Screening for Malignant Pleural Mesothelioma and Lung Cancer in Individuals with a History of Asbestos Exposure

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Purpose: We established a screening program for prior asbestos workers using low-dose computed tomography (LDCT).

Methods: Between March 2005 and October 2007 we performed LDCT (50–60 mA, 120 kV, 1.25 mm) in 516 asbestos-exposed individuals. Parenchymal nodules were followed according to lung cancer screening recommendations, morphology and location of pleural plaques was noted in detail.

Results: We included 507 men and 9 women (median 60.0 years), 395 (76.6%) were smokers. Annual repeat has been performed in 356 participants. We found plaques in 357 subjects (69.2%), commonly calcified (79.6%), flat (86.6%), and symmetric (86.8%), and mostly involving the costal (96.4%) and diaphragmatic (81.8%) pleura. Uncommon plaques were lobulated (13.2%), right-dominant asymmetric (4.5%), or with effusions (0.1%).

We found pulmonary nodules in 371 subjects (71.9%), 91 (17.6%) had at least one nodule ≥5 mm; 10 growing nodules were found on annual repeat LDCT. In 41 individuals, plaques were regarded as atypical; three had new pleural/peritoneal abnormalities on annual repeat LDCT. An interim limited computed tomography of the observed abnormality prompted 10 diagnostic biopsies, resulting in a diagnosis of six lung cancers, two pleural mesothelioma and two peritoneal mesothelioma; overall rate of screen-detected malignancies is 2.1%. There were four interval cancers, diagnosed after baseline ($n = 1$) or after the annual repeat ($n = 3$): two pleural and one peritoneal mesothelioma, and one mixed squamous/small cell carcinoma.

Conclusion: Screening prior asbestos workers detects advanced malignant pleural mesothelioma and early as well as late stage lung cancer. We expect to learn more about the appearance of "early mesothelioma" with continued screening.

Key Words: Asbestos, Pleural plaques, Mesothelioma, Screening, Computed tomography.

(*J Thorac Oncol.* 2009;4: 620–628)

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Disclosure: The authors declare no conflicts of interest.

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ISSN: 1556-0864/09/0405-0620

Asbestos defines a group of naturally occurring mineral silicates, which are used for various commercial applications including fire-proofing and insulation. Asbestos readily breaks into small dust-like fibers, which are easily inhaled, resulting in a variety diseases of the respiratory system including asbestosis, lung cancer, and malignant pleural mesothelioma (MPM).[1,2] To date asbestos has largely been banned from work and home environments, but many countries (including Canada) still produce and export asbestos under strict regulations and at reduced levels.[3,4] Asbestos-related lung diseases will remain a major health concern,[4,5] mainly due to the long latency between exposure and disease development, but also due to current accidental asbestos exposures such as during the collapse of the World Trade Center towers.

Once asbestos exposure has occurred, there is no secondary prevention of chest diseases or prophylactic treatment available. There is a direct causal relation between the degree of asbestos exposure and MPM.[6–8] While the risk of lung cancer slowly declines after smoking cessation, the risk of MPM progressively increases with time.[9] Pleural plaques and MPM share the same etiology but have a different latency period (10–20 years for plaques,[10–12] 20–40 years for MPM[13–15]), and even though plaques are not regarded as a risk factor of MPM, the presence of pleural plaques provides a risk indicator and thus a window of opportunity for MPM diagnosis. Low-dose computed tomography (LDCT) has been studied extensively in high-risk smokers, and can identify early stage, potentially curable lung cancers,[16] although its effect on mortality remains under investigation. The biology of MPM makes this malignancy another potential target for screening. LDCT is a tool that is readily available for a detailed assessment of lungs and pleura, but despite ample published literature on (advanced) MPM,[17] the appearance of "early mesothelioma" is still not known.

The purpose of this study is to assess the utility of LDCT for the early diagnosis of malignant asbestos-related lung diseases. The strategy for early lung cancer detection follows established guidelines.[18,19] As MPM originates from the pleural surface and its presence coincides with pleural plaques, a focus of this study is to analyze the appearance of pleural plaques, and to attempt to identify variations in plaque morphology that might warrant further invasive investigations to rule out malignancy.

MATERIALS AND METHODS

Study Population

Between March 2005 and October 2007, 516 individuals were enrolled. Most ($n = 338$) were recruited in collaboration with the Occupational Health Clinics for Ontario Workers Inc. in Sarnia-Lambton, an area that is characterized by record numbers of asbestos-exposed workers.[20] These individuals are registered by Occupational Health Clinics for Ontario Workers because of documented asbestos exposure. The remaining 178 participants were referred from workers' unions and other contacts, also because of their asbestos exposure.

Inclusion criteria were: asbestos exposure at least 20 years ago or documented pleural plaques (demonstrated on chest radiographs), maximum age 80 years, in general good health, in particular no pertinent signs or symptoms of pleural chest disease. Exclusion criteria were prior cancers (except nonmelanotic skin cancer).

The study was approved by the Institutional Human Subjects Review Board and informed consent was obtained. The participants also completed a detailed questionnaire on the type and duration of their asbestos exposure and their occupational history, as well as demographics, family history, prior medical history, tobacco consumption etc.

Participants underwent LDCT and follow-up of findings as outlined below. If the baseline scan was negative, participants were invited for an annual LDCT. At the time of this analysis, 356 individuals have had their annual computed tomography (CT).

Computed Tomography Scanning

A LDCT scan of the chest was performed on a multidetector unit from different manufacturers (General Electric Medical Systems, Toshiba), with different number of detector rows (4–64), all utilizing helical scanning, low-dose regimens (40–60 mA, 120 kV) and thin-slice image reconstructions (1–1.25 mm). Pleural plaques were assessed on images reconstructed on a low spatial frequency algorithm ("soft tissue reconstruction") and displayed at standard mediastinal settings (Window 400 HU, Level 40 HU), lung nodules on images reconstructed on a high spatial frequency algorithm ("lung reconstruction") and viewed on standard lung settings (Window 1500 HU, Level −600 HU). All CT scans were double read, on a PACS workstation, first by the radiologist on service, followed by a research fellow for the detailed analysis and description of the target parameters. Only cross-sectional images were read (no multiplanar reconstructions). The readers were aware that the CT scans were from the asbestos study and the research fellow was not blinded to the initial report.

Pleural plaques were assessed according to their presence (yes/no), extent (involvement of the pleural surface; mild 25%, moderate 25 to 50%, severe >50%), location (costal, diaphragmatic, mediastinal, fissural pleura), and shape (flat, lobulated). The presence and extent of calcification was recorded as none, few (<25%), some (25–75%), mostly (75–90%), completely (>90%). We noted the symmetry of plaque distribution and the presence of pleural fluid. Diffuse pleural thickening was defined as more than 5 cm in extent along the pleural surface on transverse CT images, more than 8 cm in extent on craniocaudal CT images, and more than 3 mm thick.[21]

Based on the radiologists' judgment and in discussion with the thoracic surgeon (MRJ), we followed atypical plaques. Atypical pleural plaques were defined as (a) plaques associated with pleural effusions, (b) lobulated and mass-like plaques and (c) asymmetric distribution of plaques (Figure 1). As a guideline for follow-up we defined an initial 3- to 6-months LDCT limited to the target area as a guide to initiate further investigations in the case of growth/change.

Parenchymal nodules were followed according to recommendations from lung cancer screening studies.[19] In brief, indeterminate nodules are defined as solid nodules 5 mm or larger or nonsolid nodules 8 mm or larger. These nodules were followed with a limited LDCT scans 3 to 6 months after the baseline CT. Further investigations (e.g., CT guided biopsy) were initiated if the nodule under surveillance had grown.

Further investigational procedures were recommended based on suspicious findings as baseline, or following growth at the 3 to 6 months or annual follow-up examination (Table 2, Figure 1). They ranged from CT-guided biopsy (e.g., of the lung nodules), to thoracocentesis (e.g., of pleural nodularity and effusion) to ultrasound (e.g., of new peritoneal nodules)—assuming that the ultrasound would have been followed by biopsy if required. The kind of investigational procedure was dictated by the type of abnormality, its location and accessibility, following standard of care.

RESULTS

The findings and the follow-up of the screened individuals are summarized in Figure 1.

Study Population

The demographics of the study population has been summarized in Table 1. The average pack-years of the current and former smokers was 23.4 ± 1.0.

Asbestos exposure was documented in 510 (98.8%) individuals, 249 (48.2%) had known pleural plaques (mostly documented on chest radiographs); only six individuals had no knowledge of prior asbestos exposure and were enrolled based on the presence of pleural plaques alone. The type of asbestos fiber to which the subjects were exposed was reported as unknown ($n = 230$), all ($n = 16$) or a mixture of different asbestos types ($n = 66$), mostly amphiboles ($n = 19$), chrysotiles ($n = 84$), crocidolites ($n = 12$), or asbestos in blue mud cement ($n = 89$).

Pleural Plaques

Of the 516 individuals, 357 (69.2%) had at least mild plaques, 159 (30.8%) had no plaques at baseline. Most common plaque location was the costal pleura ($n = 344$, 96.4% of 357), followed by the diaphragmatic ($n = 292$, 81.8%) and the mediastinal pleura ($n = 107$, 30.0%). The fissures were involved in 7 cases (2.0%).

In 309 cases (86.6% of 357) all plaques were flat; in 47 cases (13.2%) we found at least one lobulated plaque (Figure 2). Diffuse pleural thickening was present in 1 case (0.3%).

Seventy-three of the 357 individuals (20.4%) with pleural plaques showed no calcifications; 44 subjects (12.3%) had few,

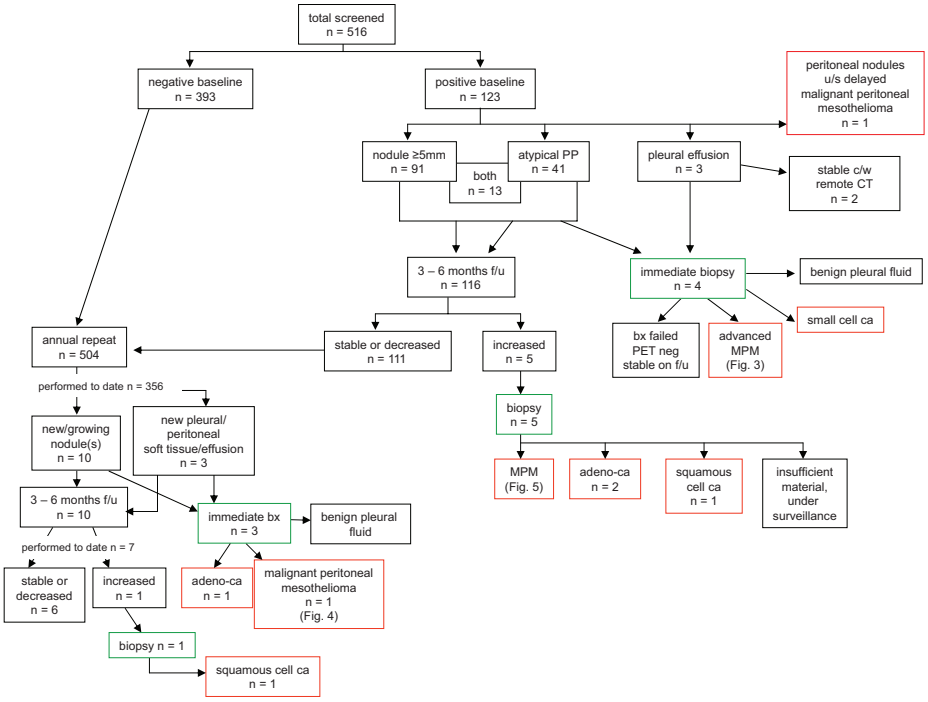

FIGURE 1. Overview of the follow up and outcome of the study participants following the baseline study and the annual repeat study. PP, pleural plaques; MPM, malignant pleural mesotheliomas; f/u, follow-up.

TABLE 1. Demographics of the Study Population

	n	%
Total	516	
Men	507	98.3%
Women	9	1.7%
Age [years]	60 (32–83)	
Smoker		
Current	104	20.2%
Former	291	56.4%
Never	121	23.4%

110 (30.8%) minor calcifications. In 101 cases (28.3%) plaques were mostly and in 29 subjects (8.1%) completely calcified.

Plaques were associated with effusions in three individuals at baseline (0.6%). In one subject, the pleural effusion was associated with nodular pleural thickening, although a subsequent biopsy revealed no malignancy. In the other two cases with pleural effusions, a remote CT scan confirmed stability for several years. Another subject had aspiration of his new pleural effusion seen on the annual LDCT, no malignant cells were found.

In 310 subjects, the distribution of plaques was symmetric (86.8%). Of the 46 cases (12.9%) with asymmetric distribution, 32 were left dominant (70%).

Based on combined radiologic/surgical judgments, 41 (7.9%) individuals were considered to have atypical pleural plaques at baseline, which were followed as outlined above. In addition, 13 of these subjects also had pulmonary nodules that required further CT surveillance (see below).

Of the 356 study participants who have had an annual LDCT to date, one developed new pleural thickening and one a new pleural effusion (see above). The other 252 study participants (99.2%) demonstrated no change.

Parenchymal Nodules

One or more pulmonary nodules were detected in 371 individuals (71.9%). In 91 cases (17.6%), at least one nodule was 5 mm or larger that required a limited LDCT in 3 to 6 months. We did not find any nonsolid nodules 8 mm or larger. Thirteen of these 371 individuals had atypical plaques as well.

In the 356 annual LDCT studies performed we found 10 new or growing nodules (2.8%), which prompted 1 immediate biopsy and 9 limited follow-up LDCT.

Follow-Up Procedures

The recommended interventions are listed in Table 2. Immediate investigation of abnormal baseline findings was recommended in five cases: a pleural effusion with thickened pleura was aspirated and revealed no malignancy; an immediate biopsy of a 2 cm parenchymal nodule failed because of its location, positron emission tomography was negative and the nodule remains stable 13 months after baseline; biopsy of a large pleural/diaphragmatic mass revealed an advanced MPM (Figure 3); biopsy of a large lung mass showed small cell carcinoma. One recommended follow-up (ultrasound) of peritoneal nodules was delayed for several months for unknown reasons; the patient was eventually diagnosed with an advanced peritoneal mesothelioma.

Immediate investigation of an abnormality found on annual LDCT was recommended in 3 participants, one had new abdominal soft tissue masses, and was subsequently diagnosed with a malignant peritoneal mesothelioma (Figure 4), one had a growing nodule diagnosed as adenocarcinoma, and one had a new pleural effusion, ultrasound-guided aspiration did not reveal malignancy.

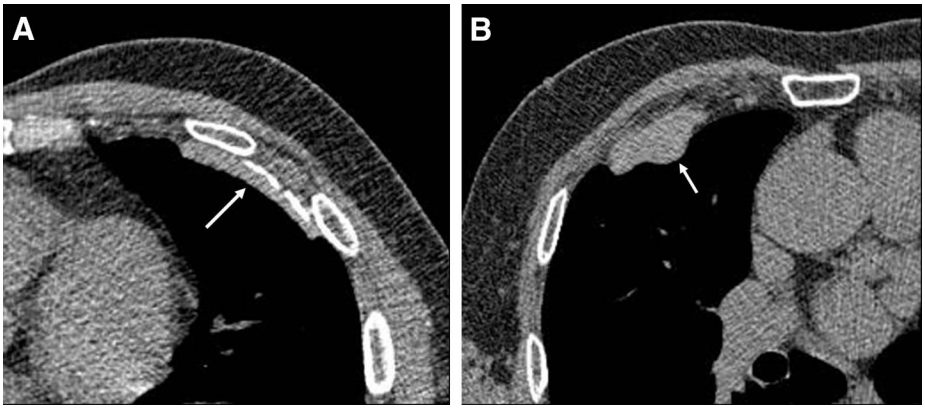

FIGURE 2. *A,* low-dose computed tomography (LDCT) images from different study participants. Post prior asbestos exposure, evidence of flat, partly calcified pleural plaques along the costal pleural surface (arrow). *B,* Post prior asbestos exposure, evidence of lobulated pleural plaques along the costal pleural surface, without calcifications (arrow).

Interim follow-up scans of atypical pleural plaques and/or indeterminate nodules were performed 3 to 6 months after baseline in 116 cases. In five cases, the abnormality had grown and biopsy was recommended. Four revealed malignancy: MPM (Figure 5), stage 1 adenocarcinoma, squamous cell carcinoma (unstaged), and an unstaged adenocarcinoma; the fifth biopsy yielded insufficient material, the nodule is under surveillance and for the purpose of this analysis regarded as benign.

Interim follow-up of plaques or nodules was recommended from the annual LDCT in 10 cases, 9 for nodules and 1 for new pleural thickening. Seven follow-up examinations have been performed to date, with five nodules decreased or stable, and one increasing in size; this was subsequently biopsied and revealed a stage 1 squamous cell carcinoma. One new focal pleural thickening had decreased on the 6 month follow-up CT. The remaining three follow-up exams are not yet scheduled.

The number of invasive procedures recommended from baseline studies was 10/516 (1.9%), 7 revealed malignancy; the malignancy rate is 7/10 (70%). The rate of invasive procedures from annual scans was 4/356 (1.1%), 3 revealed malignancy and the malignancy rate was 3/4 (75%).

Malignancies

Table 2 provides an overview of the malignancies. We identified six lung cancers, two MPM and two malignant peritoneal mesothelioma on baseline and annual scans (seven prevalence and three incidence malignancies), for an overall malignancy rate of 2.1%. In addition, we are aware of four interval cancers, diagnosed after baseline ($n = 1$) or after the annual repeat ($n = 3$): two pleural and one peritoneal mesothelioma, and one squamous cell carcinoma with a small cell carcinoma focus in an infracarinal lymph node. All malignancies were found in smokers who had an average 31 pack-year history. Three screen-detected lung cancers were stage 1 NSCLC (one squamous cell carcinoma, two adenocarcinoma), one a small cell carcinoma. Two screen-detected lung cancers are unstaged (one recently diagnosed; the other patient's health was too poor for any further procedures). Two of the screen-detected lung cancers are lost to follow-up; the patients with stage 1 lung cancer are still alive to date.

We found two MPM and two peritoneal mesothelioma. One MPM was advanced at the time of diagnosis; the other MPM seemed early stage but grew aggressively during the presurgical staging (Figure 5). Two of the patients with mesothelioma underwent explorative surgery, none underwent surgery for treatment. All mesothelioma patients died soon after diagnosis, maximal survival was 9 months.

DISCUSSION

We established a screening program for the detection of asbestos-related MPM and lung cancer, using LDCT of the chest. In addition to the lung parenchyma, we focused on the appearance of pleural plaques, to detect abnormalities which might warrant further investigation to exclude a pleural neoplasm. We identified atypical pleural morphology as lobulated plaques, asymmetric in distribution (in particular when right dominant), and plaques along the mediastinal pleura. Two MPM and two malignant peritoneal mesothelioma were detected. Lung nodules were followed up according to lung cancer screening protocols, resulting in the diagnosis of six lung cancers.

Malignant pleural mesothelioma has a highly specific causal relationship with asbestos, more than 80% of MPM are attributable to asbestos exposure.[13–15,22,23] The emphasis for development of MPM seems to be on latency rather than dose[24]: the latency period from asbestos exposure is 20 to 40 years,[13–15,25] which is reflected in the enrollment criteria for our study.

MPM is associated with a median survival time of 1 year from symptom onset, which suggests that methods to detect this malignancy earlier are needed. Symptoms are nonspecific and may similar to lung cancer.[14,15,23] It can be difficult to make a definite diagnosis of MPM even in advanced cases.[14,15] The radiologic appearance of "early mesothelioma" is as yet unknown, as to date, most radiology literature has focused on diagnostic confirmation and staging.[17]

Pleural plaques refer to circumscribed pleural thickening or fibrosis, which can be found in up to 50% of workers exposed to asbestos[26,27]: in our series pleural plaques were seen in 69% of subjects. Plaques are regarded as a reliable indicator for asbestos exposure,[11,12,28] to the extent that we enrolled individuals with documented pleural plaques even if

TABLE 2. Overview of the Interventions and Malignancies: Prevalence and Incidence Malignancies were Screen-Detected; Interventions, Final Histology, Stage and Survival is Listed Where Available

	Age	Smoking History (Pack-Year)	Time When Intervention was Indicated or Diagnosis (dx) was Made	Final Diagnosis	Stage[a]	Survival[b]	Displayed in Figure
Malignancies							
Prevalence	64	17	Immediate	Malignant pleural mesothelioma	Nonsurgical (explorative surgery)	[b]1 wk post surgery	4
	81	22	Immediate	Small cell carcinoma	Extensive	[b]<3 mo post dx	
	74	10	Immediate from baseline (but delayed for unknown reasons)	Malignant peritoneal mesothelioma	Nonsurgical	[b]<2 mo post dx	
	60	45	6 mo f/u	Mucinous adenocarcinoma	Stage 1 (T1N0M0)	30 mo	
	65	38	6 mo f/u	Squamous cell carcinoma	Unstaged	Lost to follow-up	
	70	28	3 mo f/u	Adenocarcinoma	Unstaged	Lost to follow-up	
	72	12.5	3 mo f/u	Malignant pleural mesothelioma	Nonsurgical (explorative surgery)	[b]4 mo post dx	6
Incidence	68	75	Immediate from annual	Malignant peritoneal mesothelioma	Nonsurgical	[b]1 mo post dx	5
	69	14	Immediate from annual	Adenocarcinoma	Stage 1 (T1N0M0)	15 mo	
	73	25	3 mo from annual	Squamous cell carcinoma	Stage 1 (T2N0M0)	18 mo	
Interval	77	67	dx after baseline	Squamous cell carcinoma, small cell carcinoma in subcarinal lymph node	T1/limited	Lost to follow-up	
	61	34	dx after annual follow-up	Malignant peritoneal mesothelioma	Nonsurgical	[b]9 mo post dx	
	59	45	dx after annual follow-up	Malignant pleural mesothelioma	Nonsurgical	[b]2 mo post dx	
	59	4	dx after annual follow-up	Malignant pleural mesothelioma	Nonsurgical	[b]3 mo post dx	
Inconclusive biopsies	81	66	Immediate	Failed biopsy. SUV = 1. Under surveillance			
	53	0	3 mo f/u	Failed biopsy. Under surveillance			
Effusions	64	42	Immediate	Benign			3
	63	29	Immediate from annual	Benign			

The interventions leading to the final diagnosis of the interval cancers are not known.
[a] Refers to stage I–IV in NSCLC, limited vs. extensive in SCLC, surgical or nonsurgical in malignant mesothelioma.
[b] Patient has passed away.
SUV, standard uptake value; SCLC, small cell lung cancer; f/u, follow-up.

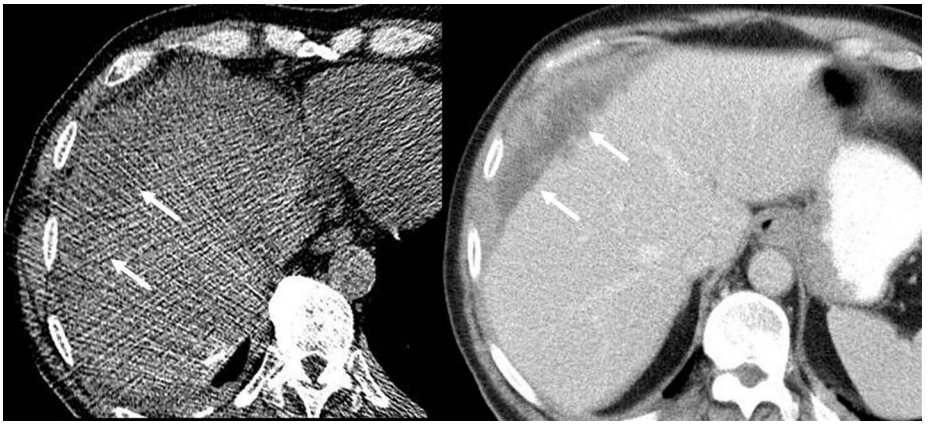

FIGURE 3. Baseline low-dose computed tomography (LCDT) (left) of a 64-year-old male shows a hypoattenuated/necrotic mass along the right pleura/diaphragm (arrows), which is better visualized on the subsequent contrast-enhanced computed tomography (CT) (right). Biopsy revealed a malignant mesothelioma.

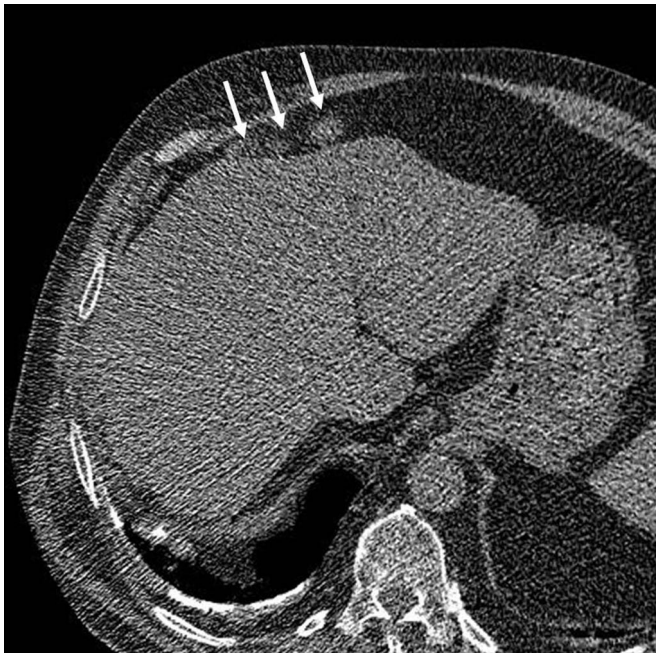

FIGURE 4. Annual repeat screening low-dose computed tomography (LDCT) of a 68-year-old man. The annual repeat demonstrates intra-abdominal, prehepatic soft tissue nodules which were not present on the baseline. Subsequent investigations revealed a malignant peritoneal mesothelioma.

their asbestos exposure was unknown. There is a direct relation between the intensity of asbestos exposure and the total area of the pleura involved by plaque formation.[29]

The relationship between pleural plaques and malignant mesothelioma is not completely understood. Both share a common etiology,[30,31] and autopsy series indicate that plaques are associated with an increased risk of mesothelioma.[27] It has been suggested that detection of pleural plaques may allow the identification of people at risk for mesothelioma,[28] but longitudinal studies to confirm this are lacking. Pleural plaques are usually detected only by radiologic examination, as they are frequently asymptomatic, and do not typically impair pulmonary function.[32–35] Diffuse pleural thickening is less common than pleural plaque formation.[31] It usually develops 20 to 40 years after first asbestos exposure and may result in a restrictive or constrictive physiologic defect.[32,36]

Pleural plaques seem circumscribed on cross-sectional imaging. Plaque calcifications may be present in approximately 20%[17] to 70%[21]: in our series plaques contained calcifications in 80%. Plaques are usually bilateral (>80%) and unilateral findings are more often left-sided than right-sided,[37] which was also found in our study.

Pleural plaques are rarely associated with fluid.[38] Pleural effusions are earlier markers and occur within 10 years of asbestos exposure, may last several months and spontaneously resolve.[26] MPM presents in up to 74% of cases with fluid alone.[14] Thus, the presence of pleural fluid in our population with remote asbestos exposure was regarded as atypical. Two pleural effusions found at baseline were stable when compared with remote CT studies and two pleural effusions had no evidence of malignancy in the aspirated fluid. Given that pleural fluid cytology is often negative even in proven cases of MPM,[39] we continue to follow these individuals closely.

Both location and imaging features of pleural plaques overlap with the description of MPM on CT[14]: the most common radiologic pattern of MPM is localized or diffuse pleural masses (92%), and 20% have other signs of asbestos exposure. Thickening of the interlobar fissure has been reported in 86%[14] in MPM. Per definition, pleural plaques originate from the parietal pleura,[27] and thus should not involve the fissures, which are covered by visceral pleura only. However, thickening of the fissures after asbestos exposure has been described in the literature in 12% of cases,[21] and there is indication in the literature that a small percentage of plaques are indeed visceral,[40] which was confirmed in our series in 2% of subjects.

Since pleural plaques and MPM overlap in their presentation, one focus of this study was to define the appearance of pleural soft tissue masses that can no longer be safely interpreted as typical pleural plaques and may be indicative of an early mesothelioma. We were not able to identify any single feature of constellation of CT changes that was predictive of MPM in the patients who developed this malignancy after their initial screening scan. Furthermore, screening did not lead to the early diagnosis of mesothelioma in any

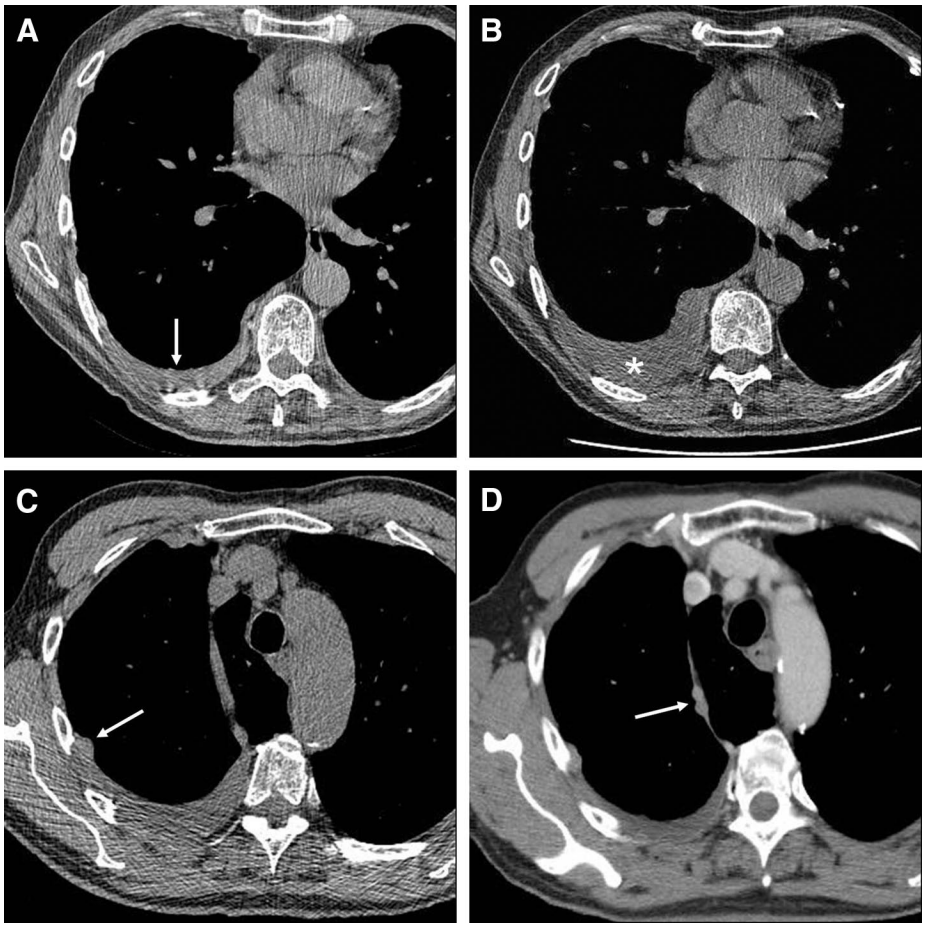

FIGURE 5. *A*, Baseline low-dose computed tomography (LDCT) of a 71-year-old man demonstrated asymmetric pleural plaques, right dominant (arrow). A 3 months follow-up was recommended. *B*, Three months later, there is interval development of a moderate pleural effusion (asterisk), (*C*) as well as new nodules along the pleural surface (arrow). Subsequent thoracocentesis and drainage to dryness was positive for mesothelioma. *D*, The contrast-enhanced staging computed tomography (CT) 2 months later showed recurrence of the pleural effusion, increase in the previously seen pleural effusions as well as new soft tissue nodules along the mediastinal surface and along the azygos lobe (arrow).

cases. One MPM found in our study had invaded the diaphragm and another quickly progressed during the staging period (Figure 5) and at that time was no longer operable. An extremely rapid growth of MPM has been previously described.[41–43]

As expected, the number of lung cancers found in our population exceeded the number of MPM. It has been reported that for every one mesothelioma case there are two asbestos-related lung cancer cases.[44] Smoking has a strong synergistic interaction with asbestos,[45,46] and an elevated lung cancer risk may also be associated with bilateral pleural plaques alone.[47] Smoking is not related to the risk of developing MPM,[14,16,27,48] and thus was not required to enroll in our study. Consequently, the lung cancer rate is rather low at 1.1%, a rate that is similar to that reported by Fasola et al.[38] in a similarly designed study. The lung cancer prevalence is much higher (4.3%) when high-risk smokers and asbestos-exposed individuals are screened.[49] In fact, in the study reported by Fasola et al.,[38] no mesothelioma was found among 1045 subjects screened, underlining the different risk profile of the 2 malignancies. Our study had a similar percentage of smokers (77%) as other studies that have reported 75% to 87% smokers.[38,49,50]

The prevalence of lung nodules (72%) and the rate of positive baseline scans (18%) is similar to other screening studies.[18,51,52] One quarter of our invasive interventions were performed for benign lesions, which is lower than the 52% intervention rate reported in a similar screening study.[38]

To our knowledge, this is the first screening study of prior asbestos-exposed individuals targeting the early diagnosis of MPM, and focusing on the morphology of pleural plaques. Several other screening studies have been conducted in this high-risk population, focusing on the asbestos-related parenchymal disease (asbestosis),[49] or on lung nodules and lung cancers as the primary end point.[38,50,51,53] Only one study reported on a pleural mesothelioma found in the screening study,[50] but its appearance and stage were not described. Our findings suggest that LDCT can find MPM in asymptomatic individuals; however, whether LDCT will result in the diagnosis of an "early" MPM where treatment may be offered with curative intent still has to be addressed. Our experience reflects the well-know aggressive features of MPM, four interval cancers are known to date, three of those were mesothelioma. The current screening regimen may need to be adjusted; in particular, the biennial screening interval following a stable annual CT is currently under discussion. Most importantly, there is need for a biomarker as an independent risk indicator (see below), which then would allow screening individuals at very high risk for mesothelioma at shorter intervals, possibly utilizing minimum dose/thicker

slice regimens to achieve sufficient signal/noise ratio with reduced radiation dose. For certain mesothelioma types, serum mesothelin-related protein is a potential biomarker for detection and treatment monitoring.[54]

Our study is limited by a short observation period. Continued screening will allow us to appreciate changes in plaque appearance, and interim mesothelioma diagnoses will provide information on its early presentation. Software developments will help in the analysis of pleural abnormalities and interval changes.[55] We have not included magnetic resonance imaging because of limited availability and high expense. T2-weighted magnetic resonance imaging images in particular allow discrimination between pleural plaques and malignant mesothelioma,[30,56,57] and might help to characterize suspicious plaques. Positron emission tomography also holds promise for mesothelioma staging,[58] but its place in the early diagnosis has not yet been assessed.

A successful screening program includes an effective treatment to improve the prognosis of the early detected disease. Unfortunately, treatment options for MPM are limited. Promising advances include trimodality treatment consisting of chemotherapy followed by extrapleural pneumonectomy and hemithorax radiation.[59–61]

In summary, we have developed a screening program in asbestos-exposed individuals, and have assessed the appearance of pleural plaques. Advanced pleural and peritoneal mesothelioma as well as early and late stage lung cancers have been found. With continued screening and observation of changes in plaque morphology we expect to learn about the "early mesothelioma."

ACKNOWLEDGMENTS

We would like to acknowledge Brenda O'Sullivan, the study coordinator of the asbestos screening program. We also would like to thank Jenny Schieman, RN, and the other staff of the Occupational Health Clinics for Ontario Workers Inc., the Master Insulators Association of Ontario and the International Association of Heat and Frost Insulators and Asbestos Workers for their collaboration and support.

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