), combined larynx and hypopharynx cancer; De Stefani et al. 1998 (43), Elci et al. 2002 (44), Shangina et al. 2006 (45) were conducted in countries with different exposure patterns to those in GB).

The meta-analysis, combining 9 studies and using the inverse weighted variance method, found an RR of 1.37 (95% CI= 1.17–1.60) associated with any exposure to asbestos (test for heterogeneity: $p=0.94$). Four of the case-control

studies presented results on dose-response relationships (28–31). The meta-SIR from the combined analysis of the highest category of exposure from these 4 studies was 1.48 (95% CI=1.10–1.97; test for heterogeneity: $p = 0.65$); for the lowest level of exposure the meta-SIR was 1.16 (95% CI=1.02–1.31; test for heterogeneity: $p = 0.99$). However, all four studies used different measures of exposure and cut-offs for categorization so the result must be viewed circumspectly.

Sensitivity analyses removing each study in turn did not substantially change the results; however, the association was weakened (meta-SIR of the 14 studies =1.28, 95% CI=1.13–1.44) with smaller homogeneity ($p=0.62$) when the five case-control studies without dose-response results were removed.

Overall conclusions

Overall, both cohort and case-control studies and also meta-analyses provide consistent evidence of an increased risk of laryngeal cancer associated with asbestos exposure. There is also some evidence that increasing exposure increases this risk, although results are limited by small numbers of cases and thus are not consistent across studies.

From the standpoint of magnitude of risk, the excess risk associated with ever exposure to asbestos varies between the studies but is of the order of 40–50%. Dose-response analyses do not consistently show an increasing risk with increased exposure and also other measures such duration of exposure and time since first exposure. However, the excess risk for the highest exposure categories tends to be higher than that associated with ever exposure and varies between 40% and over 100% i.e. double the risk at the highest exposure.

Thus, the weight of literature remains consistent with IARC's recent evaluation and laryngeal cancer is classified as an entity known to be caused by asbestos (equivalent to IARC Group 1). Based on laryngeal and lung cancer SIRs reported from published cohort studies, we estimate the RR for laryngeal cancer in an exposed cohort to be somewhat less than the RR for lung cancer. Under conditions of asbestos exposure associated with a RR for lung cancer of 2, the estimated RR for laryngeal cancer is 1.58, with an estimated AF for asbestos-causation of about 37%. When the RR for laryngeal cancer is 2, the estimated RR for lung cancer is 2.78.

Ovarian cancer

About 1.4% of women will be diagnosed with ovarian cancer during their life (46). Ovarian cancer is a heterogeneous disease, with several histopathological subtypes including serous, clear cell, endometriosis, and mucinous subtypes (47). Risk factors differ somewhat between subtypes (48). However, in general, risk factors include hereditary factors (family history of ovarian cancer, personal history of breast cancer, mutations in the genes *BRCA1* or *BRCA2*, Lynch syndrome), advanced age, nulligravida, infertility, early age at menarche, late age at natural menopause, estrogen, androgens, perineal talc exposure, endometriosis, pelvic inflammatory disease, obesity, and residence at extremes in latitude. Protective factors include multiparity, breastfeeding, oral contraceptives, progestin, hysterectomy, and tubal ligation. Impact of fertility drugs, exercise, and cigarette smoking remain to be fully established (49).

In 2009, the Monograph program of IARC conducted a review of fibers including asbestos (50). The monograph committee reached the conclusion for the first time that there was sufficient evidence for a causal association between exposure to asbestos and the risk of ovarian cancer.

Fourteen studies were included in the IARC review (4) (see table 3 in online supplement for design and findings of various studies, including those considered by IARC). In its review, the Working Group included ten occupational cohorts, three studies with community exposure, and two case-control studies. They concluded that causality was clearly established based on the strong associations observed in five cohort studies of workers with high occupational exposures (51–55), and was additionally supported by weaker but positive findings of an excess among women exposed from non-occupational sources (56–58), and in two case-control studies (59, 60). They also considered the issue of misclassification of mesothelioma and ovarian cancer. This is an important issue, since it has long been recognized that there may be severe misclassification in the diagnosis of ovarian cancer and mesothelioma.

Histopathologic confirmation can be used to distinguish between these tumors (61), however many of the studies relied on death certificates, which are known to be highly insensitive and non-specific for the diagnosis of mesothelioma. The Working Group noted that in three studies a careful pathologic review was conducted, and in all of them there were an insufficient number of misclassified cases to explain the observed positive associations. Finally, the Working Group suggested that the findings of an excess of ovarian cancer in women exposed to asbestos was biologically plausible based on the findings of accumulation of asbestos fibers in the ovaries of exposed women (62, 63).

Only two new epidemiologic investigations have been published since the time of the IARC review, both of which provide some additional support for the hypothesis that asbestos exposure is causally associated with ovarian cancer. The first was a cohort study of women who were exposed to crocidolite during childhood in Wittenoon, Australia (64). An approximately two to four fold increase in ovarian cancer incidence was observed depending on whether person-time was ended at the time when subjects were lost to follow-up (SIR=3.55, 95% CI=1.30,7.72) or not (SIR= 2.50,95%CI=0.92–5.46). The latter analysis is negatively biased since it results in an overestimation of the expected number of cases. The second study reported an excess of ovarian cancer mortality based on one case (SMR=7.69, 95%CI=1.36, 43.58) in a cohort of Chinese textile workers (65). Although the small number of cases in both of these studies precludes any strong conclusions, they are consistent with the excess of ovarian cancer observed in other cohorts previously reviewed by IARC.

Risk of ovarian cancer mortality relative to lung cancer mortality in the cohort studies considered by IARC, supplemented with additional available studies, is shown in Figure 2 (ovarian and lung cancer SMRs were obtained from 17 non-overlapping cohorts reported in 15 publications). One of the studies reported SMRs in two ways (57). “SMR1” assumed that subjects who were lost to follow up were alive at the end of the study. “SMR2” censored subjects lost to follow up at the date last known to be alive. Because the first approach generated larger estimates of person-years at risk, it resulted in smaller “SMR1” values for cancers (lung & trachea = 1.74; ovarian = 1.26). The second approach generated smaller estimates of person-years at risk and larger “SMR2” values for cancers (lung & trachea = 2.15; ovarian = 1.52). Based on linear regression analysis of all studies, and using the “SMR1” values from that individual study, when the lung cancer SMR is 2, the ovarian cancer SMR is 2.18 ($R^2 = 0.36$). When the ovarian cancer SMR is 2, the lung cancer SMR is 1.72. Essentially similar results, shown in Figure 2, were obtained when the linear regression analysis was performed using “SMR2” values from that study (when lung cancer SMR = 2, ovarian cancer SMR = 2.18; when ovarian cancer SMR = 2, lung cancer SMR = 1.71; $R^2 = 0.35$).

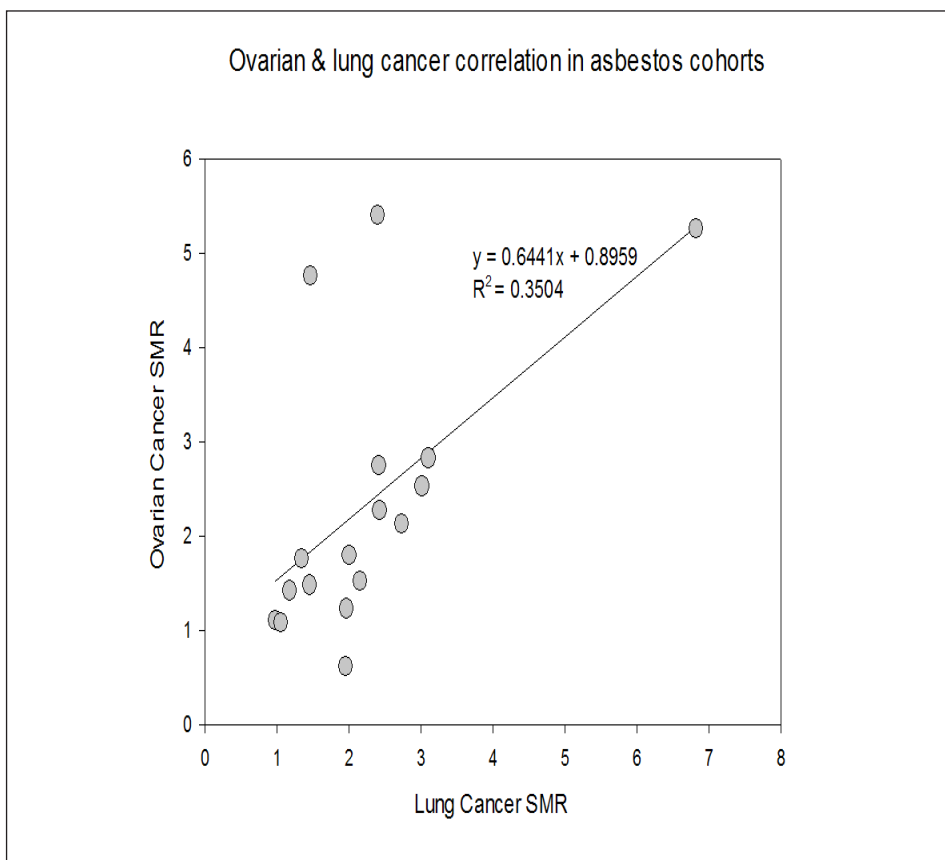


Figure 2. Ovarian and lung cancer correlation in asbestos cohorts.

Despite the conclusions by IARC and the support from recent studies, the hypothesis that asbestos is cause of ovarian cancer remains controversial (66). Two other systematic reviews and meta-analyses have been published since the IARC review. These studies reached somewhat different conclusions largely due to differences in their criteria for study inclusion (66, 67). In a meta-analysis by Camargo et al., the analysis was restricted to only include studies with clear, and unequivocal evidence of occupational exposure to asbestos (67). The meta-analysis by Reid et al. (66) included studies that involved non-occupational exposure (56, 58) and two other case-control studies that Camargo et al. decided had inadequate documentation of asbestos exposure (59, 68). In addition, the analysis by Camargo et al. was able to include the findings from two cohort studies of U.S. asbestos textile workers (69, 70). The authors of these studies provided observed and expected deaths for ovarian cancer to Camargo et al., which had not been previously published and available to Reid et al.

Camargo et al. reported a pooled relative risk (RR) estimate of 1.77 (95% CI=1.37–2.28). There was borderline evidence of heterogeneity ($p=0.06$) in this analysis. This heterogeneity was attributable to higher estimates of risk in studies of workers with asbestosis, cohorts with RR of greater than 2 for lung cancer, and studies conducted in Europe. A sub-analysis of findings for high exposure groups in each study yielded even stronger results with a nearly threefold increase in risk (RR= 2.78, 95%CI=1.36–5.66). The authors reported that they did not observe any difference in the findings between the studies that did and did not include histopathologic confirmation. Based on their findings the authors concluded that their analysis supported the IARC conclusion that exposure to asbestos is associated with an increased risk of ovarian cancer. The meta-analysis by Reid et al. (65) reported a pooled estimate of the RR (RR=1.75, 95%CI=1.45-2.10) that was remarkably similar to the pooled estimate in the study by Camargo et al. (RR=1.77, 95% CI=1.37–2.28) (67). However, they also observed that the findings were severely attenuated when they restricted the analysis to studies that included pathologic confirmation of the ovarian cancers (RR=1.29, 95%CI=0.97–1.73). Based on their findings Reid et al. concluded that although there was evidence of an increased rate of ovarian cancer among asbestos-exposed women that “result may have occurred because of disease misclassification”.

Overall conclusions

Overall, there are relatively strong and consistent findings of an increased risk for ovarian cancer among women in cohorts with relatively high asbestos exposures. Although there is insufficient data from these studies to perform an exposure-response analysis, our conclusion is also supported by the increase in risk observed among workers in the highest exposure groups in the meta-analysis by Camargo et al. Misclassification of ovarian cancer and mesothelioma is a serious concern, which may have either negatively or positively biased some of these studies. However, the fact that a significant excess of ovarian cancer has also been demonstrated in several studies with pathologic confirmation suggests that the association cannot be entirely explained by misclassification of disease.

Thus, the weight of literature remains consistent with IARC’s recent evaluation and ovarian cancer is classified as an entity known to be caused by asbestos (equivalent to IARC Group 1). Based on ovarian and lung cancer SMRs reported from published cohort studies, under conditions of asbestos exposure associated with a RR for lung cancer of 2, the estimated RR for ovarian cancer is 2.18, with an estimated AF for asbestos-causation of about 54.1%. When the RR for ovarian cancer is 2, the estimated RR for lung cancer is 1.71.

Cancers for which IARC found positive associations with asbestos exposure in humans

Colorectal cancer

Background

Colorectal cancer is the third most common cancer in men and the second in women worldwide. Incidence rates vary 10-fold worldwide, with higher rates in developed countries (6). Earlier case-control studies indicated a protective effect of dietary factors like intake of vitamins and fibres, but this has not been confirmed in later cohort studies. Alcohol consumption is positively associated with colorectal cancer risk while the effect of tobacco smoking is less clear (70). Physical activity, both occupational and during leisure-time has consistently been associated with a reduced risk of colorectal cancer. High versus low activity was associated with a 50% reduced risk (72). Asbestos exposure is more common in manual occupations and physical activity may act as a negative confounder in cohort studies using the general population for reference, and thus attenuate the risk associated with asbestos exposure. Studies based on internal comparisons do not suffer from this potential bias.

In March 2009, IARC evaluated the evidence for an association between asbestos exposure and colorectal cancer (4). The present evaluation is based on the IARC review and relevant studies published since March 2009. Literature was searched in Medline in August 2013 with search terms “asbestos and cancer” (limit: humans) as well as “asbestos and colorectal cancer”.

The IARC evaluation in 2009

The IARC evaluation included 31 cohort studies (see table 4 in online supplement). Of the 21 cohort studies that were considered more influential, 15 showed positive evidence for an association and six showed no evidence. Studies investigating dose-response and/or latency are of special interest.

An elevated mortality from cancer of the colorectum was found in a cohort of 820 male factory workers in USA, exposed to amosite asbestos. SMR was 2.77 (95% CI 1.16–2.80). The ratio of observed to expected deaths increased with increasing interval since initial exposure to asbestos (73).

McDonald et al. (1980) reported an SMR for cancer of the colorectum of 0.78 in a study of 10 939 male and 440 female asbestos miners and millers in Quebec with a predominant exposure to chrysotile asbestos (74). There was a clear trend for SMRs to be higher with heavier exposure. The relative risks for cancer of the colorectum increased in this cohort from 1.00 in workers with a cumulative exposure less than 30 mpcf-y, to 0.93 in workers with 30–300 mpcf-y,

to 1.96 in workers with 300–1000 mpcf–y, and in the group with heaviest exposure, > 1000 mpcf–y, to 5.26.

Albin et al. (1990) reported an overall SMR for cancer of the colorectum of 1.5 (95%CI: 0.7–3.0) in a cohort of 1465 Swedish asbestos-cement workers (75). A positive association between cumulative asbestos exposure and cancer of the colorectum was noted. The SMR was 1.3 (95%CI: 0.5–2.9) for a cumulative exposure of < 15 fibre–years/mL; for those with cumulative exposure of 15–39 fibre–years/ mL, the SMR was 1.1(95%CI: 0.3–3.9); and for those workers in highest exposure category with > 40 fibre–years/mL, the SMR for cancer of the colorectum was 3.4 (95%CI: 1.2–9.5). The trend towards increasing mortality from cancer of the colorectum with increasing cumulative exposure to asbestos was statistically significant, $p = 0.04$. A similar trend was seen for colorectum cancer morbidity.

An excess mortality from colon cancer was observed in a heavily exposed cohort of over 5 000 asbestos insulation board workers in London (52). The overall SMR for colon cancer in this cohort was 1.83 (95%CI: 1.20–2.66). There was evidence for a positive dose–response relationship, in that excess mortality from colon cancer was confined to men who had worked as ladders or had been severely exposed for more than two years. This positive trend was statistically significant, $p = 0.017$.

A report on the incidence of cancer of the colorectum from the Beta-Carotene and Retinol Efficacy Trial (CARET) found a relative risk of 1.36 (95%CI: 0.96–1.93) among 3897 heavy smoker participants occupationally exposed to asbestos as compared to smoker participants not exposed to asbestos (76). The relative risk for cancer of the colorectum was 1.54 (95%CI: 0.99–2.40) among participants with asbestos-induced pleural plaques, interpreted as a marker for heavy asbestos exposure. Risk for cancer of the colorectum increased with worsening pulmonary asbestosis, p for trend = 0.03.

There are a number of other cohort studies supporting an association between asbestos exposure and colorectal cancer (56, 77–84). No evidence of an association was found in six cohort studies (69, 70, 85–88).

The IARC evaluation considered the evidence for a causal association from case-control studies less strong than from cohort studies. However, positive findings were reported in five studies (89–93). No association was found in two studies (94, 95).

There are two studies, both from Sweden, investigating location-specific risk. Both studies (using different study bases) showed that asbestos exposure seems to affect the risk of cancer of colon ascendens (the right part of colon), but not other parts of colon (78, 90).

The IARC evaluation considered five meta-analyses, two of them more recent. IOM (2006) conducted a meta-analysis of 31 cohort studies examining the association between asbestos exposure and cancer of the colorectum (40). In studies comparing “any” versus no exposure, the summary relative risk was 1.15 (95%CI: 1.01–1.31). For studies comparing “high” versus no exposure, the lower-bound summary relative risk was 1.24 (95%CI: 0.91–1.69), and the upper-bound summary relative risk, 1.38 (95%CI: 1.14–1.67). The IOM also conducted a meta-analysis of the published case-control studies. Overall, 13 studies comparing “any” versus no exposure gave a summary relative risk of 1.16 (95%CI: 0.90–1.49). IOM also noted a biological plausibility for a causal association between asbestos exposure and colorectal cancer since the presence of asbestos bodies and asbestos fibers have been demonstrated in the colon of asbestos workers. The IOM (2006) considered the overall epidemiological evidence for a causal association as suggestive but not sufficient (40).

Gamble et al. performed a meta-analysis based on 40 studies focused on dose-response associations (96). They noted no association between cumulative dose of asbestos and colorectal cancer risk, and they observed no trend in cancer of the colorectum mortality with increasing percentage of deaths due to mesothelioma. However, there was a significantly elevated standardized mortality ratio of 1.60 (95%CI: 1.29–2.00) for cancer of the colorectum when the standardized mortality ratio for lung cancer exceeded 3.00, taken as evidence of high exposure to asbestos. There was no elevation of colorectal cancer risk in studies with a lung cancer SMR < 3. The authors developed a scatterplot of SMR for colorectal cancer versus SMR for lung cancer, in a similar way as in the IARC evaluation (see below), with a similar finding: colorectal cancer SMRs tended to be higher in studies showing a high SMR for lung cancer. There was no association between asbestos exposure and rectal cancer.

The IARC working group concluded that the cohort studies gave stronger evidence for an association between asbestos exposure and colorectal cancer than did the case-control studies (4). The working group developed a scatterplot of SMRs for lung cancer versus colorectal cancer from 29 cohort studies. A positive association was seen, $R^2 = 0.59$ (no p-value was given), supporting a causal relationship for colorectal cancer (Figure 3). SMRs for colorectal cancer tended to be lower than SMRs for lung cancer, indicating that the effect of asbestos, in terms of relative risk, is weaker for colorectal cancer than for lung cancer. Based on the linear regression reported by IARC, when the lung cancer SMR is 2, the colorectal cancer SMR is 1.1. When colorectal cancer SMR is 2, the lung cancer SMR is 5.2.

The IARC Working Group was evenly divided in assessing the evidence from human epidemiology studies for an association between asbestos exposure and colorectal cancer as “sufficient” or “limited”.

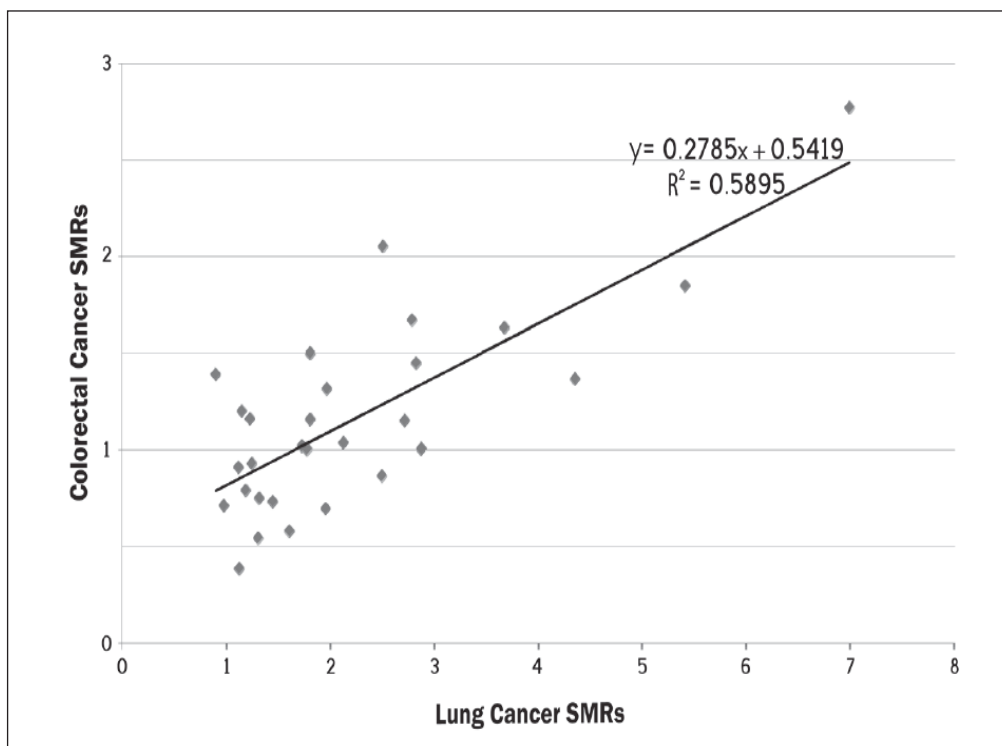


Figure 3. Colorectal and lung cancer correlation in asbestos cohorts (IARC 2012).

Studies published after the IARC evaluation

Harding et al. (2009) reported the mortality in a cohort of 98 117 British asbestos-exposed workers followed from 1971 to 2006 (19). There were 297 deaths from cancer of the colon, SMR 128 (95% CI 114–144), and 183 deaths from rectal cancer SMR 151 (130–174).

Strand et al. (2010) investigated the cancer incidence from 1953 to 2007 in a cohort of 28 300 officers and enlisted servicemen in the Royal Norwegian navy (21). An excess of mesothelioma was found among engine room crew only – supposedly more exposed to asbestos than non-engine room crew. The SIR for colorectal cancer in cohort members in vessel service > 2 years was 1.15 (0.95–1.39), but no association was seen with engine room work, and the study does not support an association with asbestos exposure.

Pesch et al. (2010) reported the mortality up to 2007 among 576 German workers exposed to asbestos (96). The SMR for colorectal cancer (7 cases) was 0.77 (0.31–1.59).

Clin et al. (2011) reported the cancer incidence 1978–2004 in a cohort of 2024 workers from an asbestos reprocessing plant in Calvados (France) (98). There were 25 cases of colorectal cancer, the SIR among workers with the highest average exposure level (9–107 fibers/ml) showed a SIR for colorectal cancer of 7.20 (0.91–56.7). P for trend with average exposure level was 0.02. The association with cumulative exposure was weaker.

Menegozzo et al. (2011) reported the mortality 1965–2005 in a cohort of 1,247 male asbestos cement workers in Naples, Italy (20). There were 14 deaths from cancer of the colon and rectum, SMR 129.9 (71.0–218.0). Dose-response data were not reported for colorectal cancer.

Pavone et al. (2012) studied the mortality in cohort of 1849 railway rolling stock and repair workers in Bologna, followed for mortality 1960–2008 (99). There were 12 cases of colon cancer, SMR 0.81 (95%CI 0.46–1.42). An increased mortality was found both for mesothelioma and lung cancer.

Three small cohort studies, from Japan (100), China (65) and Italy (101) included only few cases of colorectal cancer, no statistically significant excess was reported.

Mortality and cancer incidence in association with environmental exposure to blue asbestos during childhood, the Wittenoom residents' cohort, was reported by Reid et al. (2013) (64). The cohort included 2460 adults that have lived in an asbestos mining town before age 15. Two methods of deriving expected numbers were used which gave different results. Assumption that all lost to follow-up (20% of the cohort) were alive and disease-free at end of follow-up, which underestimates risk, gave a smoking-adjusted SIR for colorectal cancer of 1.21 (0.55–2.29). Censoring of person-years for calculation of expected numbers (but not cases) at latest date known to be alive, which results in greater estimates of risk, gave an SIR of 2.15 (0.98–4.08).

Overall conclusions

The IARC working group considered the evidence quite strong but not definitive for a causal relationship between asbestos exposure and colorectal cancer. Half of the working group considered the evidence from human epidemiology to be sufficient, half considered it limited. Of studies published after the IARC evaluation, a very large cohort of British asbestos workers supported a causal relationship, and a study of French asbestos reprocessing plant workers showed a significantly increasing SIR with average exposure (but not cumulative exposure) to asbestos. A study of Norwegian navy officers and service men, using indirect exposure indicators, a cohort of Italian railway workers, and a smaller study of German asbestos workers gave no support for an association between asbestos exposure and colorectal cancer.

Thus, a relatively large number of cohort and case-control studies show an excess of colorectal cancer in association with asbestos exposure, but the findings are not entirely consistent. A few studies showed a significant positive association with cumulative exposure to asbestos, and one study showed a significant association with average exposure. A meta-analysis taking SMR of lung cancer as an indirect indicator of asbestos exposure showed a fairly consistent pattern with increasing SMR for colorectal cancer when the SMR for lung cancer increased. SMR for colorectal cancer increased with severity of asbestosis in one study. Taken together, these dose-response data are supportive of a causal relationship between asbestos exposure and colorectal cancer. The plausibility of the theory that asbestos causes colorectal cancer has support in mechanistic data showing the presence of asbestos and asbestos bodies in the colon of exposed persons.

Most of the reported studies are cohort studies comparing the risk of colorectal cancer among workers in manual occupations with the general population, with a potential for negative confounding due to the protective effect of physical activity at work on the risk of colon cancer. This may have tended to underestimate the observed relative risk rather than overestimating it. Considering the large number of positive studies, the demonstrated dose-response, and potential for negative confounding, it seems likely that asbestos exposure is causally related to colorectal cancer. However, the reports published since the IARC evaluation are not definitive. Recognizing that the available evidence is relatively strong, colorectal cancer is classified as reasonably anticipated to be caused by asbestos (equivalent to IARC Group 2A).

Few studies have presented risk estimates separately for colon and rectal cancer. For those which have done this, asbestos seems to affect the risk of cancer of the colon, especially cancer of the right part of colon.

The magnitude of the reported relative risk varies between studies and is in the range of 1.3 to 5. Assessed study-by-study, SMRs for colorectal cancer tended to be lower than SMRs for lung cancer, indicating that the effect of asbestos, in terms of relative risk, is considerably weaker for colorectal cancer than for lung cancer. Based on IARC's analysis shown in Figure 3, under conditions of asbestos exposure associated with a RR for lung cancer of 2, the estimated RR for colorectal cancer is 1.1, with an estimated AF for asbestos-causation of about 9%. When the RR for colorectal cancer is 2, the estimated RR for lung cancer is 5.2.

Stomach cancer

Stomach cancer is one of the most frequently occurring cancers and causes of cancer death globally (6). Age-standardised incidence rates vary considerably among countries with high levels prevailing in Japan and Eastern Asia, China, Eastern Europe and tropical South America and much lower rates in Eastern and Northern Africa, North America and Southern Asia (102). On average, developed countries have a better 5-year survival rate (overall 28%) than developing countries (18%) (102). The strongest factor known to be associated with stomach cancer is chronic infection with *Helicobacter pylori*, a gram-negative bacterium (103). The prevalence of *H. pylori* infection in humans is higher in developing countries (approximately 75%) and lower (around 60%) in developed countries although it has been suggested that only 5% of infected hosts will develop this cancer (102). A high dietary intake of irritant substances, such as salts and nitrates, are known to cause chronic inflammation and gastritis (104).

Cohort studies

Cohort studies reviewed in the recent update by IARC (4) together with more recent papers identified in a systematic review and meta-analysis by Fortunato & Rushton (found in (105)) are summarized in table 5 of the online supplement. Studies have been carried out mainly in Europe and North America, but also include cohorts from China, Russia and Australia and range from very small to over 55 000 workers. Several cohorts included women although they were usually a small proportion of the total. Four cohorts involved only women (51, 53, 106) and 3 reported results for the total cohort (86, 107, 108). Asbestos exposure occurred in a range of industries with the most common occupations being insulators, generic asbestos workers, textile asbestos workers, cement asbestos workers, and miners.

The largest overall cohort RRs for stomach cancer mortality were among the earliest studies of insulation workers (82) with a RR of 3.52 (95%CI 2.19, 5.67), and among two sets of workers in Chinese asbestos factories Pang 1997 (109), Zhu & Wang 1993 (108): RRs were 4.40 (95%CI 1.64, 11.84) and 2.40 (95%CI 1.65, 3.48), respectively for stomach cancer mortality. Two studies carried out in Canada (Liddell et al 1997 (12)) and UK (Harding et al. 2009 (19)), involving 183 and 322 deaths from stomach cancer, show significantly increased RR estimates with narrow confidence intervals: RR=1.24 (95%CI 1.07, 1.44) and RR=1.66 (95% CI 1.49, 1.86) respectively. Fewer stomach cancer incidence studies have been carried out. The largest overall cohort RR for incidence was among Danish asbestos cement workers (Raffn et al. 1989 (14)) with a RR of 1.43 (95% CI:1.03–1.93). All the other incidence studies reported RRs close to one.

Estimates of cumulative (e.g. fibre-years) or duration of exposure among asbestos-exposed workers were reported in at least 11 studies but patterns were unclear in most studies. For example, no clear patterns of increase in mortality of stomach cancer by duration of exposure were found in Harding et al (19), by degree of exposure in Berry et al (52), or by cumulative exposure in Liddell et al (12); the RR for the highest cumulative exposure category (>1000 mcpf/year) in Liddell et al was 3.21. In contrast, Selikoff et al 1979 (82) found evidence of a dose–response relationship with duration of asbestos exposure to asbestos with the SMR for cancer of the stomach increasing from 0.00 in workers exposed for < 20 years, to 4.00 (95%CI: 1.47–8.71) in those exposed for 20–35 years, and to 3.42 (95%CI 1.82–5.85) in those exposed for >35 years.

Risk of stomach cancer mortality relative to lung cancer mortality in 30 exposed cohorts was reported by IARC, which found a linear relationship between SMRs for stomach cancer and lung cancer, with an R^2 value of 0.6623 (Figure 4) (4). SMRs for stomach cancer were generally lower than those for lung cancer. Based on the linear regression equation reported by IARC, under conditions of asbestos exposure associated with a lung cancer SMR of 2, the stomach cancer SMR is 1.2. When the stomach cancer SMR is 2, the lung cancer SMR is 3.96.

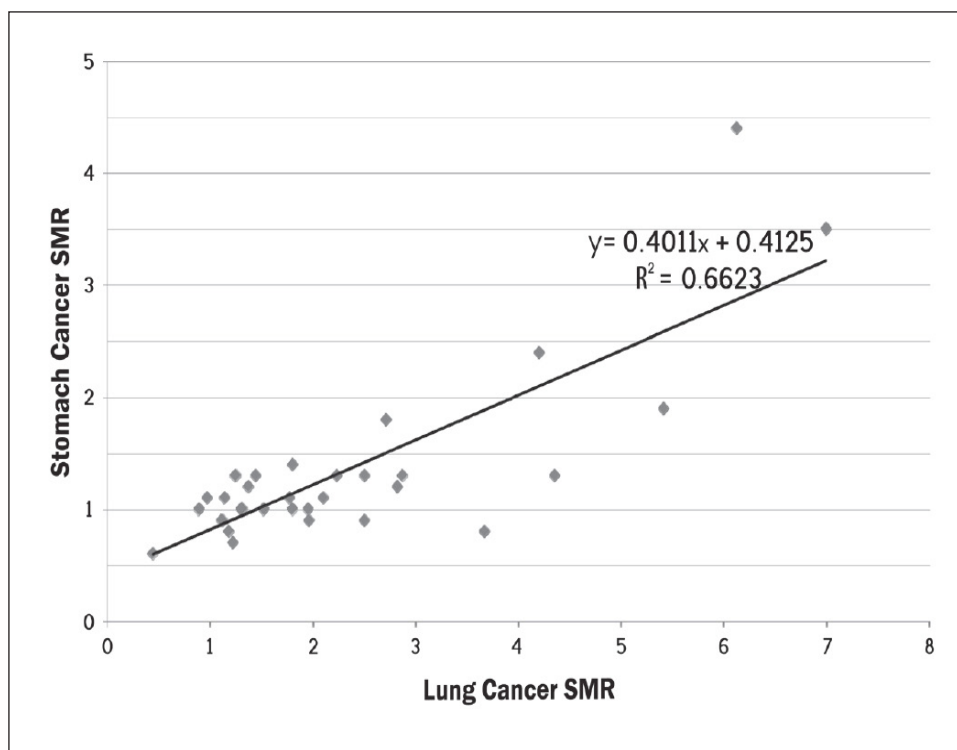


Figure 4. Stomach and lung cancer correlation in asbestos cohorts (IARC 2012).

There have been several studies carried out more recently. No results were reported for stomach cancer in the recent update of mortality and cancer incidence in association with environmental exposure to blue asbestos during childhood in the Australian Wittenoon residents' cohort (64). No elevated risk of stomach cancer was seen in the study of Norwegian navy personnel (21). A study of German workers exposed to asbestos found a SMR of 1.15 (0.37, 2.68) for stomach cancer mortality (97). A study of Italian asbestos textile workers reported an SMR of 1.20 (0.67, 1.98) (101).

Case-control studies

IARC reviewed five case control studies exploring the relationship between asbestos exposure and stomach cancer and concluded that they gave inconsistent results. A study from Poland (Krstev et al., 2005) found an OR for cancer of the stomach of 1.5 (95%CI 0.9, 2.4) for workers ever exposed to asbestos, and of 1.2 (95%CI: 0.6–2.3) for workers with tenor more years of exposure to asbestos (109). The largest case–control study (Cocco et al., 1994) reported OR of 0.7 (95%CI: 0.5–1.1) for workers ever exposed to asbestos, and of 1.4 (95%CI: 0.6–3.0) for those with 21+ years of exposure to asbestos (111).

The most strongly positive case–control study linking asbestos to cancer of the stomach is the case–control study nested within the Western Australia mining cohort (Reid *et al.*, 2004) (11). They found an OR of 1.38 (95%CI 0.99, 1.92) for cumulative exposure to crocidolite per fiber/mL-year. Smoking status was associated with cancer of the stomach, but not significantly.

Reviews and meta-analyses

IARC reviews three reviews and meta-analyses. An early one by Frumkin & Berlin (1988) stratified studies by SMR for lung cancer and percentage of deaths from mesothelioma and found an SMR of 0.91 (95%CI 0.71,1.16) for cohorts where the lung cancer SMR was <2.00 and an SMR of 1.34 (95%CI 1.07,1.67) for the lung cancer SMR > 2.00 (112). Gamble (2008) evaluated the weight of evidence for an association between asbestos and stomach cancer and concluded overall that the epidemiological evidence was weak (96).

A meta-analysis of 42 cohort studies by the IOM noted that the 'majority of cohort relative risk estimates for cancer of the stomach exceed the null value (1.0), indicating excesses, although estimates varied considerably in strength' (39). A meta-RR of 1.17 (95%CI 1.07, 1.28) was found for any versus no exposure. For high versus no exposure, the lower meta-RR was 1.31 (95%CI 0.97, 1.76), and the higher bound meta-RR was 1.33 (95%CI 0.98, 1.79). A meta-analysis of the five case–control studies gave a combined RR of 1.11 (95%CI 0.76, 1.64).

The summary OR increased when only extreme exposure was considered (OR, 1.42 95%CI 0.92, 2.20).

In addition to the above, Goodman et al. (1999) reviewed 69 asbestos-exposed occupational cohorts, 42 in Europe, 22 in North America and the remainder elsewhere (36). The earliest study was published in 1967 and the most recent in 1997. The studies covered a variety of occupations, including: asbestos products manufacture (22%); cement workers (20%); shipyard workers (12%); asbestos miners and millers (10%); and textile workers (10%). The pooled analysis had 9 cohorts that provided results for stomach cancer with a latency period of ten years and 33 without. Overall, the meta-SMR for stomach cancer, without taking into account latency, was 1.06 (95%CI 0.99, 1.13), with no significant evidence of heterogeneity ($p=0.13$). However, there was no excess risk when the analysis was based on only 4 studies taking into account latency (meta-SMR=0.92, 95%CI 0.11, 1.10).

An updated meta-analysis of cohort stomach cancer and asbestos studies that included exploration of heterogeneity and publication bias by Fortunato & Rushton (included in reference (105)) found an overall meta-SMR for stomach cancer mortality in the total cohort of 1.16 (95% CI 1.04, 1.30), with heterogeneous results across studies ($p<0.001$).

In a sensitivity analysis, results from Selikoff (1979) (82), Ohlson (1984) (113) and Zhu (1993)(108) had the most influence on the overall result. Statistically significant excesses were observed for men in studies from North America (meta-SMR=1.32, 95% CI 1.06, 1.64), but not in Europe (meta-SMR=1.04, 95%CI 0.90, 1.20) or "Other" (meta-SMR = 1.49, 95% CI: 0.58, 3.83). The pooled analysis within occupational strata demonstrated the highest meta-SMR for stomach cancer among generic asbestos workers (meta-SMR=1.51, 95% CI: 1.16, 1.97), followed by insulators (meta-SMR= 1.27, 95% CI: 0.88, 1.82). When studies were divided into tertiles according to percentage of deaths due to mesothelioma, there was a dose-response relationship of increasing stomach cancer meta-SMRs with increasing percentage of mesothelioma deaths: $\leq 0.69\%$ (SMR = 1.00, 95% CI: 0.85, 1.19); $>0.69\% \leq 2.7\%$ (SMR = 1.18, 95% CI: 1.01, 1.38); $> 2.7\%$ (SMR = 1.25, 95% CI: 1.02, 1.53).

There is also a meta-analysis (Sun et al 2008) (114) published in Chinese with an abstract in English, which included Chinese literature as well that reports a meta-SMR of 1.20 ($P<0.01$) among workers exposed to chrysotile alone or mixed asbestos. The stomach cancer SMR was significantly increased in the asbestos cement workers, the screening mine workers and the insulators, (1.27, 1.21 and 2.13 respectively, $P < 0.05$).

Overall conclusions

Overall, the cohort studies and the various meta-analyses of cohort studies generally provide consistent evidence of an increased risk of stomach cancer associated with asbestos exposure. Risk estimates tend to be higher in cohorts where heavy exposure to asbestos occurs and with long follow-up periods. There is also evidence that increasing exposure increases this risk. There are few case-control studies and these give less consistent results. There is limited information to draw conclusions about the different asbestos fibre types.

From the standpoint of magnitude of risk, the excess risk associated with ever exposure to asbestos varies between the studies but is of the order of 15–20%. Positive dose–response relationships have been observed between cumulative asbestos exposure and stomach cancer mortality in several cohort studies e.g. Selikoff & Hammond (1979) (82), Liddell et al., (1997) (12), Pang et al., (1997) (109).

IARC's recent evaluation continues to be relevant and stomach cancer is classified as an entity that is reasonably anticipated to be caused by asbestos (equivalent to IARC Group 2A). Based on IARC's analysis shown in Figure 4, under conditions of asbestos exposure associated with a RR for lung cancer of 2, the estimated RR for stomach cancer is 1.2, with an estimated AF for asbestos-causation of about 17%. When the RR for stomach cancer is 2, the estimated RR for lung cancer is 3.96.

Non-malignant entities

Ventilatory impairment and chronic airway obstruction

Over the years, the relationship between asbestos exposure, asbestos-induced parenchymal and pleural disease and chronic lung function impairment has received much attention. In 2004, the American Thoracic Society (ATS) noted that asbestos exposure was traditionally considered a cause of restrictive impairment, but its role as a cause of obstructive impairment was more controversial (115). However, ATS also noted that asbestos exposure had long been associated with physiological obstruction and described the involvement of small airways by asbestosis as a potential explanation. Several years later, a Delphi study was conducted by the American College of Chest Physicians (116). The Delphi panel could not reach consensus in answering the question of whether asbestos exposure, in the absence of interstitial fibrosis, could cause chronic obstructive pulmonary disease (COPD). Nor could it reach consensus on the question of whether a decline in small airway flow rates in a smoker can be attributed to asbestos.

Many factors are associated with chronic airway obstruction, of which COPD is the most important cause. In the U.S.A., approximately 75% of COPD cases are attributed to cigarette smoking and another 15% to occupational exposures. COPD is also associated with genetic factors like alpha-1 anti-trypsin deficiency, asthma, respiratory infections and exposure to air pollutants (117). Occupational exposure to a variety of organic and inorganic dusts, vapors, gases, and fumes have been associated with risk for COPD (118). In developing countries, exposure to smoke generated by burning biomass as fuel is a very important risk factor for COPD and, in fact, might be the most important global risk factor for COPD (119).

Longitudinal studies

Cohort studies with longitudinal assessment of spirometry results avoid some limitations of cross-sectional studies. For example, they allow comparison of individuals' findings to their own previous results, avoiding the problem encountered in cross-sectional studies that workers often have better pulmonary function than might be expected from the clinical prediction equations derived from general populations that are used to interpret results (120). A review of the literature identified 20 peer-reviewed longitudinal studies (see table 6 in online supplement). One of those reviewed (121) was a follow-up to an earlier study (122).

In general, cohorts had substantial asbestos exposures and substantial prevalence of interstitial and/or pleural findings (see table 6 in online supplement).

Although their findings vary, several general themes can be drawn from these longitudinal studies. In general, lung function decrements associated with asbestos exposure are restrictive, with forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) falling together and FEV1/FVC percent relatively spared but falling a small amount in some studies (121–131). Radiographic changes that have been associated in many studies with worse pulmonary function at initial evaluation and in some with more rapid subsequent decline are interstitial involvement characterized by irregular small opacities, and diffuse pleural thickening (DPT) (123, 127, 129, 132–135). Findings of studies evaluating associations between the presence of localized pleural thickening (LPT) or pleural plaques and pulmonary function have been less consistent, perhaps due to lesser magnitude of effect (126, 131, 136). There is a suggestion that progression with greater extent of pleural involvement may be associated with greater effect on lung function (131). Smoking contributes to the decline in lung function, in many studies with greater effect on FEV1 than FVC (123, 124, 127, 132, 134, 135, 137). In most studies, greater than additive effects of asbestos and tobacco smoke exposure have not been reported. However, a few have suggested possible interactions (126, 132).

Cumulative asbestos exposure history contributes to rate of FEV1 and FVC decline, but in general the magnitude of effect of exposure alone is less than the magnitude of effect of interstitial disease, DPT, or smoking (123, 133, 135, 138). In a study with mean duration of exposure of about ten years, decline in FVC and FEV1 accelerated after about 15 years since first exposure (122). In a few studies where there had been a long latency of several decades between asbestos exposure and baseline evaluation, the main impact of asbestos exposure on lung function appeared to have occurred by the time of the baseline evaluation (123, 132).

Relationship between radiographic changes and ventilatory impairment

The relationship between radiographic changes and lung function impairment in asbestos-exposed people was recently been examined in a structured literature review and meta-analysis (139). The review identified studies that reported lung function, radiographic findings by computed tomography or plain film, and proportion of smokers among participants. Radiographic changes were categorized as normal imaging, pleural fibrosis (including both pleural plaques [PP] and DPT), or asbestosis (interstitial disease). Information needed to be available about quality of spirometry and the reference equations used to evaluate lung function results. A total of 27 cross-sectional, one case-control, and two longitudinal studies met criteria for inclusion. The final number of participants in the meta-analysis was 9921. The mean duration of occupational exposure to asbestos, reported in 22 studies, ranged from 8.4 to 32.7 years. The latency time, reported in 9 studies, ranged from 24.5 to 43.3 years.

The overall findings were that, among exposed workers, lung function was best in those with normal imaging, worsened in the presence of pleural fibrosis and further worsened in the presence of asbestosis. The quantitative findings of the meta-analysis were as follows: FVC (mean % predicted): normal imaging – 95.7%, pleural fibrosis – 89.0%, asbestosis – 86.5%. FEV1: normal imaging – 93.6%, pleural fibrosis – 89.2%, asbestosis – 85.7%. A smaller group of studies reported FEV1/FVC (as % predicted) in a way that was usable in the meta-analysis, and there was not the same gradient by radiological finding in this parameter (mean FEV1/FVC [% predicted]): normal imaging – 96.4%, pleural fibrosis – 95.4%, asbestosis – 95.5%. In general, the impact of radiological findings on lung function was less when chest computed tomography (CT) was used in studies to identify changes than when plain imaging was used, perhaps reflecting the greater sensitivity of CT. Studies with larger proportions of non-smokers tended to report less impairment in FEV1 in all three radiographic categories. In their discussion, the authors noted that the study could not answer whether the observed statistically significant lung function impairments at the population level were also of clinical relevance at the individual level and

also noted that small decreases in group mean did not preclude clinically important disease in individuals. The authors called for further research, especially on the role of smoking, other occupational exposures (such as other mineral dusts, welding fumes) and possible synergistic effects on the development of functional impairment, especially chronic airway obstruction, in asbestos-exposed workers.

It has been suggested that asbestos exposure and cigarette smoking might interact in producing reduced FEV1/FVC ratio (140). A recent cross-sectional study not included in the meta-analysis addressed whether asbestos exposure alone in the absence of smoking causes obstructive lung disease (141). It evaluated 277 Chinese chrysotile asbestos textile workers (mean exposure duration 16.7 years, 22% nonsmokers) and 177 non-asbestos-exposed controls who worked in the electronics industry in the same geographical area. Obstructive impairment was 2.5 times more prevalent in asbestos-exposed workers than controls (34% vs. 15%). In multivariate analyses limited to nonsmokers, there were significant associations between asbestos exposure and low percent predicted FEV1, FVC and carbon monoxide diffusing capacity (DLCO) after accounting for age. The non-smoking asbestos workers had about 3% lower FEV1/FVC ratios compared to non-smoker control workers of similar age and height, but this difference did not achieve statistical significance. The authors concluded that asbestos exposure, especially when radiographic evidence of interstitial fibrosis from asbestosis is present, leads to significant decreases in FVC, FEV1 and DLCO.

However, asbestos exposure alone was not associated with a significant reduction in the FEV1/FVC ratio. In their discussion, the authors suggested that the failure to demonstrate a significant decrease in FEV1/FVC ratio in nonsmoking asbestos-exposed individuals was the result of insufficient sample size. They also noted that FEV1/FVC ratio generally reflects large airways function, but that the earliest asbestos lung lesions are peri-bronchiolar and not captured by standard lung function testing. They called for further research to assess the progression and clinical significance of asbestos-induced airway dysfunction.

Another recent investigation evaluated associations between radiographic findings and spirometry in 6475 participants in a community-based screening program in Libby, MT, where there had been widespread amphibole asbestos exposure (142). Participants were evaluated by plain chest radiography and spirometry. A total of 50 participants had parenchymal abnormalities, 58 DPT, and 708 LPT. Parenchymal abnormalities were significantly associated with restriction and mixed abnormal spirometry, but not isolated obstruction. DPT and LPT were both significantly associated with restrictive spirometric abnormalities, with the magnitude of effect greater for DPT. Among those with LPT, severity of restriction correlated with the severity of LPT. Several other large cross-sectional studies have also demonstrated a significant association

between LPT and reduction in FVC or restrictive impairment, a lesser effect on lung function of LPT than DPT, and an association between degree of lung function impairment and extent of LPT (143-145).

Several studies have sought to correlate pulmonary function impairment with anatomic changes identifiable by thin-section CT (146-149). One of these studies reported an effort to apportion pulmonary function deficit between asbestos-induced and smoking-related disease using thin-section CT (147).

In this retrospective study of asbestos-exposed individuals who had undergone chest CT, an initial multivariate analysis was used to relate CT features with reduction in total lung capacity (TLC) and DLCO. Important significant individual predictors included extent of pulmonary fibrosis and circumference of diffuse pleural thickening (asbestos-induced effects) and emphysema (felt to be a smoking-associated effect). Combined CT variables could account for 58% of the variability in TLC and 57% of the variability in DLCO. When these predictive equations were applied to a validation group, they were able to explain 52% of the variance in TLC, 40% of the variance in DLCO, and 46% of the variance in FVC. Another study of 590 asbestos-exposed workers in construction trades found that FVC and TLC were negatively correlated with fibrosis score, parenchymal bands, and extent of pleural thickening. They were positively associated with widened retrosternal space. FEV1/FVC was negatively correlated with emphysema and widened retrosternal space and positively correlated with parenchymal bands and subpleural nodules. Thickened bronchial walls did not separate between restriction and obstruction (148).

Overall conclusion

Available studies indicate that the pattern of spirometric impairment associated with asbestos exposure is primarily restrictive, with reduced FEV1 and FVC and relatively preserved FEV1/FVC ratio. Studies have also suggested that a component of airways obstruction can also be present, in particular small airways obstruction, although in the absence of other hazardous co-exposures such as tobacco smoke, obstructive changes are generally of lesser prominence and are more difficult to demonstrate. Statistically significant spirometric impairment can be demonstrated in populations with sufficient exposure to cause pleural thickening or asbestosis, even among those without radiographic changes. However, the prevalence of clinically significant spirometric impairment in such individuals is unclear. The magnitude of impairment is considerably greater in the presence of DPT and/or asbestosis. Also, some studies have also identified LPT as a risk factor for spirometric impairment. Magnitude of impairment increases with age and with smoking.

Thus, restrictive ventilatory impairment in those with sufficient asbestos exposure to potentially cause parenchymal or pleural disease, whether radiographically present or not, is known to be caused by asbestos. Large airway obstruction associated with decreased FEV1/FVC ratio has been associated with asbestos exposure in some studies, but the findings have not been as consistent as for restriction. Thus, large airway obstruction is categorized as reasonably anticipated to be caused by asbestos. Smoking interacts with asbestos exposure in producing this pattern of impairment.

Findings of asbestos-induced pleuroparenchymal disease and of emphysema have been reported to explain only about half the variance in TLC, FVC, and DLCO in those exposed to asbestos with or without tobacco smoking. Therefore, more remains to be learned about the determinants of lung function impairment in asbestos-exposed individuals, particularly in those without radiographic evidence of asbestos-induced parenchymal or pleural disease. In addition, more needs to be learned about how to attribute impairment in lung function to various potential causes when more than one potential cause is present.

Retroperitoneal fibrosis

Retroperitoneal fibrosis (RPF) or Ormond's disease was first described in 1948 and is a rare disease featuring the proliferation of fibrous tissue in the retroperitoneum compartment of the body containing the kidneys, urinary tract, aorta, and various other structures (150). Symptoms result from entrapment of the ureters, the great vessels and their branches, and the surrounding nerves and include lower back, flank and/or abdomen pain, weight loss, fever, malaise, anorexia, non-specific gastrointestinal complaints, and less frequently, urinary symptoms (151).

The pathognomonic feature of RPF is a thick retroperitoneal fibrotic mass covering the abdominal aorta and compressing the ureters (150). About 10–15% of patients with RPF will also have fibrosis outside of the abdomen (152). Histologically, RPF appears as a nonspecific inflammatory process that evolves over time from collagen bundles, with capillary proliferation, and abundant inflammatory cells, predominantly lymphocytes, plasma cells and fibroblasts, to dense matted avascular and acellular connective tissue (151). The inflammatory nature idiopathic RPF is supported by common findings of elevated erythrocyte sedimentation rate, positive antinuclear antibodies, and response to anti-inflammatory medications (150). Malignancy associated RPF is virtually indistinguishable from RPF from other causes and may only be determined by demonstration of small islands of tumor cells within the fibrotic tissue and immunohistological studies (151).

The incidence of RPF was estimated to be one per one million person-years (age standardized) in Finland. Case identification was based on diagnostic codes 5934A (other ureteric obstruction including idiopathic RPF) in ICD 9 (International Classification of Diseases, 9th revision) for 1990–1995 and D20•0 (retroperitoneal benign neoplasm) in ICD 10 for 1996–2001 (150). Prevalence of RPF was estimated to be 1.38/100,000 for the study area in Finland (150). There is a similar prevalence of 1.3 per 100,000 people in the Netherlands (153).

A frequency of 1 case per 25,000 hospital admissions was reported in the USA (152). Males are affected 2-3 times more often than females and patients are usually diagnosed in the 4th -7th decades of life (152). About 2/3 of the cases of RPF are idiopathic with the remaining cases secondary to a variety of causes including malignant disease (mostly metastatic disease from lung, breast, prostate or digestive tract, and malignant lymphoma or sarcoma), radiation therapy, abdominal surgery, pancreatitis, haematomas, infections, and as a side effect of several drugs, especially methysergide and other ergot derivatives (150, 151). Additionally, RPF has also been associated with IgG4-related abnormalities, with elevated serum IgG4 concentrations and infiltration of IgG4-positive plasma cells in affected tissues (154).

Cases and studies of asbestos and RPF

Evidence of an association between asbestos exposure and RPF is limited to case reports, two case-series, and one case-control study as described below.

Case Reports

Asbestos exposure as a possible causative factor for RPF was first reported in 1991 in a patient with significant asbestos exposure and rapidly progressive pleural and retroperitoneal fibrosis (155). Subsequently, there have been ten additional case reports describing individuals with RPF, a history of asbestos exposure, asbestos-related radiologic findings, and no other known risk factors for RPF (156–159). In one of these cases, an autopsy was performed and asbestos fibers were demonstrated to have reached the retroperitoneal space (159). All cases were males, age at diagnosis ranged from 48–67, with a history of occupational or workplace-related asbestos exposures (see table 7 in online supplement).

Case Series

Sauni et al. (158) retrospectively identified 13 idiopathic RPF cases diagnosed between 1987 and 1995 at one hospital in southern Finland. Cases were followed up questionnaires and interviews. Of the 13 cases, 7 male patients had a history of occupational asbestos exposure and five had radiographic evidence of asbestos-related abnormalities (included in table in online supplement).

Overall, male patients with RPF, in comparison to the Finnish male population, appeared to more commonly have asbestos exposure and asbestos-related radiographic findings (158). Similarly, van Bommel et. al. (153) prospectively evaluated 53 consecutive patients with idiopathic RPF at a tertiary care center in the Netherlands from April 1998–January 2008. The authors found high frequency of occupational asbestos exposure (20%) and asbestos-related pleural changes (17%) among males with RPF (153). An autopsy series of individuals who underwent medical-legal autopsy for suspicion of asbestos-related disease documented an accumulation of asbestos fibers in retroperitoneal para-aortic lymph nodes taken at the level of the renal arteries and in mesenteric lymph nodes of all of individuals with lung fiber concentrations exceeding 1 million fibers/gram of dry tissue. Asbestos fibers were also demonstrated in the para-aortic and mesenteric lymph nodes of a substantial proportion of those with lesser lung fiber burdens (160).

Case Control Study

Uibu et al. (150) performed a case-control study to assess asbestos exposure as a risk factor for RPF in three hospital districts in Finland from 1990–2001. The study included 43 patients with RPF and 179 controls (matched on year of birth, sex, hospital district/catchment area) that were all alive during the study period. Information concerning risk factors for RPF and occupational exposures were gathered through questionnaires and interviews. Cumulative asbestos exposure (fiber-years) were classified by an industrial hygienist, exposure grading was masked, and interviewers were blinded to participant status. Cases of RPF were strongly associated with asbestos exposure. The odds ratio (OR) adjusted for potential risk factors for RPF was 5•54 (1•64–18•65) for less than ten fiber-years of asbestos exposure and increased to 8•84 (2•03–38•50) for ten or more fiber-years. A follow-up study of 38 cases and 18 controls with HRCT found that 73% of asbestos-exposed RPF cases also had asbestos-related pleural pathology, however, interstitial fibrosis was not elevated among those with RPF (161).

Overall conclusions

Evidence for causation of RPF by asbestos is suggested by a limited body of literature including case reports, two case series and one case control study. Thus, the epidemiological evidence alone is insufficient to permit a firm conclusion about causation of RPF by asbestos. However, a case report and an autopsy series documenting accumulation of asbestos fibers in the retroperitoneal space supports the biological plausibility of asbestos-causation and it is reasonable to conclude that RPF can be caused by asbestos. All RPF patients should be evaluated for a history of asbestos exposure along with other risk factors.

There is limited information about intensity of exposures required to cause RPF, relative potencies of different asbestos fiber types, etc. However, available evidence suggests that those with sufficient exposure to develop asbestos-related pleural pathology are at increased risk.

Summary

Laryngeal cancer as an asbestos-related disease

IARC recently concluded that there is sufficient evidence for asbestos-causation of laryngeal cancer in humans (4). Overall, both cohort and case-control studies provide consistent evidence of an increased risk of laryngeal cancer associated with asbestos exposure. There is also evidence that increasing exposure increases this risk. Thus, laryngeal cancer is known to be caused by asbestos (equivalent to IARC Group 1).

Based on laryngeal and lung cancer SIRs reported from published cohort studies, we estimate the RR for laryngeal cancer in an exposed cohort to be somewhat less than the RR for lung cancer. Under conditions of asbestos exposure associated with a RR for lung cancer of 2, the estimated RR for laryngeal cancer is 1.58, with an estimated AF for asbestos-causation in the exposed population of about 37%. When the RR for laryngeal cancer is 2, the estimated RR for lung cancer is 2.78.

Research opportunities include elucidating the asbestos exposure characteristics associated with increased risk for laryngeal cancer; and documenting mechanisms for asbestos-induction of laryngeal cancer, including evaluation of interactions between asbestos and other known risk factors.

Ovarian cancer as an asbestos-related disease

IARC recently concluded that there is sufficient evidence for asbestos-causation of ovarian cancer in humans (4). Overall, there are relatively strong and consistent findings of an increased risk for ovarian cancer among women in cohorts with relatively high asbestos exposures. Some evidence exists to support increased risk at higher exposures, but it is limited. There is insufficient information available detailing the histopathological subtypes of ovarian cancer associated with asbestos-exposure. Still, it may now be concluded that ovarian cancer is known to be caused by asbestos (equivalent to IARC Group 1).

Based on ovarian and lung cancer SMRs reported from published cohort studies, we estimate that under conditions of asbestos exposure associated with a RR for lung cancer of 2, the RR for ovarian cancer is 2.18, with an estimated AF in the

exposed population for asbestos-causation of about 54.1%. When the RR for ovarian cancer is 2, the estimated RR for lung cancer is 1.71.

Research opportunities include elucidating the asbestos exposure characteristics associated with increased risk for ovarian cancer; and documenting mechanisms for asbestos-induction of ovarian cancer, including evaluation of interactions between asbestos and other known risk factors. In this regard, it will be important to document the histological subtypes of ovarian cancer that are associated with asbestos exposure.

Colorectal cancer as an asbestos-related disease

IARC recently concluded that there is limited evidence in human epidemiology studies for an association between exposure to asbestos and cancer of the colorectum (4). However, the IARC working group was evenly divided as to whether the evidence was strong enough to view it as sufficient or limited. Considering the large number of positive studies, the demonstrated dose-response, and potential for negative confounding, it seems likely that asbestos exposure is causally related to colorectal cancer. However, the reports published since the IARC evaluation are not consistent. Recognizing that the available evidence is relatively strong, colorectal cancer is classified as reasonably anticipated to be caused by asbestos (equivalent to IARC Group 2A).

Based on IARC's analysis of colorectal and lung cancer SMRs, under conditions of asbestos exposure associated with a RR for lung cancer of 2, the estimated RR for colorectal cancer is 1.1, with an estimated AF for asbestos-causation in the exposed population of about 9%. When the RR for colorectal cancer is 2, the estimated RR for lung cancer is 5.2.

Research opportunities include elucidating the asbestos exposure characteristics associated with increased risk for colorectal cancer; and documenting mechanisms for asbestos-induction of colorectal cancer, including evaluation of interactions between asbestos and other known risk factors. In this regard, it will be important to document risks and mechanisms separately for colon and rectal cancer and to follow up on indications that the right part of colon is at higher risk. Also, since the RR and AF for colorectal cancer in an asbestos-exposed population are lower than for lung cancer, it will be important to identify strategies to improve attribution of causation to asbestos in individuals, particularly when other risk factors are present.

Stomach cancer as an asbestos-related disease

IARC recently concluded that there is limited evidence in human epidemiology studies for an association between exposure to asbestos and cancer of

the stomach (4). Overall, most cohort studies and the various meta-analyses of cohort studies provide consistent evidence of an increased risk of stomach cancer associated with asbestos exposure. Risk estimates tend to be higher in cohorts where heavy exposure to asbestos occurs and with long follow-up periods. There is also evidence that increasing exposure increases this risk. There are few case-control studies and these give less consistent results. Stomach cancer may be viewed as reasonably anticipated to be caused by asbestos (equivalent to IARC Group 2A).

Based on IARC's analysis of stomach and lung cancer SMRs, under conditions of asbestos exposure associated with a RR for lung cancer of 2, the estimated RR for stomach cancer is 1.2, with an estimated AF for asbestos-causation in the exposed population of about 17%. When the RR for stomach cancer is 2, the estimated RR for lung cancer is 3.96.

Research opportunities include elucidating the asbestos exposure characteristics associated with increased risk for stomach cancer; and documenting mechanisms for asbestos-induction of stomach cancer, including evaluation of interactions between asbestos and other known risk factors. Also, since the RR and AF for stomach cancer in an asbestos-exposed population are lower than for lung cancer, it will be important to identify strategies to improve attribution of causation to asbestos in individuals, particularly when other risk factors are present.

Ventilatory impairment and chronic airway obstruction related to asbestos

Spirometric impairment, whether obstructive or restrictive, can have many causes. In evaluating for causation by asbestos, it is important to assess for other potential causes. Restrictive impairment has been demonstrated by many studies to occur in those with asbestos exposure at levels known to cause parenchymal or pleural disease. It has often been associated with reduction in DLCO. Although, on average, the magnitude of impairment is greater in the presence of pleural or parenchymal disease, restriction can also be demonstrated at the population level in those with unremarkable chest radiographs. Thus, restrictive abnormalities are known to be caused by asbestos. At the individual level, restrictive or mixed obstructive/restrictive patterns of ventilatory impairment can be attributed to asbestos if asbestos-related pleural and/or interstitial radiographic changes are present, particularly if alternative causes are not identified. Additional studies are needed to develop specific criteria for individual attribution of clinically significant restrictive or mixed obstructive/restrictive impairment in the absence of radiographic changes.

Large airway obstruction associated with decreased FEV1/FVC ratio has been associated with asbestos exposure in some studies, but the findings have not been as consistent as for restriction, with many studies failing to show an asso-

ciation with asbestos exposure. Thus, this type of airway obstruction is categorized as reasonably anticipated to be caused by asbestos. Many studies suggest that smoking interacts with asbestos exposure in producing this pattern of impairment. Additional studies are needed to develop specific criteria for individual attribution of clinically significant large airway obstruction to asbestos exposure.

Research opportunities include elucidating the determinants of lung function impairment in asbestos-exposed individuals, particularly those without radiographic evidence of parenchymal or pleural disease. Even in those with asbestos-induced pleuroparenchymal disease, CT findings have been reported to explain only about half the variance in TLC, FVC, and DLCO. Although studies have shown statistically significant spirometric impairment in the absence of radiographic changes at the population level, more needs to be known about the frequency with which such individuals develop clinically significant changes in lung function. Also, more needs to be learned about how to attribute impairment in lung function to various potential causes when more than one potential cause is present.

Retroperitoneal fibrosis (RPF) as an asbestos-related disease

RPF is a rare condition that most often affects men in the 4th–7th decades of life. Evidence for causation by asbestos is based on a limited body of literature, including case reports, case series, and a case-control study. Thus, the epidemiological evidence alone is insufficient to permit a firm conclusion about causation of RPF by asbestos. However, biological plausibility is supported by a case report and an autopsy series documenting accumulation of asbestos fibers in the retroperitoneal tissues of exposed individuals. Considering this information in total, it is reasonable to view RPF as being caused by asbestos. However, this is based on a very limited number of studies and the status of RPF might possibly change with new studies.

Available evidence suggests that those with sufficient exposure to develop asbestos-related pleural pathology are at increased risk, so presence of pleural findings indicates that sufficient exposure has occurred for attribution to 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 should be evaluated for a history of asbestos exposure along with other risk factors.

Research opportunities include elucidation of asbestos exposure characteristics associated with increased risk for RPF, such as intensity of exposures, relative potencies of different asbestos fiber types, etc. In addition, it will be important to elucidate the mechanisms underlying asbestos-causation of RPF.

Table 1a: Cohort studies of asbestos exposure and laryngeal cancer (adapted from Table 2.5 IARC Monograph 100C)

Study	ICD codes*	Exposure Category	Total Cohort	Observed Cases	Expected Cases	RR	LCL	UCL	Cover %
Seilkoff (1979) (male insulators starting 1943-1962)	140-148, 161	any	632	6	2.80	2.14			
	140-148, 161	From 1st exposure >35yrs	632	2	1.90	1.05			
Germani (1999) (women with asbestosis)	161	any	631	1		8.09	0.21	45.08	95
Karjalainen (1999) (men with asbestosis, incidence)	161	any	1287	5		4.20	1.40	9.80	95
Karjalainen (1999) (men with benign pleural disease)	161	any	4708	1		0.50	0.00	2.70	95
Karjalainen (1999) (women with asbestosis)	161	any	89	0	0.10				
Karjalainen (1999) (women with benign pleural disease)	161	any	179	0	0.00				
SzesDab (2002) (men with asbestosis)	161	any	902	1	0.43				95
Armstrong (1988) (men)	161	any	6505	2		0.68	0.17	2.74	95
Reid (2004) (men, incidence)	C 32.0, C32.9	any	5685	19	10.00	1.82	1.16	2.85	95
Liddell (1997) (men)	161	any	8900	36		1.11			
	161	cum expo (mpcfy) >300	7700	6	~4.3	1.40			
Meurman (1994) (men, incidence)	161	any	736	4		1.75	0.48	4.47	95
	161	heavy	736	3		1.95	0.40	5.69	95
	161	heavy & >5yrs	212	2		3.60	0.44	13.00	95
Piolatto (1990) (men)	161	any	1058	8	3.00	2.67			p<0.05
	161	duration >20 yrs	1058	5	1.10	4.60			?
	161	cum expo (fiber-yrs) >400	1058	5	1.30	3.85			p=0.05
Sluis-Cremer (1992) (men)	161	any	7317	5	2.30	1.86	0.60	4.34	95
Seilkoff (1991) (male members insulation unions 1967)	161	any	17800	18	10.57	1.70			p<0.05
Levin (1998) (white men)	161	any	753	1	0.5	2.21	0.06	12.29	

All include cancer of the larynx ; Seilkoff (1979) and Seidman (1986) also include pharynx and buccal cavity

Table 1b: Studies presenting standardized incidence ratios for laryngeal and lung cancer in asbestos-exposed cohorts*

Citation	Gender	Location	Number Exposed (Fiber Type)	# of Laryngeal Cancer Cases	Laryngeal Cancer Risk (95% CI)	Lung Cancer Risk (95% CI)	Comments
Karjalainen et al. Cancer Causes Control 1999; 10(1):51-57	Men	Finland	1287 Fibre type not specified)	5	SIR: 4.20 (1.40-9.80)	SIR: 6.7 (5.6-7.9)	Men with asbestosis
Meurman et al. Occup Environ Med 1994; 51(6):421-425	Men	Finland	736 (any anthophyllite exposure)	4	SIR: 1.75 (0.48-4.47)	SIR: 2.88 (2.27-3.60)	Anthophyllite mine workers
Raffn et al. Br J Ind Med 1989; 46(2):90-96	Men	Denmark	7996 (mostly chrysotile, some crocidolite, amosite)	14	SIR: 1.66 (0.91-2.78)	SIR: 1.80 (1.54-2.10)	Asbestos cement workers
Smaliyte et al. Scand J Work Environ Health 2004; 30(1):64-70	Men	Lithuania	1285 (Chrysotile)	7	SIR: 1.40 (0.70-2.90)	SIR: 0.9 (0.7-1.3)	Asbestos cement workers
Tola et al. Br J Ind Med 1988; 45(4):209-218	Men	Finland	7775 (Fibre type not specified)	24	SIR: 1.20 (0.77-1.79)	SIR: 1.18 (1.03-1.35)	Shipyard workers
Tola et al. Br J Ind Med 1988; 45(4):209-218	Men	Finland	4918 (Fibre type not specified)	8	SIR: 0.69 (0.3-1.36)	SIR: 0.93 (0.76-1.12)	Machine shop workers
Strand et al. Am J Ind Med 2010; 53(1):64-71	Both	Norway	11,491 (fibre type not specified)	18	SIR: 0.98	SIR: 1.18	Norwegian naval personnel who served aboard ships. Calculated by combining all durations of service

*Only studies identifying more than one case of laryngeal cancer are listed.

Table 2: Laryngeal cancer and exposure to asbestos, case-control studies with adjustment for tobacco and alcohol consumption

Reference	Exposure	Country	Type of Study*	Study size period	Exposure Assessment
1. Brown et al. (1988)	12 industries 8 occupational categories Job titles 12 chemicals (asbestos)	US	Ho	183 M Ca 250 M Co 1975-1980	Jobs held at least 6 months, after 1939 Industrial hygienist classified job titles for exposure to specific exposures
2. Imbernon et al. (1995)	Cohort of workers in the electricity and gas industry	France	In	116 M Ca 457 M Co 1978-1989	All jobs in the company EDF JEM Industrial hygienist
3. Muscat et al. (1995)	Exposures (asbestos) Occupations	US	Ho	194 M Ca 184 M Co 1985-1990	1. 6 jobs held at least 1yr occupation and linkage system applied to determine exposure probability and intensity 2. Self-reported exposure (at least 8hrs per week)
4. Olsen et al. (1984)	Exposures (asbestos)	Denmark	Ho	326 Ca (276 M, 50 W) 1134 Ca (1134 M, 163 W) 1980-1982	Questions about their exposure to specific chemicals and physical agents
5. Wortley et al. (1992)	Exposures (asbestos) Occupations	US	Po	235 Ca 547 Co 1983-1987	Job history Industrial hygienist performed JEM exposure assignments
6. Zaganiski et al. (1986)	Industries Occupations (asbestos workers)	US	Ho	92 M Ca 181 M Co 1975-1980	1. Job history (all jobs) 2. Self-reported exposure (at least 20hrs per week for 6 months or more)
7. Dietz et al. (2004)	Cement dust related occupational groups	Germany	Po	257 Ca (236 M, 21 F) 769 Co (702 M, 67 F) 1998-2000	1. Jobs held at least 6 months 2. Quantification using job-specific supplementary questionnaires validated for asbestos

Adjustment for smoking and alcohol consumption (and other potential cofounders)		1	2	3	Comments
Ever versus never exposed	Dose-response relationships				
Exposed: 88 Ca, 99 Co RR=1.46 (0.98-2.18) CRR=1.46	Not studied	HQ	Y	Y	
Exposed: 38 Ca, 107 Co Adj for SES OR=1.5 (0.9-2.4)	Asbestos exposure, cumulative (all subjects) (fibers/cm3) Quartile1: RR=1.1 (0.5-2.8) (8 Ca, 30 Co) Quartile 2: RR=1.3 (0.5-3.3) (7 Ca, 23 Co) Quartile 3: RR=2.1 (0.9-4.3) (14 Ca, 31 Co) Quartile 4: RR=1.6 (0.7-3.7) (9 Ca, 23 Co)	-	Y	Y	Case-control study nested within the cohort of 170,000 workers. They did not have information about smoking and alcohol consumption. They used socio-economic status (smoking habits vary considerably in relation to SES)
1. Occupation Exposed: 63 Ca, 48 Co RR=1.2 (0.7-2.0) CRR=1.3 2. Self-reported exposure to asbestos Exposed: 15 Ca, 13 Co RR=0.8 (0.3-1.9) CRR=1.1	Not studied	HQ	Y	Y	Use RR from the analysis using occupations and not this one with the self-reported exposure: 3 Ca of 15 Ca did not work in occupations classified as asbestos related
only men Exposed: 17 Ca, 34 Co OR=1.8 (1.0-3.4) COR=1.8	Not studied	LQ	Y	Y	
NS but results not shown Meta-SIR=1.22 (0.86-1.72)	Highest exposure code for subject (code 0: never exposed, 1-3=L-M-H) Low: OR=1.2 (0.6-7.1) (3 Ca, 6 Co) Medium: OR=1.3 (0.8-2.0) (57 Ca, 94 Co) High: OR=1.1 (0.6-1.9) (30 Ca, 54 Co)	-	Y	Y	No overall RR for subjects ever exposed to asbestos. However, no significant dose-response relationship. Combined analysis of the RRs for the 3 levels: meta-SIR=1.22 (0.86-1.72), test for heterogeneity: p=0.91 in agreement with authors' comment: suggestion of increased risk associated with asbestos
1. Asbestos workers Exposed: 11 Ca, 18 Co OR=1.1 (0.4-2.9) 2. Self reported exposure to asbestos: Exposed: 10 Ca, 24 Co OR=0.8 (0.4-1.7)	Not studied	HQ	Y	Y	Use the RR from the analysis using occupations
Only men Exposed: 59 Ca, 104 Co 2. NS but results not shown High exposed group (>1000hrs) OR=1.3 (0.8-2.1) COR=2.1	Not studied	HQ	N	Y	

Reference	Exposure	Country	Type of Study*	Study size period	Exposure Assessment
8. Gustavsson et al. (1998)	17 specific substances	Sweden	Po	157 M Ca 641 M Co 1988-1990	Jobs held at least 1yr Occupational hygienist assigned exposure intensity Probability to 17 specific occupational exposures
9. Marchand et al. (2000)	Asbestos Man-made vitreous fibers	France	Ho	296 M Ca 295 M Co 1989-1991	1. Job history (all jobs) 2. Job-exposure matrix (JEM): prob of exposure, concentration, frequency
10. Ahrens et al. (1991)	21 industries 31 occupations Job titles 19 substances (asbestos)	Germany	Ho	85 M Ca 100 M Co 1984-1986	Jobs held at least 6 months Self-reported exposure
11. Berrino et al. (2003)	Job titles	France Italy Spain Switzerland	Po	315 Ca (215 larynx) 819 Co 1979-1982	All jobs held for at least 1 year after 1944 JEM Industrial hygienists, occupational physicians (probability of exposures to specific agents)
12. De Stefani et al. (1998)		Uruguay	Ho	112 M Ca 352 M Co 1993-1995	1. Jobs held at least 1yr 2. Specific questions concerning use of several substances
13. Elci et al. (2002)		Turkey	Ho	940 M Ca 1519 M Co 1979-1980	Job history Industrial hygienist performed JEM exposure assignments
14. Shangina et al. (2006)	43 agents	Romania, Poland, Russia, Slovakia	Ho	316 M Ca 728 M Co (cancers) 1999-2002	Jobs held at least 1yr - 13 specific jobs, 73 agents - intensity, frequency, confidence IH estimation

Ca: case, Co: control

* Ho: hospital-based study, In: industry-based study, Po: population-based study

1 Exposure assessment method from the book "Asbestos: Selected Cancers", 2006. HQ: high quality, LQ: low quality

2 studies included in the review by Browne & Gee (2000): Y: yes, N: no

3 studies included in the meta-analysis: Y: yes, N: no

Adjustment for smoking and alcohol consumption (and other potential cofounders)		1	2	3	Comments
Ever versus never exposed	Dose-response relationships				
1. > median of cumulative dose among exposed Co Exposed: 34 Ca RR high=1.69 (1.05-2.74)	Cumulative exposure distribution among exposed Co (exposure intensity*prob of exposure *duration of exposure)	-	N	Y	No overall RR for subjects ever exposed to asbestos, only RR for subjects ever exposed to high/low level of asbestos Use the RR for high exposure to asbestos
2. < median of cumulative dose among exposed Co Exposed: 28 Ca RR low=1.21 (0.73-2.02)	Quartile1: RR=1.16 (1.02-1.32) (13 Ca, 43 Co) Quartile 2: RR=1.35 (1.04-1.74) (15 Ca, 45 Co) Quartile 3: RR=1.56 (1.06, 2.30) (16 Ca, 44 Co) Quartile 4: RR=1.82 (1.08-3.04) (18 Ca, 45 Co)				
Exposed: 216 Ca, 185 Co OR=1.24 (0.83-1.90)	Cumulative exposure distribution (exposure intensity*prob of exposure*duration of exposure) Low: OR=1.10 (0.66-1.82) (67 Ca, 67 Co) Intermediate: OR=1.20 (0.73-1.99) (72 Ca, 67 Co) High: OR=1.47 (0.87-2.46) (77 Ca, 51 Co)	HQ	N	Y	
Self-reported exposure to asbestos Ca and Co exposed: 36 (19.5%) OR=1.1 (0.5-2.4) COR=1.2	Not studied	LQ	Y	N	Not included in the meta-analysis because only self-reported exposure
Exposed: 215 Ca, 380 Co OR=1.6 (1.0-2.5)	Not studied	-	N	N	Not included in the meta-analysis because combined analysis with 100 Ca of hypopharyngeal cancer (ICD-10 C13)
Exposed: 23 Ca, 70 Co OR=1.8 (0.9-3.2)	Not studied	LQ	N	N	This study was conducted in Uruguay. Exposure might be not portable in GB
Exposed: 150 Ca OR=1.0 (0.8-1.3)	Not studied	HQ	N	N	This study was conducted in Turkey. Exposure might be not portable in GB
Exposed: 26 Ca, 65 Co OR=0.86 (0.51-1.45)	Not studied	-	N	N	This study was conducted in East Europe. Results were mainly observed for Poland. Exposure might be not portable in GB

Table 3. Ovarian cancer and exposure to asbestos, study characteristics and findings

Authors, year	Country	Outcome studied	Industry Type	Asbestos Type Size	Size
Acheson et al, 1982	Leyland and Preston, UK	Mortality (SMR)	Gas mask assemblers	Mixed (mainly crocidolite)	757
	Blackburn, UK	Mortality (SMR)	Gas mask assemblers	Chrysotile	570
Wignall & Fox, 1982	UK	Mortality (SMR)	Gas mask assemblers	Crocidolite (from Western Australia)	535
Gardner et al, 1986	UK	Mortality (SMR)	Cement	Chrysotile	657f 1510m
Newhouse et al, 1989	UK	Mortality (SMR)	Production of friction materials	Chrysotile	4,346f 9104m
Rosler et al, 1994	Germany	Mortality (PMR)	Mixed (mainly textile)	Mixed (mainly chrysotile)	616
Tarchi et al, 1994	Italy	Mortality (SMR)	Mining	Chrysotile	120f 367m
Germani et al, 1999	Italy	Mortality (SMR)	Textile (compensated for asbestosis)	Mixed (mainly chrysotile)	276
		Mortality (SMR)	Cement (compensated for asbestosis)	Mixed	278
Berry et al, 2000	UK	Mortality (SMR)	Textiles and prefabricated cement pipes	Mixed	700f 4400m
Szeszenia-Dabrowska et al 2002	Poland	Mortality (SMR)	Mixed (asbestosis - mainly asbestos processing plants)	Mixed	490f 907m
Mamo et al, 2004	Italy	Mortality	Textile	Chrysotile	645
Wilczynska et al, 2005	Poland	Mortality (SMR)	Asbestos product plant workers; various products	Not specified; likely mixed	1382f 2805m
McDonald et al, 2006	UK	Mortality (SMR)	Gas mask assemblers	Crocidolite	1,073; 722 traced

Period of employment	Folow-up	Peson-years	Total deaths	Total cancers	Lung cancer SMR Obs/Exp SMR or SIR (95% CI)		Ovarian cancer results	Comparison
1927-1939	1951-1980	18,781	219	66	2.41+++	12/4.4	2.75 (1.42-4.81)	Local area mortality rates
1927-1945	1951-1980	14,324	177	44	1.45+++	5/3.4	1.48 (0.48-3.44)	Local area mortality rates
1939-1944	1951-1977	-	133	64	2.73	6/2.8	2.13	
1941-1954	1941-1984	-	102f 384m	26f 95m	1.42f 0.97mf	3/2.7	1.11 (0.23-3.25)	National death rates
1941-1979	1941-1986	-	522f 2055m	148 530m	0.66f 1.05mf +++	11/10.1	1.08 (0.61-1.79)	
-	1977-1988	6,236	64	32	3.39	2/1.8	1.09 (0.13-3.95)	National death rates
-	1965-1989	-	28f 72m	8f 33m	4.14f 1.46mf +	2/0.42	4.76 (0.58-17.2)	Death rates in Tuscany region
-	1980-1997	3,761	123	40	6.82	4/0.76	5.26 (1.43-13.47)	National death rates
-	1980-1997	3,932	129	54	2.39	5/0.93	5.4 (1.75-12.61)	National death rates
1936-1942 1933-1964 (worked at least 30d)	Up to 1980	17,146f	-	129f 408m	7.46f 3.01mf	9/3.56	2.53 (1.16-4.8)	England and Wales death rates
1970-1997 (dx period)	Up to Dec. 31, 1999	-	121f 300m	34	6.21f 2.06mf	1/1.27	0.79 (0.02-4.39)	National death rates
1951-1978	1981-1995	7,450	84	36	5.23	1/0.78	1.28 (0.02-7.12)	Regional mortality rates
1945-1980	Up to 1999	42,168f 76,574m some not exposed	414f 1353m	124f 272m	2.09f 1.34mf	8/4.5	1.76 (0.76-3.47)	National death rates
1940-1944	1963-2003	-	632	228	2.5 if all were f; 2.0 if adjusted for 7% m*	10/5.6	1.8 (0.9-3.3)	England and Wales death rates

Authors, year	Country	Outcome studied	Industry Type	Asbestos Type Size	Size
Hein et al, 2007	US	Mortality (SMR)	Textile	Chrysotile	1265f 1807m
Magnani et al, 2007	Italy	Mortality	Cement	Mixed	777
Pira et al, 2007	Italy	Mortality (SMR)	Textiles	Mixed	1,077f 889m
Reid et al, 2008	Australia (Wittenoom)	Mortality (SMR)	Women exposed environmentally and domestically	Crocidolite	2552
Loomis et al, 2009	US	Mortality (SMR)	Textile	Chrysotile	1,795f 3975m
Reid et al, 2009	Australia	Incidence (SIR)	Mining and milling	Crocidolite	416

Abbreviations: SMR, standardized mortality ratio; SIR, standardized incidence ratio; Obs/Exp, observed/expected deaths or cases; CI, confidence interval.

+ Trachea, bronchus and lung.

++ 3 plants only – data provided by authors.

+++ Lung and pleura.

++++Lung and trachea; SMR data shown for this study are based on subjects being censored at time last known to be alive (see text).

* Respiratory cancer other than mesothelioma

	Period of employment	Folow-up	Peson-years	Total deaths	Total cancers	Lung cancer SMR Obs/Exp SMR or SIR (95% CI)		Ovarian cancer results	Comparison
	1940-1965	1979-2001	49,922f	709f 1252m	169f 294m	2.22f 1.95mf +	6/9.68	0.62 (0.23-1.35)	National death rates
	1950-1986	1965-2003	22,367	371	169	2.21f 2.42mf	9/4	2.27 (1.04-4.32)	Regional mortality rates
	1946-1984	up to Dec. 31, 2004	36,886f 25,139m	254f 476m	130f 195m	6.47f 3.10mf	8/2.8	2.83 (1.22-5.57)	National death rates
	1943-1992	1950-2004	-	419	149	2.15 ++++	9/5.92	1.52 (0.69-2.88)	Death rates for Western Australian women
	1950-1973	up to Dec. 31, 2003	59,949f	608f 1975m	160f 482m	1.73f 1.96mf +	9/7.34	1.23 (0.56-2.33)++	National death rates
	1943-1966	1960-2006	-	-	-	-	1/1.54	0.65 (0.02-3.64)	

Table 4. Colorectal cancer and exposure to asbestos, cohort studies evaluated by IARC.
From Table 2.7 in IARC Vol 100C.

	Citation Label	CanType	LICD	UICD
Germani99	(women with asbestosis)	colon	153	153
	(women with asbestosis)	rectum	154	154
Karjalainen99	(men with asbestosis, incidence)	colon	153	153
	(men with benign pleural disease)	colon	153	153
	(women with asbestosis)	colon	153	153
	(women with benign pleural disease)	colon	153	153
	(men with asbestosis)	rectum	154	154
	(men with benign pleural disease)	rectum	154	154
SzesDab02	(men with asbestosis)	colon	153	153
	(men with asbestosis)	rectum	154	154
	(women with asbestosis)	colon	153	153
	(women with asbestosis)	rectum	154	154
Aliyu05	(men, incidence)	colorectal	153	154
	(men, incidence)	colorectal	153	154
	(men, incidence)	colorectal	153	154
	(men, incidence)	colorectal	153	154
	(men, incidence)	colorectal	153	154
Armstrong88	(men)	"intestines including rectum" ?	152	154
Reid04	(men)	colon/rectum	153	154,1
	(men, incidence)	colon/rectum	C18.0	C20.9
MacDonald93	(men)	"colon/rectum"	152	154
Meurman94	(men, incidence)	"colorectum" ?	153	154
	(men, incidence)	"colorectum" ?	153	154
	(men, incidence)	"colorectum" ?	153	154
Piolatto90	(men)	"intestinal" ?	152	154
	(men)	"intestinal" ?	152	154
Selikoff79	(male insulators starting 1943-1962)	"colon-rectum" ?	153	154
	(male insulators starting 1943-1962)	"colon-rectum" ?	153	154
	(male members insulation unions 1967)	"colon-rectum" ?	153	154
Acheson84	(men)	colon	153	153
	(men)	rectum	154	154
Levin98	(white men)	large intestine	153	153
	(white men)	rectum	154	154
Pira05	(men + women)	colorectal	152-154	159
	(men + women)	colorectal	152-154	159
Peto85	(men)	"colon/rectum" ?	153	154
	(men)	"colon/rectum" ?	153	154
	(women)	"colon/rectum" ?	153	154
Raffn96	(men, incidence)	colon ?	153	153
	(men, incidence)	colon ?	153	153
	(men, incidence)	rectum ?	154	154
	(men, incidence)	rectum ?	154	154

	ExpGrad	ExpCat	Total Cohort	Obs Cases	Exp Cases	RR	LCL	UCL	Cover %
	1	any	631	8		2,38	1,03	4,70	95
	1	any	631	1		0,62	0,02	3,45	95
	1	any	1287	3		0,90	0,20	2,50	95
	1	any	4708	8		1,10	0,50	2,10	95
	1	any	89	2		4,60	0,60	16,50	95
	1	any	179	1		3,40	0,10	19,10	95
	1	any	1287	4		1,30	0,30	3,20	95
	1	any	4708	8		1,20	0,50	2,40	95
	1	any	902	1		0,51			95
	1	any	902	2		0,77			95
	1	any	489	2		1,99	0,24	7,19	95
	1	any	489	1		0,86			95
	1	any	3897	85		2,00	1,60	2,50	95
	34	pleural abnormality (positive)	1847	51		1,40	0,88	2,23	95
	35	radiographic profusion (3/2 to 3/+)	24	1		1,38	0,18	10,60	95
	36	yrs in high risk trade (>40)	156	3		0,49	0,12	2,00	95
	37	From 1 st expo (longest = 42+ yrs)	707	29		1,20	0,48	3,04	95
	1	any	6505	14		0,70	0,41	1,18	95
	1	any	5685	49	37	1,31	0,99	1,74	95
	1	any	5685	88	84	1,05	0,85	1,29	95
	1	any	10918	73	88,9	0,82			
	1	any	736	3		0,55	0,11	1,60	95
	26	heavy	736	1		0,28	0,01	1,56	95
	20	heavy & >5yr	212	1		0,76	0,02	4,25	95
	1	any	1058	6	6,6	0,90			p>0.05
	5	duration >20 yrs	1058	3	2,3	1,30			p>0.05
	1	any	632	23	8,3	2,77			
	33	From 1st expo >35yrs	632	16	6,2	2,58			
	1	any	17800	121		1,37			p<0.01
	1	any	4820	6	4,4	1,37			p>0.05
	1	any	4820	4	3,2	1,24			p>0.05
	1	any	753	6	2,9	2,07	0,76	4,51	
	1	any	753	0	0,7				
	1	any	1966	16		1,45	0,83	2,35	95
	7	duration >10 yrs	1966	5		1,67			p>0.05
	1	any	3211	20	26,7	0,75			
	27	duration >10 yrs, >20 yrs since 1st	3211	5	4,86	1,03			
	1	any	283	4	2,02	1,98			
	1	any	7887	51	45,49	1,12	0,83	1,47	95
	28	1 st employed 1928-1950, >15 yrs since 1 st expo	7887	23	14,05	1,64	1,04	2,46	95
	1	any	7887	51	38,22	1,33	0,99	1,75	95
	28	1 st employed 1928-1950, >15 yrs since 1 st expo	7887	16	12,48	1,28	0,73	2,08	95

	Citation Label	CanType	LICD	UICD
Botta91	(men)	colon & rectum ?	153	154
	(women)	colon & rectum ?	153	154
Smailyte04	(men, incidence)	colon, rectum	153	154
	(men, incidence)	colon, rectum	153	154
	(men, incidence)	colon, rectum	153	154
	(women, incidence)	colon, rectum	153	154
Albin90	(men)	colon, rectum	153	154
	(men)	colon, rectum	153	154
Jakobsson94	(men, incidence)	right colon	153,0	153,1
	(men, incidence)	left colon	153,2	153,3
	(men, incidence)	rectum	154	154
Gardner86	(men + women)	colon	153	153
	(men + women)	rectum	154	154
Hughes87	(men)	colon, rectum	153	154
	(men)	colon, rectum	153	154
Woitowitz86	(men + women, exposure done after1972)	colon + rectum	153	154
	(men + women, exposure done before1972)	colon + rectum	153	154
Berry00	(male factory workers)	colon	153	153
	(male factory workers)	colon	153	153
	(male insulators)	colon	153	153
	(female factory workers)	colon	153	153
	(female factory workers)	colon	153	153
	(male factory workers)	rectum	154	154
	(male factory workers)	rectum	154	154
	(male insulators)	rectum	154	154
	(female factory workers)	rectum	154	154
	(female factory workers)	rectum	154	154
Hodgson86	(men)	colon ?	153	153
	(men)	colon ?	153	153
	(men)	rectum ?	154	154
	(men)	rectum ?	154	154
Seidman86	(male producers of shipyard insulation)	colon & rectum ?	153	154
Enterline87	(men)	colon	153	153
	(men)	rectum	154	154
Finkelstein04	(men)	colorectal ?	153	154
Tola88	(men, incidence)	colorectal	153	154
	(men, incidence)	colorectal	153	154
Battista99	(men)	"intestine & rectum" ?	152	154
Puntoni01	(men)	colon & rectum	153	154
Sanden87	(men, incidence)	rectum	154	154
	(men, incidence)	rectum	154	154
	(men, incidence)	colon	153	153

	ExpGrad	ExpCat	Total Cohort	Obs Cases	Exp Cases	RR	LCL	UCL	Cover %
	1	any	2608	11	16,9	0,65	0,32	1,16	95
	1	any	759	7	3,9	1,80	0,73	3,70	95
	1	any	1285	17		1,60	1,00	2,60	95
	7	duration >10 yrs	1285	8		2,40	1,20	4,40	95
	21	from 1st expo (>24 yrs)	1285	7		1,60			
	1	any	602	3		0,80	0,10	1,80	95
	1	any (all >20 yr latency)	1465	26		1,50	0,70	3,00	95
	29	cum expo (>40 fiber-yrs/ml) & >20 yr latency	1118			3,40	1,20	9,50	95
	1	any	981	12	5,04	2,38	1,23	4,16	95
	1	any	981	1	4,72	0,22	0,00	1,18	95
	1	any	981	13	7,87	1,65	0,88	2,83	95
	1	any	2090	6	9,2	0,65			
	1	any	2090	5	6,2	0,81			
	1	any (all latency >20 yrs)	5492	21	23,3	0,98			
	5	duration >15 yrs	5492	4	3,3	1,21			
	1	any	3070	5		0,79			p>0.05
	1	any	665	3		2,15			p>0.05
	1	any	3000	17	9,16	1,86			
	30	severe & >2yrs	3000	8	1,97	4,06			
	1	any	1400	7	1,62	4,32			
	1	any	700	3	3,29	0,88			
	30	severe & >2yrs	700	1	1	1,00			
	1	any	3000	5	6,02	0,83			
	30	severe & >2yrs	3000	0	1,53				
	1	any	1400	1	1,18	0,85			
	1	any	700	4	1,89	2,12			
	30	severe & >2yrs	700	0	0,47				
	1	any	31500	6	16,7	0,36			p<0.01
	5	duration >20 yrs	31500	3	8,6	0,35			
	1	any	31500	10	12,9	0,78			
	5	duration >20 yrs	31500	7	6,8	1,03			
	1	any	820	22	11,9	1,85			p<0.05
	1	any	1074	14	14,24	0,93			p>0.05
	1	any	1074	9	5,66	1,59			p>0.05
	1	any (with 20 yrs latency)	24500	96		1,16	0,94	1,42	95
	1	any	7775	35	44,1	0,79	0,55	1,10	95
	15	shipyard pipefitters	608	1	3,5	0,29	0,01	1,59	95
	1	any	734	6	6,45	0,93	0,41	1,84	90
	1	any	3984	59	58,9	1,00	0,76	1,29	95
	1	any (with 20 yrs latency)	3787	3	6,6	0,83			
	31	heavy (with 20 yrs latency)	3787	2	3,1	0,65			
	1	any	3787	0					

Table 5 : Cohort studies of asbestos exposure and stomach cancer (adapted and updated from Table 2.6 IARC Monograph 100C)

Citation Label	LICD	UICD	Exposure Gradient	Exposure Category
Acheson <i>et al.</i> 1982 (women: manufacture of gas masks)	151	151	1	any
Acheson <i>et al.</i> 1984 (men: manufacture of inhalation board)	151	151	1	any
Armstrong <i>et al</i> 1988 (men: crocidolite miners & millers)	151	151	1	any
Amandus and Wheeler1987 (men: vermiculite miners and millers)	151	151	1	any
Battista <i>et al</i> 1999 (men: railway carriage construction & repair)	151	151	1	any
Berry <i>et al</i> 2000 (women: asbestos factory workers)	151	151	1	any
	151	151	30	severe & >2yrs
Berry <i>et al</i> 2000 (male factory : asbestos factory workers)	151	151	1	any
	151	151	30	severe & >2yrs
Berry <i>et al</i> 2000 (male insulators)	151	151	1	any
Botta <i>et al</i> 1991 (men: asbestos cement factory)	151	151	1	any
Botta <i>et al</i> 1991 (women: asbestos cement factory)	151	151	1	any
Cheng & Kong 1992 (Men and women: chrysotile asbestos products workers)	151	151	1	any
DeKerk <i>et al</i> 1989 (men: crocidolite miners & millers)	151	151	14	duration (>5 yrs)
	151	151	32	ave. concentration (>50 f/ml)
Finkelstein & Verma 2004 (men: pipe trades workers)	151	151	1	any (with 20 yrs latency)
Frost <i>et al</i> 2008 (Men and women: asbestos removal workers)	151	151	1	any
Gardner <i>et al</i> 1986 (men + women: asbestos cement factory)	151	151	1	any
Germani <i>et al</i> 1999 (women compensated for asbestosis)	151	151	1	any
Harding <i>et al</i> 2009 (Men and women: asbestos survey)	151	1511	1	any
Hughes <i>et al</i> 1987 (men: asbestos cement factory)	151	151	1	any, all latency >20 yrs
	151	151	5	duration >15 yrs
Karjalainen <i>et al</i> 1999 (men with asbestosis, incidence)	151	151	1	any
Karjalainen <i>et al</i> 1999 (men with benign pleural disease)	151	151	1	any
Karjalainen <i>et al</i> 1999 (women with asbestosis)	151	151	1	any
Karjalainen <i>et al</i> 1999 (women with benign pleural disease)	151	151	1	any
Kogan <i>et al</i> 1993 (men + women: friction products manufacture)	151	151	1	any
Krstev <i>et al</i> 2007 (Men and women: shopyard workers)	151	151	1	any
Levin <i>et al</i> 1998 (white men: asbestos pipe insulation manufacture)	151	151	1	any
Liddell <i>et al</i> 1997 (men: asbestos miners and millers)	151	151	1	any
	151	151	19	cum expo (mpcf.y) >300
Loomis <i>et al</i> 2009 (Men and women: asbestos textile workers)	151	151	1	any
Meurman <i>et al</i> 1994 (men, incidence: asbestos miners)	151	151	1	any
	151	151	26	heavy
	151	151	20	heavy & >5yr

	Total Cohort	Obs Cases	Exp Cases	RR	LCL	UCL	Cover %
	1327	9	7.50	1.20			
	4820	7	7.50	0.94			p>0.05
	6505	17		1.16	0.72	1.87	95
	575	2	1.60	1.24	0.15	4.49	
	734	13	9.95	1.31	0.77	2.08	90
	700	5	3.51	1.42			
	700	3	0.88	3.41			
	3000	21	16.97	1.24			
	3000	5	3.85	1.30			
	1400	2	2.61	0.77			
	2608	17	20.90	0.81	0.47	1.30	95
	759	4	2.90	1.36	0.37	3.48	95
	1172	7		1.29	0.93	1.80	
	360	0		0.00	0.00	6.40	95
	360	1		0.40	0.00	4.20	95
	24500	21		0.67	0.41	1.02	95
	52387	49		1.34	1.00	1.79	
	2090	15	13.7	1.09			
	631	2		0.45	0.05	1.61	95
	9811	322		1.66	1.49	1.85	
	5492	22	19.50	1.13			
	5492	1	2.70	0.37			
	1287	4		0.70	0.20	1.90	95
	4708	11		1.30	0.60	2.30	95
	89	1		2.20	0.10	12.10	95
	179	0	0.20		0.00	17.40	95
	2834	14	24.00	0.58			
	4702	23		0.86	0.56	1.32	
	753	0	1.1				
	8900	183		1.24			
	7700	40	23.90	1.67			
	5770	8		0.51	0.24	1.09	
	736	13		1.42	0.76	2.43	95
	736	7		1.24	0.50	2.56	95
	212	2		0.99	0.12	3.56	95

Citation Label	LICD	UICD	Ex- po-	Exposure Category
Neuberger & Kundi 1990 (men: asbestos cement factory)	151	151	1	any
Olshon <i>et al</i> 1984 (Men: railroad shop workers)	151	151		
Pang <i>et al</i> 1997 (men)	151	151	1	any
Pang <i>et al</i> 1997 (women)	151	151	1	any
Pesch <i>et al</i> 2010 (Men: asbestos screening survey)	151	151	1	any
Peto <i>et al</i> 1985 (men: asbestos textile workers)	151	151	1	any
	151	151	27	duration >10 yrs, >20 yrs since 1st
Peto <i>et al</i> 1985 (women: asbestos textile workers)	151	151	1	any
Pira <i>et al</i> 2005 (men + women: asbestos textiles)	151	151	1	any
	151	151	7	duration >10 yrs
Puntoni <i>et al</i> 2001 (men: shipyard workers)	151	151	1	any
Raffn <i>et al</i> 1989 (men, incidence: asbestos cement factory)	151	151	1	any
	151	151	14	duration >5 yrs
	151	151	14	first employed 1928-1940
Reid <i>et al</i> 2004 (men: crocidolite miners)	151	151	1	any
Reid <i>et al</i> 2004 (men, incidence: crocidolite miners)	C16.0	C16.9	1	any
Sanden & Jarvholm 1987 (men, incidence: shipyard workers)	151	151	1	any
	151	151	1	any (with 20 yrs latency)
	151	151	31	heavy (with 20 yrs latency)
Seidman <i>et al</i> 1986 (men: producers of shipyard insulation)	151	151	1	any
Selikoff <i>et al</i> 1979 (male insulators starting 1943-1962)	151	151	1	any
	151	151	33	From 1st expo >35yrs
Selikoff & Seidman 1991 (male members insulation unions 1967)	151	151	1	any
Smailyte <i>et al</i> 2004 (men, incidence: asbestos cement factory)	151	151	1	any
	151	151	7	duration >10 yrs
	151	151	21	from 1st expo (>25 yrs)
Smailyte <i>et al</i> 2004 (women, incidence: asbestos cement factory)	151	151	1	any
Szeszenia-Dabrowska <i>et al</i> 2000 (men: asbestos cement factory)	151	151	1	any
Szeszenia-Dabrowska <i>et al</i> 2002 (men compensated for asbestosis)	151	151	1	any
Tola <i>et al</i> 1988 (men, incidence: shipyard workers)	151	151	15	shipyard pipefitters
Zhu & Wang 1993 (men + women: asbestos factory)	151	151	1	any

	Total Cohort	Obs Cases	Exp Cases	RR	LCL	UCL	Cover %
	2816	54		1.29	0.93	1.80	
	3442	41		0.57	0.42	0.79	
	160	5	0.64	7.87			
	370	0	0.50	0.00			
	576	5		1.15	0.46	2.85	
	3211	29	29.99	1.00			
	3211	9	5.00	1.80			
	283	2	1.08	1.85			
	1966	15		1.20	0.67	1.98	95
	1966	2		0.57			p>0.05
	3984	67	58.60	1.14	0.86	1.45	95
	7996	43	30.09	1.43	1.03	1.93	95
	1884	15	11.83	1.27	0.70	2.07	95
	269	8	4.73	1.69	0.73	3.33	95
	5685	21	15.00	1.39	0.91	2.14	95
	5685	27	22.00	1.31	0.82	1.75	95
	3787	3	3.40	0.88	0.18	2.60	
	3787	3	2.80	1.07			
	3787	1	1.30	0.77			
	820	11	5.78	1.90			p<0.05
	632	19	5.40	3.52			
	632	13	3.80	3.42			
	17800	38	29.36	1.29			p>0.05
	1285	14		0.90	0.50	1.50	95
	1285	3		0.60	0.20	1.90	95
	1285	4		0.60			
	602	4		1.20	0.40	3.20	95
	2525	16		1.07	0.63	1.81	
	902	5		0.70	0.23	1.63	95
	608	2	6.10	0.33	0.04	1.18	95
	5893	28		2.50			p<0.01

Table 6. Ventilatory impairment in longitudinal studies of asbestos exposure cohorts

Reference	Subjects	Follow Up	Average Exposure Duration / Amount	Prevalence Interstitial Changes
Bader et al 1965	17 asbestos factory workers at baseline, 13 followed over time	10 yr (Initial PFT 1954-55, 1-3 studies over next 10 yr)	11.5 yr	100%
Murphy et al 1978	101 asbestos-exposed shipyard pipe-coverers. Also, 95 controls (ship-fitters and pipefitters)	approx 6 yr (1965-66 and 1972)	N.R.	small opacities $\geq 1/0$: 31/77 pipe-coverers
Jones et al 1980	204 asbestos cement workers (145/204 had both CXR & PFT followed)	3 yr (1973 and 1976)	21 yr; cum. exp. 289 mppcf * yr	12% $\geq 1/0$
Becklake et al 1982	1015 Quebec chrysotile asbestos miners and millers	approx 8 yr (1967-68 and 1974)	those with follow up PFT: 23.3 yr, cum. exp. 343 mpcf*yr; those with follow up PFT & CXR: 13.9 yr, cum. exp. 115 mpcf* yr	Follow up PFT: 9.4% $\geq 1/0$; Follow up PFT & CXR: 4.2%
Siracusa et al 1984	Workers in a plant that manufactured asbestos cement and polyvinyl chloride (PVC) starting in 1963. Asbestos use progressively decreased after 1974 and ended in 1978.	7 yr - 65 asbestos workers and 30 PVC workers were studied in 1973 and again in 1980 (76 asbestos workers and 51 PVC workers total in 1980)	mean duration of exposure/time since exposure 1980 group: asbestos low exposure - 10.4 yr/15.7 yr, asbestos high exposure 10.6 yr/14.9 yr (low and high based on working in mixing/grinding or not)	N.R.
Ohlson et al 1985	75 Swedish former asbestos cement workers and a referent group of 56 workers at nearby industrial plants without asbestos exposure	4 yr (1976 and 1980)	inclusion criteria of at least 10 yr employment; median cumulative exposure 17.5 fiber-yr	0%
Siracusa et al 1988	Workers in a plant that manufactured asbestos cement and polyvinyl chloride (PVC) starting in 1963. Asbestos use decreased and ended between 1974 and 1978. Workers in a cement plant were also studied.	11 yr (1973, 1980, 1984). Workers studied at all times: 61 exposed to asbestos (13 heavy based on history of working in mixing and grinding areas), 29 to PVC, 36 to cement.	Total dust, asbestos cement working area, 1973: 10.9 mg/m ³ (geometric mean, 6 samples). Mean employment duration, heavy exposure group, 7.6 yr	N.R.
Jones et al 1989	167 asbestos cement workers	Mean of 9.75 yr (initial evaluation in 1973)	Initial group of 244 workers in 1973: duration 21.3 yr, average exposure 12.8 mppcf	8% small opacities $\geq 1/0$ alone; 9% also had pleural abnormalities

	Prevalence Pleural Changes	Summary of Lung Function Findings
	N.R.	VC fell significantly in 12 of 13; correlated with pulmonary compliance. In half, change not associated with worsening of CXR or symptoms. VC felt to be sensitive index of progression
	pleural thickening 17/73 pipe-coverers	Asbestos coverers: Baseline - FVC 101% predicted, FEV1/FVC 73.9%, DLCO 104% predicted; 6 yr follow up - FVC 93% predicted, FEV1/FVC 71.4%, DLCO 96% predicted.
	21% with any pleural thickening	Over the 3 years, cumulative dust exposure was a significant predictor of decline in FEV1 and FVC and approached significance for TLC. Significantly larger declines in FEV1 and FVC were seen in those with progression of pleural thickening. Progression of irregular small opacities was associated with significantly greater decline in FEV1, FVC, and FEF25-75 (MMEF).
	N.R.	Level of asbestos exposure was significantly associated with progression of breathlessness. FVC and MMEF on follow up were treated as categorical variables with a change < 10% considered unchanged, 10%-20% doubtful change, and > 20% definite change. Age and smoking had significant impacts proportion of workers changing categories, but cumulative exposure history did not.
	N.R.	Observed yearly decline for entire asbestos exposed group: FVC 48 ml/yr, FEV1 49 ml/yr. Decline appeared to accelerate with time since first exposure: < 15 yr: FVC 24.3 ml/yr, FEV1 37.6 ml/yr; > 15 yr FVC 52.5 ml/yr, FEV1 50.9 ml/yr. In evaluation of cross-sectional data from 1980, number of years since first asbestos exposure was significantly associated with values for FVC and FEV1, and pack-yr smoking significantly associated with FEV1 but not FVC. The effect of smoking and asbestos exposure on pulmonary function was reported as less than additive in this study.
	32% PP on follow up exam	Four-year decrements in FEV1 and FVC were greater in the exposed group than in referents. When evaluated by exposure terciles (< 14 fiber-years, 15-22 fiber-years, > 23 fiber-years), the linear trend for FEV1 decline was statistically significant (-4.56, -8.2, and -8.7%, respectively). The linear trend for FVC nearly achieved significance (-4.5, -7.3, and -8.2%, respectively). Multivariate analysis of variance showed cumulative asbestos exposure and smoking to be independent risk factors for lung function decline. Presence of pleural plaques (PP) was not a risk factor.
	N.R.	Asbestos workers had faster declines in FEV1 and FVC than the other groups. Particularly for the heavy-exposure group, decline was not linear and accelerated over time. Lung function decline continued despite cessation of asbestos exposure. In models predicting decline of FEV1 and FVC over 20 years, both declined together. The effect of asbestos exposure and smoking on lung function decline was noted to be additive and, in this population, the impact of smoking was felt to be minor relative to the impact of asbestos exposure.
	15% pleural abnormalities alone; 9% also had small opacities	In multivariate analyses, smoking history was significantly associated with lower baseline FEV1, MMEF, TLC and diffusing capacity, and with higher RV and TLC. Presence of small opacities ILO classification 1/0 or greater was significantly associated at baseline with lower FVC, FEV1 and RV and higher diffusing capacity. Presence of pleural thickening or calcification was associated with lower FVC, FEV1, MMEF and RV. Average exposure was associated with lower FVC, FEV1, and MMEF. During follow up, rates of decline of FVC and FEV1 across the studied population were small at 17 ml/year and 20 ml/year, respectively. Although smoking and progression of pleural thickening or calcifications were significantly associated with worsening pulmonary function during follow up, presence of small opacities and exposure level were not.

Reference	Subjects	Follow Up	Average Exposure Duration / Amount	Prevalence Interstitial Changes
Rom et al 1992	96 heavily exposed U.S. white male insulators and boilermakers. 77 had > 1 PFT (32 smokers and 45 ex-smokers)	Mean of 3 visits over a mean of 30 months for those with > 1 PFT	mean 31 yr exposure	100% opacities graded > 1/0
Schwartz et al 1994	115 asbestos-exposed workers identified in a survey of sheet metal workers or from the University of Iowa clinics	followed for an average of 2 yr	mean duration 31.7 yr, mean yr since last exposure 10.5	HRCT chest: 27% IS changes alone, 26% both IS changes and pleural fibrosis
Nakadate 1995	242 middle aged workers from two Japanese asbestos-product factories that produced calcium silicate boards and joint materials including asbestos	6 years of annual follow up	Exposure categorized as present in those who had worked for > 1 yr in areas where asbestos was processed and absent in others.	≥ 1/0 and < 2/1: "negative exposure" group 109/199; "positive exposure" group 27/43
Ostiguy et al 1995	494 long term workers in a copper refinery with mixed exposures including asbestos; 396 of these had been previously studied (evaluations in 1983-4 and 1991)	7 years between evaluations. Most data presented in paper are for the cross-sectional data from 1991	Mean time at plant for all 494 workers was 20.6 yr. Mean time at plant for those at least 50 years old was 28.5 yr	<u>Chest radiograph: 1/0 – 8 of 494 workers; 1/1 or greater – 4 of workers</u>
Brodin et al 1996	446 asbestos-exposed men enrolled in Seattle Asbestos Lung Cancer Chemoprevention Trial	Mean follow-up of 3.7 yr	N.R.	13% ≥ 1/0 only; 23% both parenchymal and pleural abnormalities
Yates et al 1996	64 men with asbestos-related DPT recruited from the London Medical Boarding Centre for Respiratory Diseases	36 subjects had longitudinal PFT data over a mean period of 8.9 yr	Mean = 15 yr of asbestos exposure	asbestosis was an exclusion criteria
Rui et al 2004	103 workers exposed to asbestos primarily in ship building and repairing	mean follow up of 3.7 yr	mean duration asbestos exposure = 25 years	asbestosis was an exclusion criteria

	Prevalence Pleural Changes	Summary of Lung Function Findings
	Bilateral PP in 49/96; DPT in 23/96	Across all 77 individuals, mean decline in FVC: 92 ml/year, FEV1: 66 ml/year, and TLC: 14 ml/year. Individuals with reduced lung function at their initial visit had markedly less decline in FEV1 and FVC. Nonsmokers had mean decline in FVC of -131 ml/year and FEV1 of -52 ml/year. Ex-smokers had decline in FVC of -65 ml/year and FEV1 of -76 ml/year. In nonsmokers, TLC declined by -50 ml/year, while for ex-smokers it increased by 10 ml/year, consistent with a developing obstructive defect. Multivariate analysis showed cigarette smoking to be more strongly associated with decline in FEV1 than FVC. Radiographic irregular opacities and rales were associated with more rapid declines in FEV1, FVC, and TLC. Among those with pleural findings, DPT was associated with significantly lower values of FEV1, FVC, and TLC than PP.
	HRCT chest: 7% pleural fibrosis alone, 26% both IS changes and pleural fibrosis	During follow up, average decline of 1.5% in TLC and 2.5% DLCO. Lower measures of TLC independently related to moderate to severe dyspnea, DPT, and higher concentrations of fibronectin in BAL. Lower measures of DLCO independently related to moderate to severe dyspnea, increased pack-years cigarette smoking, honeycombing on HRCT scan, and higher levels of inflammatory markers in BAL.
	N.R.	In multivariate analyses, pre-existing pneumoconiosis was significantly associated with more negative FEV1/height ² slope. A similar trend was noted for FVC/height ² , but it was not significant. Smoking only affected FEV1/height ² slope.
	Chest radio-graph: pleural plaques 54 of 494 workers. Of those at least 50 years old, 44 of 208 had pleural plaques	In the cross-sectional evaluation of all workers, circumscribed pleural plaques of low grade width or extent had no significant influence on FVC, FEV1, or MMEF. In a case-control longitudinal evaluation, the presence of these plaques was associated with a difference in loss of FVC in ml/yr reported to not achieve statistical significance (data shown as mean \pm SEM): pleural plaques present – 31 \pm 12 (54 workers); pleural plaques absent – 15 \pm 6 (247 workers)
	28% pleural thickening \geq 3mm bilaterally or 5mm unilaterally; 23% both parenchymal and pleural	Decline in entire group: FVC 49 ml/yr; FEV1 50 ml/yr; FEV1/FVC 0.4% loss in ratio/yr. Never smokers (n=71): FVC 54 ml/yr; FEV1 54 ml/yr; FEV1/FVC 0.4% loss in ratio/yr. Current smokers (n=74): FVC 56 ml/yr; FEV1 68 ml/yr; FEV1/FVC 0.8% loss in ratio/yr. Development of a new respiratory symptom, or to a lesser extent persistence of symptoms during follow up, were associated with significantly greater ventilatory losses as compared with asymptomatic individuals.
	100% with DPT; discrete PP without DPT excluded	Restriction at baseline. In those with longitudinal PFTs, rate of decline in FEV1 (35 ml/year) and FVC (39 ml/year), but not FEV1/FVC percent, were significantly different from predicted. Rate of decline was more marked in smokers and ex-smokers than in nonsmokers.
	36/103 had PP	Multivariate analyses showed that a history of occupational exposure to asbestos exposure was significantly associated with predicted 10-year declines in FEV1 and FVC. Trends were also present for association with 10-year declines in FEV1/VC and TLC, but these did not attain statistical significance. There was no association between the presence of PP and decline in pulmonary function.

Reference	Subjects	Follow Up	Average Exposure Duration / Amount	Prevalence Interstitial Changes
Alfonso et al 2004	1392 former workers and residents of Wite-noon, Australia	819 workers followed a mean of 3.3 years, 573 residents followed a mean of 5.7 years	Mean cumulative f/ml -year: residents - 6.9; workers - 24.7. Mean yr since last asbestos exposure: residents - 32.4 yr; workers - 33.1 yr	Small opacities $\geq 1/0$: residents - 1.4%; workers - 17.6%
Sichletidis et al 2006	198 residents of Northern Greece with pleural plaques related to environmental asbestos exposure, particularly chrysotile and tremolite	23 subjects had lung function testing in 1988-1990. 18 survivors had follow up testing in 2003.	Other studies evaluating local exposures cited in paper. Regional prevalence of pleural plaques in people at least 40 years cited as 5.2 – 39.6%.	Chest radiographs: No interstitial disease found by 2 experienced physicians separately (ILO system not cited)
Moshammer & Neuberger 2009	309 Austrian asbestos cement workers	Followed in screening program for a mean of 14.9 yr	Mean cumulative f/ml -year: 72.6; median - 40.4	Irregular small opacities 112/301; rounded small opacities 111/301; large opacities 3/301
Wang et al 2010	243 male workers of an asbestos plant in China that had produced asbestos textiles and asbestos building materials such as cement and tiles since the 1950s	174 workers were tested at least twice over 10 years (125 had 5-year data and 124 had 10-year data)	Personal samples exceeded 3 fibers/ml during the years of operation. Mean exposure duration 13.6 yr in those with baseline data and 21.6 yr in those with 10-yr data	27% at baseline, no new cases during follow up
Algranti et al 2013	502 former asbestos cement workers with at least 2 spirometry tests performed 4 years apart	mean follow up of 9.1 yr, mean # PFTs = 3.5	Mean duration of exposure = 13.5 yr; used a semiquantitative index to evaluate cumulative exposure. Mean latency at study entry = 25.6 yr	8.6% at baseline, 12.7% at last follow up

	Prevalence Pleural Changes	Summary of Lung Function Findings
	N.R.	At baseline, cumulative dose of asbestos was associated on average with 0.9 ml lower FEV1 per fiber/ml-year and over time with a 0.08 ml/year decline per fiber/ml-year. Values for FVC were 1.5 ml and -0.1 ml/year respectively. In contrast, radiographic asbestosis was associated with an average 313 ml lower baseline FEV1 and -13 ml/year decline in FEV1 over time. Values for FVC were 381 ml and -20 ml/year, respectively. Cumulative asbestos exposure and radiographic asbestosis were not significantly associated with changes in FEV1/FVC percent at baseline or during follow up. Current smoking was associated with an average decrease in baseline FEV1 of 350 ml and decline over time of -13 ml/year. Respective values for FVC were -283 ml and -3.3 ml/year. Current smoking significantly decreased baseline FEV1/FVC percent and increased its decline over time. Ex-smoking status did not significantly affect baseline FEV1 or FVC or their decline over time, but did have a small statistically significant effect on FEV1/FVC percent. There was no significant interaction between asbestos exposure and smoking on the baseline levels or rates of change of lung function.
	In 18 survivors, mean \pm SD plaque surface area (cm ²) increased: 1988: 11.27 \pm 12.98; 2003: 18.06 \pm 15.71	In the overall cohort, out of 72 deaths, 11 were from malignant lung neoplasm and 4 from mesothelioma. In those with longitudinal lung function, mean % predicted values fell as follows: TLC: 95.65% to 76.48%; FVC: 94.74% to 80.12%; FEV1: 93.43% to 89.1%. FEV1/FVC percent increased from 79.84% to 84.95%. A significant linear relationship was found between expansion in plaque surface area and loss of TLC (r = -0.486, p = 0.041). It is concluded that the study shows evidence that, over the years, pleural plaques due to environmental asbestos expand and respiratory function deteriorates.
	pleural thickening 34/301	Significant predictors of longitudinal FEV1 decline (in order of magnitude) were DPT, smoking, presence of irregular small opacities, and > 70 fibers x years/cm ³ cumulative asbestos exposure. Significant predictors of FVC decline (in order of magnitude) were DPT, presence of irregular small opacities, smoking, and > 70 fibers x years/cm ³ cumulative asbestos exposure. This level of asbestos exposure was significantly related to maximum expiratory flow rate at 25% FVC, but not at 50% or 75% FVC. Reductions in all of these lung function values were significantly associated with mortality, so the authors recommended monitoring lung function as an indication of need for more intensive care.
	N.R.	DLCO was the most rapidly declining measure in the population, with an annual decline of 5% over 5 years after adjustment for age, height and smoking. Workers with asbestosis had more rapid declines. Workers with greater cumulative exposure also tended to have greater decline after adjustment for age, height, smoking and presence of asbestosis. The adjusted annual decline in FVC was 3% and FEV1 was 2.7% at 5 years, with slightly lower declines at 10 years. In a multivariate analysis, FVC and FEV1 fell more in those with heavier asbestos exposures (in the 3rd and 4th quartiles of cumulative exposure). This was only statistically significant for FVC in the 4th quartile of exposure. In this analysis, asbestosis was also associated with a markedly increased decline in FVC, but not FEV1.
	pleural thickening 33.9% at last follow up (based on HRCT)	FEV1 was significantly related to cumulative asbestos exposure at entry, pack-years of smoking at entry and during follow-up, and the presence of asbestosis at follow-up. FVC level was significantly related to cumulative asbestos exposure and body mass index at entry, and smoking pack-years, asbestosis and pleural thickening at follow-up. Mean group rate of FEV1 decline was -38 ml/year. Asbestos exposure was not associated with increasing rates of FEV1 and FVC decline. Small but statistically significant differences were found in FEV1 regression slopes with age, estimated by terciles of cumulative exposure. Heavy smokers in the heaviest asbestos exposure tercile had accelerated FEV1 decline when compared to nonsmokers in the lowest asbestos exposure tercile. The authors concluded that the impact of exposure on pulmonary function in these asbestos-cement workers was largely during the working period and that smoking and asbestos exposure were synergistic.

Table 7. Reported Cases of Retroperitoneal Fibrosis (RPF), their age, occupation, asbestos exposure, and radiographic findings*

Reference	Age at diagnosis (years) & Gender	Occupation (latency (years))**	Asbestos Exposure	Radiographic & Other Findings
Uibu T., 2009	52 male	Insulator (27)	Insulator 34 yrs, with "heavy" asbestos exposure estimated >25 fiber-years to amphiboles (anthophyllite, amosite, and crocidolite)	Diffuse pleural fibrosis, plaques, calcifications & bilateral interstitial fibrosis, rounded atelectasis; Lung tissue analysis 59 million fibers/gram, amphibole asbestos. Asbestos fibers also demonstrated in retroperitoneal tissues.
Cottin V. 2009	65 male	NA (37)	5 years asbestos exposure	Bilateral calcified pleural plaques; thick calcified mass that extended from one pleura to the contralateral pleura with mediastinal retrosternal involvement.
Cottin V. 2009	55 male	NA (NA)	4 years asbestos exposure	bilateral pleural plaques, left pleural effusion, diffuse pleural thickening, thick calcified retrosternal mass in continuity with the pleura on both sides (bridging fibrosis),
Boulard 1995	51 male	Road Builder (25)	NA	Bilateral pleural plaques and calcifications
Boulard 1995	54 male	Boilermaker (20)	NA	Unilateral pleural thickening
Sauni 1998	53 male	Insulator (> 29)	27 years repairing pipes and insulation	bilateral pleural plaques, diffuse and irregular small lung opacities, asbestosis by CT
Sauni 1998	50 male	Plumber & carpenter (31)	Repair of pipe & insulation 10 years and construction work for 21 years	bilateral pleural plaques and round atelectasis
Sauni 1998	67 male	Carpenter (>17)	15 years construction work	bilateral pleural plaques and unilateral round atelectasis
Sauni 1998	48 male	Automobile mechanic (30)	30 years passive exposure repairing bus engines	Unilateral pleural plaque
Sauni 1998	51 male	Painter (>22)	Painting with asbestos coated pigments 10 years and 1 year in a shipyard	Bilateral pleural plaques

* Table adapted from Sauni 1998. Included cases do not have a reported history of other usual risk factors for RPF at the time of diagnosis including ergotamine medication, abdominal aortic aneurysm, abdominal trauma or infection.

** Latency=approximate time from first exposure to time of presentation

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4

Pathology and biomarkers

Victor L. Roggli, *Duke University Medical Center, USA, Chairman*

Sisko Anttila, *HUSLAB, Finland*

Agnes Kane, *Brown University, USA*

Kouki Inai, *Institute of Support Center of Remote Medicine, Japan*

Henrik Wolff, *Finnish Institute of Occupational Health, Finland*

Introduction

Since the publication of the *1997 Helsinki criteria for diagnosis and attribution of asbestosis and asbestos-related cancers* (1), there have been a number of advances in our understanding of the pathology of these disorders and the identification of biomarkers for asbestos-related diseases.

The World Health Organization has included additional histological patterns in the major categories of lung cancer, and the classification of adenocarcinomas of the lung has undergone extensive revisions. In addition, there have been advancements in the classification of interstitial lung disorders from which asbestosis must be distinguished. A wide variety of immunohistochemical markers have been developed to assist in the characterization and diagnosis of malignant mesothelioma and its distinction from other malignancies. Furthermore, the separation of benign mesothelial reactions from mesothelioma, which has implications for the early diagnosis of mesothelioma, has improved. There have also been advances with respect to the use of biomarkers and molecular studies for the early diagnosis of mesothelioma, which has the potential to improve the sensitivity and specificity of current imaging modalities. Finally, a number of molecular markers have been examined for their utility in identifying asbestos-related lung cancers. It is the purpose of this study to review the advances that have been made in this area since the publication of the 1997 Helsinki document.

Histological types of lung cancer associated with asbestos exposure

The World Health Organization (WHO) defines six major types of lung cancer: adenocarcinoma, squamous cell carcinoma, small cell carcinoma, large cell carcinoma, sarcomatoid carcinoma, and adenosquamous carcinoma. (2, 3)

The histological classification of lung cancer, especially adenocarcinoma, has undergone substantial revision in recent years, in part driven by clinical studies showing remarkable responses among cancers with certain molecular profiles to specific chemotherapeutic agents. (4) Although histological classification may be most accurately applied to resection specimens with generous samplings of tumor, guidelines have been published for the classification of lung cancers in small biopsy specimens. (5, 6)

In the author's experience (VLR) of the 1051 lung cancer specimens for which smoking history was available, the distribution of the six histological types was as follows: adenocarcinoma – 39.4%; squamous cell carcinoma – 27.5%; small cell carcinoma – 12.4%; large cell carcinoma – 12.4%; sarcomatoid carcinoma – 6.2%; and adenosquamous carcinoma – 2.2%. Over 90% of these cancers occurred in smokers or ex-smokers, ranging from about 90% of adenocarcinomas, to 98% of squamous cell carcinomas, and 100% of small cell carcinomas. The histological types are described below in more detail.

Adenocarcinoma: The WHO recognizes several patterns of adenocarcinoma of the lung, including acinar, papillary, bronchioloalveolar cell carcinoma and solid variants with mucous production. (2, 3) More recent studies have indicated that the micropapillary pattern should be considered a specific variant, as this pattern often implies a poor prognosis clinically. (4) Furthermore, the International Association for the Study of Lung Cancer, the American Thoracic Society and the European Respiratory Society have recommended that the term bronchioloalveolar cell carcinoma be dropped, because in the literature, this term has been applied to lung cancers with vastly different clinical behaviors and outcomes. (4) Most mucinous bronchioloalveolar cell carcinomas have been reclassified as invasive mucinous adenocarcinoma, since there is nearly always an invasive component in adequately sampled tumors. Some variants with nearly 100% five-year disease-free survival have also been recognized, including adenocarcinoma in situ and minimally invasive adenocarcinoma. Most non-mucinous bronchioloalveolar cell carcinomas have been reclassified into one of these two categories. (4) Less common variants of pulmonary adenocarcinoma recognized by the WHO include fetal adenocarcinoma and colloid adenocarcinoma. (2, 3) Pulmonary adenocarcinomas with enteric differentiation have also been recognized more recently. (4, 7)

Squamous cell carcinoma: The second most common of the histologic patterns recognized by WHO, squamous cell carcinoma, is characterized by tumor growth as sheets or nests which demonstrate one or more of the following: keratin pearl formation, intercellular bridges, and individual cell keratinization. (2, 3) Basaloid carcinoma and lymphoepithelioma-like carcinoma are recognized variants. Some cases may also occur with an endobronchial papillary growth pattern. One should use caution not to confuse apoptotic cells with hyper eosinophilic cytoplasm, and pyknotic nuclei with individual cell keratinization.

Small cell carcinoma: This variant is considered a high grade neuroendocrine carcinoma, which is frequently widespread at the time of diagnosis, often manifested by bulky mediastinal lymph node metastases. Small cell carcinoma is characterized by cells with a high nuclear to cytoplasmic ratio, scant cytoplasm, and frequent nuclear molding. Mitotic figures are frequent and nucleoli inconspicuous. Chromatin is described as showing a salt and pepper distribution. Rosettes may be present and focal necrosis is a frequent finding. Crush artifact is often seen in small biopsy specimens. When a small cell carcinoma pattern is present in a tumor that also displays large cell, squamous or adenocarcinoma differentiation, the tumor is referred to as combined small cell carcinoma. (2, 3)

Large cell carcinoma: With the advent of sensitive and specific immunohistochemical markers for adenocarcinoma and squamous cell carcinoma, this category continues to shrink as a percentage of lung cancers in general. These tumors form sheets and nests of cells with large nuclei and typically prominent nucleoli; mitotic figures are usually readily identified. (2, 3) The term large cell carcinoma should probably only be used on resection specimens where the tumor is extensively sampled and no evidence of adeno- or squamous differentiation is apparent. Recognized variants include large cell neuroendocrine carcinoma and rhabdoid phenotype. (3)

Sarcomatoid carcinoma: This category was newly proposed after the original 1997 Helsinki document and includes variants that were previously included in the squamous, large cell or adenocarcinoma categories. (1, 3) Variants of sarcomatoid carcinoma include pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma and pulmonary blastoma. These tumors typically include a spindle cell or mesenchymal element that may be confused with soft tissue sarcomas. Carcinomas including sarcomatoid, giant cell, adenocarcinoma or squamous cell carcinoma mixtures are referred to as pleomorphic carcinoma. If the sarcomatoid component includes heterologous elements (osteosarcomatoid, chondrosarcomatoid or rhabdomyosarcomatoid differentiation) the term carcinosarcoma is preferred.

Adenosquamous carcinoma: Lung carcinomas that contain both adenocarcinoma and squamous cell carcinoma components are referred to as adenosquamous carcinoma. Conventionally, at least 10% of each component should be present in the tumor. This diagnosis is difficult or impossible to make on small biopsy specimens and should be reserved for resection specimens. (5, 6)

One of the authors (VLR) has studied 76 primary lung cancers in patients with asbestosis as defined by the recent 2010 classification (8) who also underwent fiber analyses. (9) The distribution of histological types using the recent WHO classification is shown in Table 1. The distribution of histological types is similar for patients with asbestosis, pleural plaques without asbestosis, and

lung cancer patients with neither plaques nor asbestosis. Hence, the histological type of a lung cancer has no value in either proving or disproving a relationship with asbestos. Any of the six major histological categories mentioned above may occur as a consequence of asbestos exposure.

Table 1. Histological Typing of Lung Cancer in 76 Cases of Asbestosis with Fiber Analysis

Histological Type	Number	Percentage
Adenocarcinoma	31	40.8
Squamous cell carcinoma	17	22.4
Small cell carcinoma*	12	15.8
Large cell carcinoma**	5	6.6
Sarcomatoid carcinoma	5	6.6
Adenosquamous carcinoma	6	7.9
TOTAL	76	100

*Includes two combined small cell carcinomas (one squamous, one large cell)

**Includes one large cell neuroendocrine carcinoma

A number of far less common primary lung malignancies are recognized by WHO, including primary pulmonary sarcomas, lymphomas, salivary gland-like carcinomas, melanomas, intrapulmonary thymomas, teratomas, clear cell tumors, and carcinoid tumors. (2, 3) Clin et al. have reported that there is an association between pulmonary carcinoid tumors and asbestos exposure. (10) For the remaining tumors, there is no evidence that these primary pulmonary malignancies are asbestos related. The same is true for pulmonary blastoma, a rare variant of sarcomatoid carcinoma.

There is no major difference in the proportion of peripheral versus central cancers in patients who were exposed to asbestos in comparison to those who were not. Thus the central versus peripheral distribution of lung cancer among asbestos workers is similar to that of lung cancer patients with no background of asbestos exposure. (9, 11)

Some studies have recorded a predominance of lower lobe carcinomas among asbestos-exposed workers (12–20), whereas others have not. (9, 21–24) Nevertheless, the overlap is great enough that the lobar distribution is hardly sufficient to assign attribution to asbestos exposure in an individual case. (11)

Asbestosis: Histological criteria for diagnosis

Asbestos bodies are the hallmark of asbestos exposure. They are golden brown, beaded, segmented or dumbbell shaped structures that are formed when macrophages deposit an iron-rich protein and mucopolysaccharide coating on the surface of asbestos fibers that have been deposited in the lung parenchyma. They may also be found in regional lymph nodes. This coating is typically deposited on fibers that are at least 20 microns in length. Other mineral fibers may also be coated with similar material to form non-asbestos ferruginous bodies or pseudoasbestos bodies. Many of these have black or broad yellow sheet silicate type cores so that they can be readily distinguished from true asbestos bodies at the light microscopic level. However, some such as erionite or refractory ceramic fibers, may have thin translucent cores similar to asbestos. These ferruginous bodies can only be distinguished from true asbestos bodies by analytical electron microscopic techniques. (25, 26)

Only a small percentage of asbestos fibers in the lungs become coated to form asbestos bodies. Nonetheless, there is a strong statistical correlation between asbestos bodies and amphibole fibers that are 5 μm or greater in length. Different amphibole asbestos types have a varying ability to form asbestos bodies probably due to their length distribution; e.g., the relation of asbestos bodies to asbestos fibers was significantly higher in the lung tissue of workers who were principally exposed to commercial anthophyllite, as compared to those who were exposed to crocidolite or amosite. (27) There is also individual variability with respect to the efficiency of the coating process. Finally, there is a poor correlation between asbestos body concentrations and chrysotile fibre burdens. (25)

Within the lung, asbestos bodies occur in both the interstitium and within the alveolar spaces. The latter are the likely source of asbestos bodies (and fibers) found in sputum or in bronchoalveolar lavage (BAL) specimens. There is a reasonably good correlation between the concentrations of asbestos bodies in lung parenchyma as compared with sputum or BAL fluid. (25, 27)

When sensitive quantitative techniques are employed, asbestos bodies may be found in the lungs of most individuals from industrialized nations. Asbestos bodies may also be found in low levels in BAL fluid of some individuals from the general population. They are not observed in sputum samples from individuals in the general population. In the interpretation of quantitative asbestos analyses, it is important that laboratories determine an appropriate reference range. (25, 28) Furthermore, laboratories should employ techniques which enable the detection of the asbestos type or mixtures of fiber types that workers in their region have been exposed to. For example, if several asbestos fiber types with different coating efficiency have been used, fiber analyses using analytical electron microscopy rather than the analysis of asbestos body counts may be necessary.

Asbestos bodies, asbestos fibers and asbestosis

In 1982, the Asbestos Committee of the College of American Pathologists defined minimal histological criteria for a diagnosis of asbestosis as discrete foci of fibrosis in the walls of respiratory bronchioles in association with the accumulations of asbestos bodies in histological sections. In 1997, the Helsinki criteria took this one step further by requiring at least two asbestos bodies per cm² of lung parenchyma. More recently, this approach was adopted by the Asbestosis Committee of the College of American Pathologists and Pulmonary Pathology Society. This latter group further determined that diffuse alveolar septal fibrosis should also be present before a diagnosis of asbestosis is rendered histologically. In cases where the fibrosis is confined to the walls of bronchioles, the term 'asbestos airways disease' is preferred. These criteria apply to the histological diagnosis of asbestosis, irrespective of fiber type. (1, 8, 29)

Studies have shown a good correlation between asbestos fiber concentrations in lung parenchyma and the severity of interstitial fibrosis. Furthermore, regression studies show a threshold for fibrosis when fiber concentrations are compared to a reference population. The best correlation was with the concentration of commercial amphibole fibers that were 5 µm or greater in length. Similar observations were made for cases with asbestosis associated with non-commercial amphiboles, although the number of cases in this latter category was small. (25, 30)

By constructing 95% confidence intervals around the regression line for fibrosis and commercial amphibole concentration, Schneider et al. showed that there was almost no overlap between *bona fide* asbestosis cases and cases of diffuse interstitial lung disease that did not meet the histological criteria for asbestosis, despite some asbestos exposure history. The vast majority of these cases were patients with lung samples, demonstrating a typical usual interstitial pneumonia (UIP) pattern with peripheral and lower lobe accentuation, honeycomb changes, and readily identified fibroblast foci. It was concluded that a fiber analysis was not necessary in cases with a typical UIP pattern and no asbestos bodies upon careful examination of an iron-stained section. However, in cases with a UIP pattern in which pleural plaques are present and/or some asbestos bodies are present in histological sections (but fewer than 2 AB/cm²), a fiber analysis by an experienced laboratory is recommended. In such cases with a fiber burden compatible with asbestosis, then a diagnosis of asbestosis is likely. (30, 31)

Biomarkers for the histopathological diagnosis of malignant mesothelioma

Mesothelioma diagnosis

Malignant mesothelioma is a cancer that may involve any of the serosal membranes, which include the pleura, peritoneum and pericardium. The most common location is the pleura. A variety of cancers may arise in or metastasize to the pleura, and thus be confused with mesothelioma. Furthermore, mesothelioma may assume any of a number of histological patterns with significant overlap with other malignancies that may involve the serosal membranes. Consequently, the diagnosis of mesothelioma can be challenging.

The World Health Organization recognizes four major histological patterns of malignant mesothelioma: epithelioid, sarcomatoid, desmoplastic and biphasic. Less common variants of mesothelioma include well-differentiated papillary mesothelioma, localized malignant mesothelioma, and adenomatoid tumors of the pleura or peritoneum. (3) Because of the differential diagnostic considerations mentioned above, the diagnosis of malignant mesothelioma is best made with knowledge of the gross distribution of tumor, either from imaging studies or observations of the surgeon at the time of surgical sampling (or both). (32, 33) Even armed with this information, the diagnosis may be difficult for the pathologist, especially when dealing with small biopsy specimens. Therefore, a variety of biomarkers have been developed to assist with the more common differential diagnostic considerations. (34)

General guidelines

There are no known markers with 100% specificity and sensitivity for mesothelioma, so a panel of antibodies is typically used to assist in diagnosing mesothelioma. It is recommended that at least two positive (mesothelial) and two negative (carcinomatous) markers be used for making a histopathological diagnosis of malignant mesothelioma. Because the usage of these markers has not yet been standardized, it is recommended that each laboratory performing immunohistochemical studies determine which positive and negative markers best fit its needs. It is further recommended that markers used should have at least 80% sensitivity and specificity. (34) Furthermore, different markers work best for pleural and peritoneal tumors.

Mesothelial positive biomarkers

Several immunohistochemical markers have been reported with specificity for mesothelioma. These include calretinin, cytokeratins 5/6, WT-1, D2-40, thrombomodulin, HBME-1 and mesothelin. Calretinin has been recognized as a specific mesothelial marker for the longest duration (since 1996) and has stood the test of time. (3, 32–35) Nuclear staining is the most specific, although in the typical case, both nuclear and cytoplasmic staining is observed. In one of the authors' (VLR) the experience with over 200 cases of epithelial pleural or peritoneal mesotheliomas, calretinin was positive in 98% of cases, usually showing diffuse strong staining. As tumors become more poorly differentiated, the percentage of cases staining for the marker drops off. For example, in 84 cases of biphasic pleural or peritoneal mesotheliomas, calretinin was positive in 92%, and more cases were observed with weak or focal staining. Finally, in 36 cases of sarcomatoid mesothelioma, only 47% showed positive staining, which was usually focal.

Similar considerations apply to the other positive markers. Cytokeratins 5/6 (cytoplasmic staining), WT-1 (nuclear staining) and D2-40 (membranous staining) stain a high percentage of epithelial mesotheliomas but do not stain the great majority of pulmonary adenocarcinomas. In the experience of one of the authors (VLR), these markers are positive in 89–92% of epithelial pleural or peritoneal mesotheliomas. For biphasic pleural mesotheliomas, the percentage of positive staining drops down to 78–83%, and for biphasic peritoneal mesotheliomas, 50–75%. For sarcomatoid mesotheliomas, staining for cytokeratins 5/6 and WT-1 is so infrequent that these markers are not useful in this setting. Interestingly, D2-40 stains a substantial proportion of sarcomatoid mesotheliomas (in our hands, 55% of cases).

The single most useful marker for sarcomatoid or desmoplastic mesotheliomas is broad spectrum staining for cytokeratins. Over 90% of sarcomatoid mesotheliomas are keratin positive, and the staining is diffuse and moderate to strong in the majority of cases. Most soft tissue sarcomas, on the other hand, stain negative for cytokeratins. It should be noted that staining for cytokeratins is not useful for distinguishing sarcomatoid mesothelioma from sarcomatoid carcinoma of the lung. (36) Although cytokeratins will stain both malignant and reactive mesothelial spindle cells (as for example in cases of fibrous pleurisy), such staining is still useful for highlighting the invasion of adipose tissue by keratin positive spindle cells, a reliable marker for malignancy. (37, 38)

Mesothelial negative biomarkers

Just as there are markers that stain mesotheliomas but not tumors with which it may be confused, there are markers that stain a variety of adenocarcinomas (with which mesothelioma is most likely to be confused) but not mesotheliomas. Some of these negative markers include carcinoembryonic antigen (CEA), CD15 (Leu M-1), BerEP4, B72.3, MOC-31, Bg8, and TTF-1. The markers chosen depend both upon the tumor site (pleural vs. peritoneal) and tumor morphology. For pleural tumors, a useful negative pair of markers would include CEA and TTF-1, since a high percentage (greater than 90% in our hands) of pulmonary adenocarcinomas (with which pleural epithelial mesotheliomas may be confused) stain positive with these two markers. In contrast, epithelial pleural mesotheliomas stain in only 10% of cases for CEA, typically with only focal positivity. Only 0.5% of pleural mesotheliomas show nuclear positivity for TTF-1 (focal staining).

For peritoneal tumors, pulmonary adenocarcinoma is less likely to be in the differential diagnosis, so a more useful pair of negative markers is BerEP4 and B72.3. Only 9% of peritoneal mesotheliomas stain for BerEP4 (typically with only focal positivity) and none stain for B72.3 (0%). Peritoneal mesotheliomas in women must be distinguished from serous papillary carcinomas of the peritoneum and ovary, and many of these tumors will stain positive for mesothelial markers. Therefore, it is recommended that for peritoneal malignancies in women, stains for estrogen (ER) and progesterone (PR) receptors be added to the panel, since these are positive in a substantial percentage of serous papillary carcinomas, but only rarely so in mesotheliomas. (34)

Biomarkers in the distinction between malignant and reactive mesothelial cells

A variety of diseases and injuries to the serosal membranes may result in proliferation of mesothelial cells as a response to injury. In some cases, such proliferations may be florid and difficult to distinguish from mesothelioma. The positive and negative markers described above are of no use in this differential diagnosis, since both benign and malignant mesothelial cells stain for positive markers and neither stain for negative markers.

A variety of biomarkers have been proposed to aid in the distinction between benign and malignant mesothelial cells. These include glucose transporter-1 (GLUT-1), epithelial membrane antigen (EMA), p53, and desmin. Some studies have reported that mesotheliomas will stain positive for GLUT-1, EMA and p53, whereas reactive mesothelium tends to be negative for these markers. Similarly, reactive mesothelium stains positive for desmin, whereas mesothelioma tends to be negative for this marker. Although a panel using these four markers

has been proposed, their specificity and sensitivity are not sufficient to incorporate them into routine practice at this time. (34) More recent studies have suggested that homozygous loss of *P16/INK2A* may be a reliable marker for the separation of benign and malignant mesothelial proliferations (see Ref. 34 and discussion below).

Biomarkers for screening and early diagnosis of malignant mesothelioma

Sensitive and specific biomarkers for malignant mesothelioma (MM) are urgently needed for screening of asbestos-exposed workers in order to diagnose this aggressive tumor at an earlier stage when surgical resection combined with radiation and chemotherapy may be more effective in prolonging survival (39). Malignant mesothelioma in the general population is a rare disease (~1–2 cases per million) and screening should be limited to high-risk populations with a history of exposure to asbestos fibers or erionite. Ideally, the screening procedure should be noninvasive, cost-effective, and beneficial for treating patients at an earlier stage of the disease. These benefits must outweigh the risks, expenses, and physical and psychological stress associated with false-positive tests and extensive follow-up to establish a definitive diagnosis (39, 40).

This section will review the current rationale for screening for malignant mesothelioma, limitations of current imaging techniques, and the pleural fluid and serum biomarkers that have been evaluated for sensitivity and specificity in the early diagnosis of malignant mesothelioma.

Rationale for screening and early detection

In the 20th century, worldwide commercial production of asbestos reached a peak of greater than 5 million tons in 1975 and WHO estimates that 125 million workers are exposed to asbestos (41). Although commercial production of asbestos ended in Europe, Australia, South Africa, and the United States between 1983 and 2002, asbestos production continues in Canada, Russia, Kazakhstan, Brazil, and China. Continued production and consumption of asbestos-containing products in developing countries including Russia, China, Brazil, India, and Thailand raises concern about the ongoing and future burden of asbestos-related diseases worldwide (42).

In addition to occupational exposures, the presence of asbestos in homes, workplaces, and public buildings, as well as exposure to naturally-occurring asbestos fibers and persistent environmental contamination from abandoned mining sites contribute to ongoing residential and environmental exposures

(43–45). Mortality associated with pleural malignant mesothelioma is estimated to be highest in Europe, Australia, and New Zealand, with increasing mortality predicted for Asia, South America, and Eastern and Southern Europe (46). Significant occupational, residential, and environmental exposure to asbestos fibers and erionite are strong risk factors for the development of malignant mesothelioma (41). Familial clusters of MM have been reported (reviewed in 47) although some of these cases may be due to a shared exposure to asbestos fibers. Polymorphisms in DNA repair genes have been associated with malignant mesothelioma in residents of Casale Monferrato, an area of Italy with high asbestos exposure (48). Familial *BAP1* mutations in the gene encoding *BRCA1-associated protein 1* have been identified in two families predisposed to development of malignant mesothelioma, as well as in 2 of 26 patients with both uveal melanomas and malignant mesothelioma (49). A variety of genetic and chromosomal alterations have been identified in malignant mesothelioma, for example, deletion in the *CDKN2A* tumor suppressor gene locus and mutations or deletions in the *NF2* locus (50).

Although these alterations are not unique to malignant mesothelioma, fluorescence in situ hybridization to detect homozygous deletion at the *CDKN2A* gene locus may be useful as an early diagnostic marker for malignant mesothelioma (50). No specific gene expression signature has been associated with asbestos exposure or malignant mesothelioma, and variability in gene expression profiles in individual cases or in limited case series is common due to differences in microarray platforms, instability of RNA extracted from patient samples, and contamination of tumor samples with host tissue (51). Newer molecular techniques to investigate molecular alterations in malignant mesothelioma may provide more insight into the pathogenesis and progression of this rare tumor.

The natural history of malignant mesothelioma is characterized by a long latent period following asbestos exposure (usually 30–40 years) and diagnosis at early, noninvasive stages is uncommon because the symptoms, including dyspnea, weight loss, and chest pain, are nonspecific (52). In a combined series of 3400 patients, the median survival period was 6–12 months (33) because malignant mesothelioma is usually diagnosed at advanced stages when the tumor has already spread diffusely on the pleural surfaces and extension into the chest wall, mediastinum, and pericardium prevents complete surgical resection.

In a series of 176 selected patients diagnosed at earlier stages and treated with extrapleural pneumonectomy followed by radiation and chemotherapy, survival rates were 38% after 2 years and 15% after 5 years (53). It is hoped that a sensitive and specific serum or pleural fluid biomarker will be identified to improve detection and treatment of malignant mesothelioma at early clinical stages.

Limitations of imaging techniques for screening malignant pleural mesothelioma

Asbestos exposure can lead to nonmalignant pleural lesions including pleural plaques, diffuse pleural fibrosis, rounded atelectasis, and benign asbestos pleurisy (54). These nonmalignant lesions can occur as early as 10 years after asbestos exposure, and bilateral pleural plaques are a marker of exposure to asbestos or erionite. These individuals are at an increased risk of developing asbestos-related malignancy, although not all individuals exposed to asbestos develop pleural plaques or other nonmalignant pleural lesions (reviewed in 55).

Pleural effusion can be an initial manifestation of malignant mesothelioma; however, nonmalignant conditions including pneumonia, pulmonary embolism, heart or renal failure, and other malignancies including lung cancer and metastatic carcinoma are the most common causes of fluid accumulation in the pleural space (55). Numerous noninvasive imaging techniques can detect pleural effusions as well as pleural lesions; however, there are advantages and disadvantages to each of these techniques for the early diagnosis of malignant mesothelioma (40, 56). Computed tomography (CT scanning) is more sensitive than chest radiography for the detection of pleural thickening and effusions; however, radiation exposure is a major concern for repeated screening of asbestos-exposed populations. The screening of asbestos-exposed workers in the United Kingdom using chest radiography was ineffective in screening for malignant mesothelioma (57). Low-dose CT scanning of asbestos workers in Europe and Canada was also ineffective in detecting early disease (58, 59).

Although ultrasound examinations are highly sensitive in detecting pleural effusions and malignancies (60) they are not widely used. Positron-emission tomography (PET) combined with CT scanning is used in the staging of lung cancer; however, this is not useful as a screening tool for malignant mesothelioma because inflammatory lesions can produce false positive results (61). Magnetic resonance imaging (MRI) currently has limited spatial resolution and is subject to artifacts due to motion. Adverse reactions to contrast media limit its use for repeated screening (62).

Novel optical imaging techniques are under development using bioluminescent, fluorescent, or multifunctional probes based on nanotechnology (63). These probes may provide safer, less expensive tools for non-invasive screening for malignant mesothelioma and diagnosis at earlier stages in asbestos-exposed populations.

Pleural fluid biomarkers for early diagnosis of malignant mesothelioma

The current algorithm proposed for the diagnosis of pleural effusion includes thoracentesis and examination of the pleural fluid in all patients except those with heart, liver, or chronic renal failure (64). Pleural fluid cytology is a simple screening tool for diagnosis of malignancy; unfortunately, in two large series of 556 and 815 patients, the sensitivity of cytology for diagnosis of malignant mesothelioma was only 56–68% (56).

Newer techniques in flow cytometry (65) and fluorescence in situ hybridization for detecting the deletion of the *P16/INK2A* gene locus in combination with cytology (66–68) may improve sensitivity and specificity for the early diagnosis of malignant mesotheliomas using pleural fluids. However, not all cases of malignant mesothelioma are accompanied by pleural effusions, and malignant cells in the sarcomatoid subtype are usually not exfoliated. The International Mesothelioma Interest Group recommends that cytologic diagnoses be confirmed histopathologically on tissue biopsy in conjunction with clinical and radiologic findings (34).

Soluble biomarkers in pleural effusions have been evaluated for the early diagnosis of malignant mesothelioma. Several studies were conducted between 1999 and 2007 that evaluated the effectiveness of pleural fluid biomarkers for the early diagnosis of malignant mesothelioma and discrimination from nonmalignant pleural effusions or metastatic pleural disease (reviewed by 39). These biomarkers included cytokeratin fragment 21-1, tissue polypeptide antigen (representing fragments of cytokeratins), cell surface antigens (CA 15-3, CA 19-9), carcinoembryonic antigens (CEA), and hyaluronic acid. None of these biomarkers, applied to pleural fluid or serum, had sufficient sensitivity and specificity for the diagnosis of malignant mesothelioma.

Gueugnon et al. (69) conducted microarray analysis in 101 patients with nonmalignant effusions, metastatic adenocarcinoma, or a recent histopathological diagnosis of malignant mesothelioma and identified an elevated expression of C-C motif chemokine (CCL2) and a reduced expression of galectin-3 as potential biomarkers. CCL2 or monocyte chemoattractant protein 1 is a protumorigenic chemokine and levels in pleural effusions from patients with three major subtypes of malignant mesothelioma were significantly higher than levels in patients with metastatic adenocarcinoma or malignant pleural effusions. However, at a sensitivity of 96%, the specificity of CCL2 was less than 50%.

Galectin-3 is the gene product of *LGALS3*, a multifunctional protein involved in tumor invasion and metastases. Galectin-3 levels are significantly lower in patients with malignant mesothelioma in comparison with patients with metastatic adenocarcinoma. At 100% sensitivity for this biomarker, specificity is 67%.

Blanquart et al. (70) recently reported improved diagnosis of malignant mesothelioma using a combination of CCL2, galectin-3, and soluble mesothelin-related peptides (SMRP) in discriminating between malignant mesothelioma patients and patients with metastatic adenocarcinoma or nonmalignant pleural effusions. In this series of 106 cases, only one sample was classified as false positive and six samples classified as false negative.

A recent series of 275 patients with pleural effusions was evaluated using cytology and SMRP levels to differentiate between malignant mesothelioma and nonmalignant effusions or pleural metastases. A combination of both pleural markers improved diagnosis of malignant mesothelioma (71). Future studies are needed to evaluate whether these pleural fluid markers can provide similar sensitivity and specificity for early diagnosis of malignant mesothelioma using serum samples.

Serum biomarkers for screening and early diagnosis of malignant mesothelioma

Since the most recent meeting of international experts on the advances in the screening of asbestos-related diseases held in 2000 (72), several serum biomarkers have been evaluated as candidates for screening and early diagnosis of malignant mesothelioma (summarized in Table 2). A recent review of serum and cytological markers for early, non-invasive diagnosis of malignant mesothelioma concluded that soluble mesothelin-related protein (SMRP) has most widely been evaluated (73). However, these authors do not consider its diagnostic performance to be adequate for early diagnosis.

Mesothelin is expressed by normal mesothelial cells and only 50–60% of patients with the epithelioid subtype of malignant mesothelioma have elevated SMRP levels (74). The mesothelin gene promoter is methylated in normal pleural mesothelial cells, as well as in a subset of malignant mesotheliomas, which may account for the poor sensitivity of SMRP as a serum biomarker for malignant mesothelioma (75). In addition, mesothelin is also overexpressed in some ovarian and pancreatic carcinomas (74). Longitudinal screening of asbestos-exposed individuals may be more useful than a single baseline assessment of SMRP level, although it has been noted that SMRP levels increase with age and in patients with diminished renal function (74, 76). Serum or plasma SMRP levels may be useful to detect disease recurrence following surgical resection of epithelioid malignant mesothelioma (77, 78).

Table 2. Serum and plasma biomarkers for early diagnosis of malignant pleural mesothelioma

Biomarker	Description	Sensitivity/ specificity	Selected References
Soluble mesothelin-related proteins (SMRP)	Soluble protein similar to mesothelin, a membrane-anchored glycoprotein expressed on mesothelial cells	73/95% lacks sensitivity for non-epithelial subtypes	89, 90
Megakaryocyte potentiating factor (MPF)	Cleaved from mesothelin anchored to cell surface	34/95% lacks sensitivity for non-epithelial subtypes	74, 90, 91
Osteopontin	Secreted glycoprotein involved in cell migration, cell-matrix interactions, and inflammation need to use plasma, not serum	47/95.5% lacks specificity for malignant mesothelioma	76–81, 90
Fibulin-3	extracellular glycoprotein encoded by epidermal growth factor – containing fibulin-like extracellular matrix protein 1 (<i>EFEMP1</i>) gene	96.7/95.5% 100/94.1% for stage I or II	82
MicroRNA's	plasma miR-625-3P peripheral blood cells miR-103 serum miR-126	not assessed 78–83/71–76% 80/60% - better correlation with mesothelioma in combination with SMRP	83, 92–94
Proteomics profiling	259 cases; 64 candidates protein biomarkers including markers of inflammation and cell proliferation	91/94%; 77% of stage I superior to SMRP (68/88%) in this series	95

Megakaryocyte potentiating factor (MPF) is a cytokine derived from mesothelin and elevated serum levels are detected in 50–70% of patients with the epithelioid subtype of malignant mesothelioma. Serum levels of MPF are also elevated in patients with other pleural or lung diseases, including lung cancer. This biomarker requires further validation in larger asbestos-exposed populations (78). Combining both SMRP and MRP did not improve diagnostic performance in a recent prospective study (74).

Osteopontin is an extracellular cell adhesion protein that also functions as a cytokine and in promotion of tumor metastasis. Serum osteopontin levels are elevated in asbestos-exposed patients with pleural plaques and pulmonary fibrosis with even higher levels in patients with malignant mesothelioma (79).

However, osteopontin is susceptible to cleavage by thrombin in serum and plasma, and osteopontin levels are elevated in patients with chronic inflammation, nonmalignant pleural effusions, and lung, breast, ovarian, gastrointestinal, and prostate cancer (76, 80, 81).

Most recently, elevated levels of fibulin-3 were detected in plasma and pleural effusions in three patient cohorts with malignant mesothelioma (82). This new biomarker appears to have high sensitivity and specificity for detection of malignant mesothelioma at early stages (Table 2); however, this study must be validated in prospective longitudinal studies and confirmed in asbestos-exposed individuals with nonmalignant pleural effusions.

Emerging biomarkers

Microarray profiling of microRNA (miRNA) expression in peripheral blood cells and proteomics-based screening of serum from asbestos-exposed and malignant mesothelioma patients have identified new potential biomarkers for the early diagnosis of malignant mesothelioma (Table 2). A circulating microRNA was also found to be elevated in the plasma of patients with malignant mesothelioma (83). Quantitation of microRNA levels in plasma and serum is technically challenging and is compromised by hemolysis (84). Additional investigation of these novel biomarkers in larger asbestos-exposed populations is required.

Proteomic analysis of N-glycosylated proteins expressed on the surface of malignant mesothelial cells may identify additional novel protein biomarkers for malignant mesothelioma (85). A new electrochemical surface-imprinting method was recently developed as a substitute for ELISA assays using hyaluronan-linked protein 1 (HAPLN1) as a model serum biomarker for malignant mesothelioma (86). HAPLN1 or cartilage link protein (CRTL1) is highly expressed in malignant mesothelioma and may be important in host-tumor interactions and in promoting tumor cell proliferation and invasion (87). This serum protein has potential for developing multifunctional diagnostic and therapeutic (theranostic) probes based on biocompatible, biodegradable polymeric nanoparticles to enable highly sensitive imaging of early malignant mesothelioma, and targeted delivery of antitumorogenic drugs to treat these tumors at earlier stages (88).

Markers of asbestos attribution in lung cancer

Development of techniques for rapid and simultaneous screening of alterations in tens of thousands of genes and proteins as regards expression levels, gene copy numbers and DNA sequence, as well as epigenetic changes, have made it possible to discover previously unknown asbestos-related molecular changes in cancer. The use of these techniques in research requires careful planning of the initial test settings as regards exposure assessment and standardization of all other patient characteristics, and subsequent epidemiological validation of the findings in a larger patient population. The sizes of study populations are restricted by the facts that suitable patient materials are not readily available, and all molecular techniques are still relatively time-consuming and expensive. The development of markers for clinical practice requires the validation and standardization of detection methods and the combination of different markers in molecular assays. Experimental studies using cell lines and animal data are necessary to give mechanistic and supporting information.

The calculation of the sensitivity and specificity of a molecular assay for asbestos relation is not so obvious, because it is not known which of the individual cancer cases are truly asbestos-related. Furthermore, determination of the dose-response requires that detailed exposure history and/or pulmonary asbestos body or fiber counts are available. The only means to evaluate a test is by comparison with the present criteria of attribution preferably in prospective international multicenter studies. However, when such a molecular assay has successfully passed all the study phases, it could remarkably enhance the recognition of asbestos-related lung cancer. In addition, it could possibly pick up some asbestos-related cancers which cannot be conventionally recognized, for example lung cancer in a smoker or non-smoker with low-level exposure, or exclude the asbestos effect in the lung cancer of a smoker.

A number of molecular alterations in lung cancer have been associated with asbestos exposure. In the following, those markers are reviewed in detail with evidence of the specific asbestos effect in lung cancer and preferably at least preliminary information about sensitivity and specificity and dose-response in relation to asbestos exposure. Several investigators have found increased prevalence of *TP53* and *KRAS* mutations as well as LOH at 3p14 and 3p21 in asbestos-exposed smokers, but it has not been possible to separate the effects of the two carcinogens (see Table 3 for references). In addition, some recently described alterations are not yet properly validated, such as asbestos-related changes in microRNA and gene expression, such as ADAM28 (96-98).

Table 3. Asbestos-related molecular alterations in lung cancer

Alteration	Putative consequence or carcinogenic association	Type of study	References
AI and loss at 2p16		Lung cancer of asbestos-exposed individuals	105
LOH at 3p14	<i>FHIT</i> exon loss	Lung cancer of asbestos-exposed individuals	115, 116
LOH at 3p21	Possible down-regulation of tumor suppressors	Lung cancer of asbestos-exposed individuals	99, 117
LOH/homozygous deletion at 9p21.3	Loss of <i>P16/CDKN2A</i>	Lung cancer of asbestos-exposed individuals	108, 109
CNA at 9q33.1	Loss of <i>DBC1</i>	Lung cancer of asbestos-exposed individuals	111
AI and loss at 19p13	Possible down-regulation of tumor suppressors, e.g. <i>KEAP1</i>	<i>In vitro</i> ; lung cancer of asbestos-exposed individuals	100, 112
Polyploidy	Aneuploidy and chromosomal instability	<i>In vitro</i> ; lung cancer of asbestos-exposed individuals	111, 118
Up-regulation of <i>TP53</i>	Decreased or abnormal tumor suppressor activity possibly due to mutations	<i>In vitro</i> ; lung cancer of asbestos-exposed individuals	119, 120
Serum Ras (p21)	Up-regulation due to mutations	Asbestos-exposed lung cancer patients.	121
<i>KRAS</i>	Specific mutations	Lung cancer of asbestos-exposed individuals	122, 123

AI and loss at 2p16

The chromosomal region 2p21-p16.3 was originally described as one of the 18 asbestos-related alterations in lung cancer, detected by genome wide gene copy number and gene expression profiling (99, 100). Furthermore, in an experimental study applying gene expression arrays on A549 and Beas-2B lung cell lines, treatment with crocidolite asbestos was shown to induce altered gene expression at 2p22 (101). Several other alterations of chromosome 2 have been detected in lung cancer, such as the amplification of the *MYCN* locus at 2p24 (102, 103), and the fusion gene, *EML4-ALK*, resulting from inversion at 2p21.1-p14 (104). No information is available on the possible association of these changes with asbestos exposure.

Kettunen et al. (105) studied the 2p22-2p16 region further in order to localize the specific asbestos-targeted core region and to assess the frequency of the alterations of this region among 205 lung cancers of asbestos-exposed and non-exposed individuals. They showed that low copy number loss and allelic imbalance (AI) at 2p16 in lung cancer were significantly associated with high pulmonary asbestos fiber counts (≥ 5 million/g dry-weight tissue, $P=0.02$ and $P=0.003$, respectively). Lost DNA at 2p16 was demonstrated by FISH in 22% of lung tumors of the highly exposed (≥ 5 million fibers/g d-w), in 17% of the exposed ($1- <5$ million fibers/g d-w), and in 9% of the non-exposed cases.

The association was seen in all histological lung cancer types, although quite small numbers of each type were studied. A subsequent study with a larger number of cases, determined the sensitivity and specificity of AI and loss at 2p16 in the detection of the patients' past asbestos exposure. The sensitivity of AI in the detection of moderate and high exposure was 50–69% and 56–75%, respectively, depending on the microsatellite marker (106). Loss at 2p16 was detected by FISH with a sensitivity of 8–10%. However, a specificity of 54–63% was obtained for AI, and 99% for loss at 2p16 determined by FISH (probe RP11-703K23) (106). To conclude, loss at 2p16 in lung cancer is more specific than AI of the same region to the patients' past asbestos exposure. Because loss at 2p16, determined by FISH, is a rare event in lung cancer, the sensitivity of this alteration for asbestos exposure is quite low, whereas the specificity is very high.

Loss at 9p21.3/P16

The *P16/CDKN2A* tumor suppressor gene, located in the 9p21.3 region, may be silenced in lung cancer by promoter methylation and the point mutation of the gene, and by homozygous deletion or LOH (AI), in combination with another alteration at 9p21.3. Homozygous deletion at 9p21.3 is a frequent aberration in malignant mesothelioma, and it has been suggested as a marker of malignancy in mesothelial proliferations, as well as a prognostic marker (see molecular markers of MM).

In lung cancer, promoter hypermethylation of *P16/CDKN2A* associates strongly with tobacco smoking, whereas homozygous deletion has been shown to be more common in never smokers than in smokers and ex-smokers (107, 108). Point mutations have been detected solely in tobacco smokers (108). Kraunz et al. found a higher frequency of homozygous deletions in the asbestos-exposed than in the non-exposed among 171 consecutive lung cancer cases with smoking and exposure information collected by questionnaires. However, the difference was not statistically significant. Andujar et al. (109) studied 75 lung cancer cases, with detailed information of smoking habits and asbestos exposure (including pulmonary asbestos body counts), for the mechanisms of inactivation of *P16/CDKN2A*. They demonstrated a higher incidence of homozygous

deletion and LOH in the asbestos-exposed than in the non-exposed after adjustment for age and cumulative tobacco consumption ($P=0.0062$).

The lung cancers of the asbestos-exposed showed similar frequencies of homozygous deletion (50%) and methylation (24%) as malignant mesotheliomas (40% and 19%, respectively), while lung cancers of the non-exposed showed opposite frequencies (24% and 49%). To our knowledge, no attempts have been made to estimate the sensitivity and specificity of homozygous deletion and LOH (AI) at 9p21.3 for asbestos-related lung cancer. This could perhaps be achieved by combining of the data from several studies and adding the determination of asbestos exposure by using similar methods throughout, preferably quantitative pulmonary asbestos fiber or body counting.

Copy number alterations at 9q33.1

The differential gene copy numbers at 9q33.1-34.3 between asbestos-exposed and non-exposed patients' lung tumors were originally detected in a profiling study on two groups of lung cancer patients, exposed and non-exposed, matched for age, gender, smoking, and distribution of histological cancer types (99). The 9q33.1 region harbors a tumor suppressor 'deleted in bladder cancer 1' (DBC1), which has been shown to be frequently silenced by homozygous deletion or methylation in non-small cell lung cancer (110). Aberrations at 9q have also been described in malignant mesothelioma, where losses have often been found to initiate at 9q33.1. This may indicate that this region contains a potential breakpoint hotspot for asbestos-induced DNA damage (106).

Nymark et al. (109) further studied allelic imbalance (AI) at 9q33.1-34.3 with 15 microsatellite markers in 52 lung tumors and copy number alterations in this same region by FISH in 95 lung tumors from asbestos-exposed and non-exposed patients. Asbestos exposure was classified according to pulmonary fiber counts into three groups: from 0 to 0.5 million, from 1 to 9.99 million, and 10 million or more per gram dry-weight lung. AI at 9q33.1-q34.3 was observed in 100% (17/17) of asbestos-exposed and in 64% (14/22) of non-exposed patients' lung tumors and the most significant difference was found at 9q33.1 ($P=0.002$). Copy number alterations at 9q33.1 studied by FISH were also more frequent among the asbestos-exposed, and a dose-response trend was observed ($P=0.03$). The association between 9q33.1 alterations and asbestos exposure was observed for all main histological lung cancer types. However, losses were more common than gains in non-small cell lung cancer, whereas losses and gains occurred equally in small cell lung cancer (111). This study, also found more frequent polyploidy in asbestos-exposed than in non-exposed patients' lung tumors.

Nymark et al. (106) expanded the patient material in order to assess the specificity and sensitivity of 9q33.1 alterations as regards asbestos relation in lung cancer. The best microsatellite markers at this region detected asbestos exposure with a sensitivity of 60–63% and a specificity of 63%, whereas with a FISH probe RP11-440N22 a sensitivity of 28–35% and a specificity of 80% was reached.

Loss at 19p13

Of all genomic regions, loss at 19p13 in lung cancer associated most significantly with asbestos exposure in the genome-wide gene copy number and expression profiling studies (99, 100). While allelic imbalance (AI) in this region correlated with asbestos exposure in other histological cancer types, except in adenocarcinomas, losses at 19p13 determined by FISH associated with asbestos in all histological cancer types (100, 112). The AI site in which the most significant asbestos-association was observed (D19S216) co-localizes with the border of minimal-deleted region at 19p13 in lung cancer (100, 113), which suggests that this region contains a breakpoint hotspot possibly targeted by asbestos fibers (106). Ruosaari et al. (112) showed, *in vitro*, using BEAS-2B cells, that crocidolite induced centromere-negative micronuclei that harbored chromosomal fragments, and furthermore, an increased frequency of rare 19p fragments was observed. The 19p13 region contains a tumor suppressor *KEAP1*, which is an important regulator of the redox-sensitive NRF2-mediated signaling pathway (114).

Nymark et al. (106) further studied 118 lung tumors for losses and over 100 tumor and normal tissues for AI at 9p13. They were able to detect asbestos exposure by AI at 9p13 with a sensitivity of 61–68%, depending on the microsatellite marker and exposure level, and with a specificity of 60–62%. By using FISH probe RP11-333F10, sensitivity was 22–24% and specificity 96%. The sensitivity with almost all markers tested at 19p13, 9q33.1, and 2p16 was higher in the patient group with pulmonary fiber counts of five million or more as compared to the group with lower fiber counts, possibly indicating a smaller role of asbestos in the pathogenesis of lung cancer in those with lower exposure (106). When Nymark et al. (106) combined the results from the three regions, they found a clear dose-dependency between pulmonary fiber count and either AI or copy number alteration or both, in at least two of the three regions ($P < 0.001$). By combining FISH results from the three regions, a specificity of 100% was reached, whereas sensitivity remained low. AI from all regions gave a sensitivity of 74–76% and a specificity of 89% (106).

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