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International expert meeting on new advances in the radiology and screening of asbestos-related diseases

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International expert meeting on new advances in the radiology and screening of asbestos-related diseases

At a meeting held in Helsinki in January 1997, a group of 19 experts from 8 countries that do not produce asbestos formulated criteria for the diagnosis of asbestos-related diseases and their attribution to asbestos. Published later in the same year in the *Scandinavian Journal of Work, Environment and Health* (1), the criteria for the attribution of lung cancer have met widespread acceptance and are consistent with approaches to attribution and compensation in several countries (eg, Belgium, France, Germany, the Nordic countries, and the state of New South Wales in Australia). Studies on asbestos and lung cancer published subsequently have generally consolidated the approach of the Helsinki Criteria (ie, probabilistic attribution mainly on the basis of cumulative exposure), although there are some indications that the 25 fiber-year dose required for attribution — at which the asbestos-attributable relative risk of lung cancer is estimated to reach 2.0 or more — may be somewhat restrictive.

A second Helsinki meeting was held on 9—11 February 2000, which was attended by 30 experts from 8 countries. The chairmen were Professor Douglas W Henderson (Flinders Medical Centre, Australia) and Professor Jorma Rantanen (Finnish Institute of Occupational Health, Helsinki, Finland). The objectives of the meeting were to address recent developments in the assessment of asbestos-related disorders, especially pneumoconiosis, by computed tomography (CT) and screening for lung cancer in high-risk asbestos-exposed groups of workers. The meeting was particularly timely for at least 3 reasons: (i) substantial developments have taken place in CT technology, (ii) research on screening has shown substantial new evidence, and (iii) it is expected that surgical treatment of early-stage lung cancers will improve prognosis.

Thousands of asbestos-related lung cancers will be diagnosed and treated by clinicians across industrialized countries in the next 20 to 30 years and even later in the developing countries. It is extremely important to detect these cancers at their earliest stage for the early implementation of effective therapy, for the improvement of survival and quality of life, and for more efficient compensation. Thus the large number of existing and forthcoming asbestos-related lung cancers also requires evaluation of the potential effectiveness and feasibility of screening programs for the detection of asymptomatic early-stage lung cancer in high-risk groups.

Asbestos still a world-wide health hazard

Despite international and national actions, occupational exposure to asbestos in industrialized countries continues to be a major cause of morbidity and mortality from both lung cancer and mesothelioma. Up to 20 000 asbestos-related lung cancers and 10 000 mesotheliomas occur annually across the population of western Europe, Scandinavia, North America, Japan, and Australia (combined population about 800 million). The cancer incidence is expected to peak between 2010 and 2020 in these countries despite regulatory restrictions on the use of asbestos or bans imposed during the 1980s and 1990s. About half of all mesothelioma cases will occur in construction workers. Currently, over 70% of world asbestos production is used in eastern Europe and Asia, and, therefore, asbestos-related diseases are likely to continue in these regions at least into the middle of the 21st century.

As a consequence of past, current, and future exposures to asbestos, a world-wide epidemic of asbestos-related diseases will continue to result in the loss of work ability, years of healthy life and quality of life for workers and their families. Because the national incidence of mesothelioma can be correlated with the per capita consumption of asbestos, the burden of asbestos-related cancers constitutes a compelling case for the prohibition of the production and use of all asbestos types, not only across industrialized countries (where epidemiologic data are available), but also throughout eastern Europe, Africa, Latin America and Asia (ie, a world-wide phase-out). About 15 industrialized countries, including countries in the European Union, have already banned asbestos as advocated by international scientific and occupational health authorities.

Radiological aspects

All the participants in the meeting agreed that an international classification scheme should be established for pulmonary and pleural abnormalities for reading CT scans of persons with a history of occupational asbestos exposure. This system would be comparable to the 1980 Classification of Radiographs of Pneumoconioses of the International Labour Office. CT allows the early identification of the adverse health effects of asbestos exposure and is useful for the diagnosis of both malignant and nonmalignant diseases. The standardized reading of CT

examinations is of great value in the surveillance and screening of asbestos-exposed people (2). Several national groups have experience with the systematic recording of abnormalities, and 4 classification systems (Japanese, German, French, Finnish) were discussed during the meeting. Technical recommendations for thin-section CT scanning were made as follows:

- Thin collimation with a slice thickness of 1 to 2 mm
- A minimum of 6 slices, with 1 cut at the carina and 1 cut above and 4 cuts equally spaced below (more cuts may be helpful if resources and safety considerations allow)
- An exposure time of 1 second or less, with kilovolts between 120 and 150 and mAs between 40 and 100 (perhaps as high as 150 if the body habitus requires)
- A scan done at full inspiration using a high resolution or bone reconstruction algorithm
- Two window settings, 1 for parenchymal visualization and a 2nd for mediastinal and pleural visualization

Table 1. Detection rate, sensitivity, specificity and positive predictive value of computed tomography (CT) screening studies.

Study	Lung cancer +	Lung cancer -	Total	Results
Sone et al, 1998 (5); Sone et al, 2000 (9)^a				
Initial screening in 1996				
CT +	25	305	330	Detection rate 0.4%
CT -	19	5965	5984	Sensitivity 57%
Total	44	6270	6314	Specificity 95%
First annual repeat in 1997				
CT +	28	169	197	Predictive value 8%
CT -	5	4823	4828	Detection rate 0.6%
Total	33	4992	5025	Sensitivity 85%
Second annual repeat in 1998				
CT +	9	164	173	Specificity 97%
CT -	0	4867	4867	Predictive value 14%
Total	9	5031	5040	Detection rate 0.2%
Henschke et al, 1999 (6)^b				
Initial screening				
CT +	27	206	233	Sensitivity 100%
CT -	0	767	767	Specificity 79%
Total	27	973	1000	Predictive value 12%
First annual repeat				
CT +	6	24	30	Detection rate 0.6%
CT -	0	970	970	Sensitivity 100%
Total	6	994	1000	Specificity 98%
Vehmas et al, 2000 (12)^c				
Initial screening				
CT +	5	60	65	Predictive value 20%
CT -	0	537	537	Detection rate 0.8%
Total	5	597	602	Sensitivity 100%
Total				
Predictive value 8%				

^a N=6341, general population, mean age 61 years, 55% male, 54% nonsmokers.

^b N=1000, general population, over 60 years of age, median age 67 years, 54% male, over 10 pack-years of smoking, median 45 pack-years.

^c N=602, construction workers with bilateral pleural plaques, mean age 63 years, 98% male, mean 24 pack-years of smoking, over 10 years of asbestos exposure.

tion, the parenchymal window width being between 1500 and 2000 HU with a window level of between -300 and -700 HU and the mediastinal window width being between 150 and 350 HU with a window level between 20 and 50 HU

- A matrix of 512 pixels or greater and the number of the images not exceeding 12 on a standard 35 cm × 43 cm film (image size 10 cm × 10 cm).
- The subject's position prone, if possible.

Screening asbestos-exposed workers for lung cancer

Medical screening denotes the use of medical testing for the presumptive identification of a disease before an individual would ordinarily seek medical care; therefore, the aim of screening is the detection of presymptomatic disease. An important precondition is the availability of an intervention method that can favorably affect the health of the individual. The ultimate goal of medical screening should be the secondary prevention of disease (ie, the identification of illness at a stage when its evolution can be reversed, arrested, or slowed). Positive screening tests may indicate the presence of disease or a strong likelihood of disease and the need for confirmatory testing. The tests used for screening must be acceptable to those at risk of disease, with acceptable sensitivity, specificity, and predictive value for the screened population, available at reasonable cost, and sufficiently standardized to be performed with consistency, accuracy, and reproducibility.

The benefits of screening for respiratory tract cancers have been an area of significant controversy in the past. Originally, large clinical trials in the United States using chest radiography and sputum cytology were widely interpreted as failing to support mass screening for lung cancer in high-risk populations. Recently, the original data have been re-evaluated as demonstrating potential benefit to the patient (3, 4). In addition, newer imaging and intervention techniques in the early identification and treatment of lung cancers in high-risk groups have shown promise.

Spiral computed tomography

Two recent reports of screening for lung cancer employing low-dose spiral CT are particularly encouraging (5, 6). Spiral CT is becoming widely available in industrialized countries. Current research provides promising information on the sensitivity, specificity, and positive predictive value of this technique for the detection of lung cancers at an early stage (table 1). When stage I cancer is resected, the 5-year survival can be as high as 70%. In the absence of resection, the survival is a mere 12% (7). New computer software for assessing the progress of the tumor between repeated examinations has also been developed (8). Recent research findings from lung cancer

screening projects, briefly described below, show the progress since the 1997 Helsinki meeting.

Japanese experience. A voluntary population-based lung cancer screening program using a mobile spiral CT unit is underway in Japan. To date, nearly 18 000 examinations have been conducted on a general population (mostly aged over 40 years, mean age at the first examination 61 years) including 45% women and 54% never-smokers. Altogether 62 lung cancers were detected among 6341 participants (0.98%), and they included both prevalent cases and the incident cases found during 2 repeat examinations at 1-year intervals. In single CT examinations, the mean detection rate (0.36%) was nearly 10 times greater than the results of mass screening by conventional radiography (0.03–0.05%). Of the lung cancer cases, 83% were at pathological stage IA, and 66% were less than 15-mm in diameter. The sensitivity of the CT examination was calculated at 57%, and the specificity at 95%. The positive predictive value in this population was 8% in the initial screening. In the first annual repeat CT screening, there was 85% sensitivity and 97% specificity, with a positive predictive value of 14%. Conventional chest radiographs were negative for 63% of the cancers detected with spiral CT. Furthermore, the authors estimate that approximately 30% of the prevalent cancers appeared to be rapidly growing and 5% were extremely aggressive and fast growing (5, 9).

In another Japanese study of 1369 persons (men over 50 years, mean age 60 years), 15 peripheral lung cancers were detected by a total of 3457 CT examinations (made twice a year). Fourteen (93%) of the cases were stage I. For 11 (73%), the results of the chest radiology were negative, and the tumors were detected only by low-dose spiral CT (10).

Early Lung Cancer Action Program. The Early Lung Cancer Action Program (ELCAP) screened a general volunteer population of 1000 smokers [minimum 10 (median 45) pack-years] 60 years of age and over (median age at the first screen 67 years). About 14% reported some exposure to asbestos. The first round of low-dose spiral CT testing identified 233 people with noncalcified nodules requiring further evaluation. Of these, 27 lung cancers were ultimately resected. Biopsies were done on 28 of the 233 participants with noncalcified nodules; 27 had malignant noncalcified nodules and 1 had a benign nodule. Others (206 cases) underwent further evaluation, including conventional CT and antibiotic treatment, but not thoracoscopy. The ELCAP investigators indicated that 3 malignancies identified in the follow-up examination after an interval of 1 year may have been detected at the initial examination and could, therefore, be considered false-negative results. In the whole study population, malignant disease was detected 4 times more frequently

with the low-dose CT than with chest radiography (2.7% versus 0.7%), and stage I tumors were detected 6 times more frequently with low-dose CT than with radiography (2.3% versus 0.4%). The cell type distribution indicated a significant predominance of adenocarcinoma (about 70%). Very few central tumors were detected during the first 2 rounds of the screening examinations. After an interval of 1 year, additional noncalcified nodules were detected at a rate of 30 per 1000, with 6 malignancies confirmed per 1000 interval spiral CT tests performed. Altogether, 33 lung cancers were detected in the 2 CT examinations of the study population (6, 11).

Screening of Finnish construction workers. The screening study of Finnish construction workers was also instructive. Altogether 602 men between the ages of 38 and 81 (mean 63) years, with ≥ 10 (mean 26) years of asbestos exposure, were screened using spiral CT. They were all current or former smokers with a minimum of 10 years of tobacco use (mean 24 pack-years), and 96% of them had bilateral pleural plaques. Sixty-five had abnormal scans, 5 lung cancers and 1 mesothelioma being detected. No false-negative cases have been identified thus far; the sensitivity of the study was considered to approximate 100%, and the specificity was over 90%. With the 65 suspected cases, the predictive value of a positive test was about 8% for this population. The detection rate of lung cancer by the first CT was approximately 0.8% (12).

Other potential screening tests

Chest X ray. Chest X-ray examinations are commonly used to monitor for pneumoconiosis among workers exposed to asbestos. In general, their benefit for the early identification of lung cancer has not been demonstrated due to their low sensitivity and specificity, although the evaluation of existing data may be of some interest to guide clinical practice where newer imaging techniques may not be available. Occasionally, a few early-stage lung cancers are also found. The prognosis of lung cancer cases found in a single chest radiograph screening was better than those detected through the ordinary health care system (5-year survival 19% versus 10%) (13).

Sputum cytology and bronchoscopy. Periodic use of standard sputum cytology has been evaluated for the mass screening for lung cancer and was shown to be of limited value. Newer automatic computerized cytological methods are undergoing experimental evaluation and may prove useful in combination with other screening approaches (eg, spiral CT). Cytological examination with special biomarkers may be effective in the early identification of central tumors that would otherwise be missed by spiral CT. At this point, sputum cytology alone cannot be recommended for screening because the automated techniques are currently experimental and not

generally available. There is insufficient standardization for cytological methods, and this lack affects their value in screening and, particularly, in comparative studies (14). Bronchoscopy, including autofluorescence endoscopy, is impractical as a screening tool because of its cost, availability, and low patient acceptance because of the invasiveness of the procedure.

Programmatic issues

The detection frequency, as well as the true population incidence, of cancers and the disease characteristics following the baseline screening will influence the number and stage of cancers detected. Data from ELCAP indicate that nearly 3% of prevalent cancers were identified at first testing and that 0.6% of incident cancers were found after a 1-year interval (table 1). In considering the frequency of examinations, the cost and logistics of the program are inevitably weighed against the available information on the rapidity of tumor growth and progression and the variation or uncertainties over identifying cancers at a later stage where cure is less probable. In any such analysis, the realistic costs of supportive and palliative medical care for more advanced lung cancer patients should be taken into account, including the costs of numerous CT, which may be taken during the later phases of the disease.

The studies on the high-risk population in ELCAP, the Japanese population-based voluntary screening program, and the Finnish asbestos-exposed construction worker screening did not provide data on the effect of screening on survival or mortality. However, according to historical data, the treatment of smaller tumors can be expected to have better outcomes (higher cure rates, longer survival, lower mortality) than the treatment of larger tumors. Actual cure and survival rates may also depend on cell type and treatment strategy (7).

Translating research experience into practical screening applications would require radiologists trained in the detection of malignant abnormalities, easily available high-quality biopsy procedures for small nodules (a significant challenge in the nonresearch, community setting), and high-quality cytology diagnosis and reporting. Those currently involved in research using low-dose spiral CT estimate that 5 to 6 screening examinations could be done per hour once proper training and procedures are implemented. The unintended consequences of any screening program, such as the risk of radiation exposure from CT scans, should be considered in the overall assessment of the potential value of the proposed program. The possible adverse psychological effects of screening should be weighed against the psychological burden of cancer detected too late for successful intervention. Any program of medical screening and health surveillance should be implemented with a consideration of issues of quality assurance, confidentiality, notifica-

tion, and ethical conduct, consistent with the guidelines published by the World Health Organization (15).

Conclusions and recommendations

The value of spiral CT is sufficiently compelling that clinicians and others should consider its use for case evaluation and the clinical management of those at high risk of lung cancer. Until this screening technique is more fully evaluated, it is not recommended for screening the general population for lung cancer. However, it has great potential in the screening of well-defined high-risk groups, such as asbestos-exposed workers. Such studies should be initiated provided certain criteria are met. Investigations of occupational groups would supplement the results from ongoing research to elucidate the value of CT screening for the early detection of lung cancer also in the general population.

Decisions concerning the use of spiral CT in clinical evaluation, ongoing monitoring, and the eventual establishment of screening programs for high-risk asbestos-exposed workers should take into consideration the following known risk factors or risk markers of lung cancer:

- Cumulative exposure to asbestos of any fiber type (the Helsinki Criteria provide guidance for the doubling of lung cancer risk)
- Latency time from first exposure to asbestos (over 10 years of latency is needed before the risk increases significantly)
- Cumulative exposure to tobacco (both current and former smokers have increased risk; however, risk diminishes after smoking cessation)
- Age
- Presence of abnormal radiographic findings or the impairment of lung function
- Exposure to other lung carcinogens, such as radon, silica or polycyclic aromatic hydrocarbons.

It should be possible, and would be useful, to develop a matrix based on known risk factors and the available epidemiologic literature to indicate the level of lung cancer risk by a scoring system which could guide both screening decisions and clinical care (eg, criteria such as people over 50 years of age, over 20 pack-years of smoking, over 25 fiber-years of asbestos exposure with appropriate latency from first exposure could be taken as a guideline).

CT examinations (often employing a high-resolution protocol) are used in the surveillance of asbestos-exposed workers, particularly those with pulmonary symptoms. If feasible, the CT techniques used should also facilitate the detection of small noncalcified nodules as a suspect marker of early lung cancer. To assure the comparability

of findings, groups conducting research on lung cancer screening should employ consistent and standardized criteria for reporting pathological data (eg, tumor phenotype and stage).

At present, there are no clear health benefits from screening for mesothelioma because of the lack of adequate treatment and intervention. However, lung cancer screening directed at asbestos-exposed cohorts may provide important information leading to the earlier identification of mesotheliomas (eg, through the evaluation of small pleural effusions detected by CT) and potentially improved outcomes depending on the introduction of new treatment modalities. By analogy with other cancers, one might suspect that innovative therapies for mesothelioma are more likely to be effective for early-stage minimal-bulk tumors than for advanced mesotheliomas.

Preliminary results reported by the ELCAP investigators indicate a high rate of smoking cessation (23%) among program participants. If this finding is confirmed and translates to long-term cessation, it would be another significant benefit of the health screening of asbestos-exposed workers. It is not clear whether this is a specific benefit associated with the particular approach of the ELCAP investigators in their interaction with the screened population, a function of volunteers willing to participate in health screening, or a specific outcome from the use of the CT and associated counseling. The impact of screening programs on smoking should be further analyzed and followed longitudinally.

After reviewing the data from the Japanese, ELCAP, and Finnish experiences, we believe that it is highly desirable to follow the results of the ongoing investigations in order to apply them quickly when scientifically validated. A validated approach to the population-based screening of high-risk asbestos-exposed workers for the early detection of lung cancer would be of particular value. There is an urgent research need to include one or more defined cohorts of asbestos-exposed workers in several countries in ongoing research investigating the usefulness of spiral CT and sputum cytology for lung cancer screening. We must continue to refine our knowledge about the value of screening methods through the systematic evaluation of widely practiced health examinations and screening tests. Systematic well-designed screening projects of high-risk groups would provide valuable information also in this respect.

Ultimately, screening tests and programs are intended to detect disease and to have a beneficial effect on morbidity and mortality. Screening should not be substituted for the primary prevention of disease through the elimination of hazardous exposures. Unfortunately, in the case of workers with past exposures to asbestos, primary prevention is no longer possible, and secondary prevention through effective screening and associated health counseling is the only method remaining.

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