Feasibility of a screening programme for lung cancer in former asbestos workers

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Background Low-dose computed tomography (CT) has been found to detect more Stage IA lung cancer than chest x-ray.

Aims To investigate whether lung cancer screening with CT was effective and acceptable in former asbestos workers.

Methods CT scanning was carried out following the protocol previously described in the literature. A questionnaire was used to assess cumulative asbestos exposure. An economic analysis was also performed. Informed consent was obtained from all patients.

Results A total of 1119 male asbestos workers (58% of invited) were examined, of whom 65% were smokers or ex-smokers. Mean age was 57.1 years with mean cumulative exposure to asbestos of 123 fibres/ml × years. Pleural plaques were found in 375 workers (32%), while 338 workers (29%) were included in the radiological follow-up, which led to 25 biopsies (13 of lung, 9 of pleura, 3 of both) and five screen-detected lung cancers (0.4%), one in Stage I. Incidence rate was 149 per 105, equal to that in the male general population of similar age. The expenses for diagnosis were 1014 and 244962 Euro per screened subject and screen-detected lung cancer case, respectively.

Conclusions Screening adherence and frequency of detection were low, while costs and radiation dose were high. In spite of a high cumulative asbestos exposure, lung cancer risk was not increased relative to the general population. The screening programme was not felt to be cost-effective from the perspective of the government as a third-party funding agency.

Key words Asbestos; health surveillance; lung cancer screening; low dose computed tomography.

Introduction

In most industrialized countries, the incidence of lung cancer in asbestos workers is expected to peak between 2010 and 2020 despite regulatory restriction on asbestos use or bans imposed during the 1980s and 1990s [1]. Detecting these tumours at an early stage could potentially allow early more effective treatment with improved survival and increased quality of life.

Four large randomized clinical trials carried out during the 1970s suggested that neither chest x-ray (CXR) nor sputum cytology were beneficial screening tests for the early detection of lung cancer [2,3]. In 1000 symptom-free volunteers, aged 60 years or older, with at least 10 pack-years of cigarette smoking and no previous cancer, low-dose computed tomography (CT) detected more malignant diseases than CXR (2.7 versus 0.7%) and Stage IA lung cancers (2.2 versus 0.4%). Resection of Stage IA cancer achieves a 5-year survival rate of >70% [4].
According to Morrison [5], the demonstration that a given screening programme is effective is usually no more than the beginning of a screening policy. There are nearly always questions on the benefits of screening, whether it should include a broader or narrower section of the population and whether it should be conducted with different tests, improved testing methods or a combination of tests for instance. Answering these questions may require observing the effect on morbidity or mortality and may be difficult within a short time frame by which time technological improvements of the screening tools and accumulating knowledge may have rendered the results obsolete. If an answer has to be obtained reasonably quickly, the period of screening must be fairly short. Therefore, in a one-time screening programme, where each subject was tested once, we evaluated the effectiveness and feasibility of a screening programme for the detection of asymptomatic early-stage lung cancer in former asbestos workers.

Methods

As part of a post-occupational medical surveillance programme, which was authorized and financially supported by Veneto Region and Italian Ministry of Health, we conducted a screening for early diagnosis of lung cancer in former asbestos workers from January 2000 to June 2003. We chose to examine those previously engaged in the manufacture of asbestos–cement products, railway rolling stock fabrication and repair or employed as insulators in shipyards or elsewhere, who were presumed to have been exposed to the highest concentrations of asbestos fibres. We identified the relevant companies through the application forms completed by their workers according to an Italian law (decree no. 257/92) providing benefits for workers formerly exposed to asbestos. A comprehensive list of retired workers (being at work in 1970 or later) was obtained from each company. Such a procedure led to 5379 former asbestos workers.

Having ascertained vital status, a letter containing information about the purpose and methods of the study and an invitation to participate was sent to 2000 workers and their family physicians. Subjects were examined using the same protocol for collecting clinical and occupational history and performing CT examinations. Incidental findings were discussed with the patients and their family physicians and, where appropriate, referred for specialist evaluation. Smoking cessation was recommended and facilitated for all subjects. Participating subjects were followed up until July 2005. Informed consent was obtained by all subjects.

Assessment of asbestos exposure was carried out using a questionnaire based on job-specific modules [6]. The interviewer chose the suitable module in relation to the interviewee’s past occupation; a new module was filled whenever the worker reported a change in environmental conditions or job performed. Using defined scales, examiners scored the determinants of exposure: raw materials used (with fibre content and friability); jobs done (specified in terms of mechanical disturbance applied to materials through the tools used by the worker) and factors modulating exposure (particle emission speed, source surface, presence of localized air exhaust systems, dimension and physical characteristic of the rooms, etc.). Through integration of all scores, an exposure intensity was determined. In some subjects, information on exposure intensity was gathered through a job-exposure matrix built through direct knowledge or literature data describing exposure levels in different jobs/tasks and different calendar periods. Lastly, by multiplying intensity (concentration in fibres/ml, f/ml), frequency (percent of the working time spent at a certain exposure level) and length of exposure in years, and by summing up as many products as were necessary to take into account the different jobs done, a semiquantitative estimate of cumulative exposure (f/ml × years) was calculated. The interviewers were trained in the use of the questionnaire in order to minimize information bias.

Low-dose CT, the screening test for early diagnosis of lung cancer, was carried out following the technique described in the Early Lung Cancer Action Project (ELCAP) by Henschke et al. [4]. The diagnostic workup of screen-detected non-calcified nodules (NCNs) was guided by the ELCAP protocol in order to avoid invasive procedures in benign nodules. Thus, all NCNs >10 mm in diameter were referred for biopsy, while high-resolution CT follow-up after 3, 6, 12 and 24 months to exclude growth was recommended for NCNs of <10 mm. The characteristics (size, shape, location, margin and presence of benign calcification) of any nodule detected at CT were recorded. Pleural plaques were classified into: (i) small plaques with greater diameter between 1 and 4 cm, (ii) intermediate class and (iii) widespread plaques involving the greater part of a hemithorax [7]. A subject was referred to a respiratory physician in the presence of: class 1 (women only), class 2 or 3 (if thickness of plaques was ≥15 mm) and any class with associated pain and/or pleural effusion.

The list of 5379 former asbestos workers was reported to the Epidemiological Department of Veneto Region (SER) for record linkage with the regional archive of hospital discharge records. Information on hospital admissions for lung cancer was obtained; repeated admissions of the same subject were identified, and prevalent cases were excluded.

For the purpose of cost analyses, the screening programme was subdivided in three processes: (i) definition of the protocol and training of interviewers, (ii) preparation of lists of asbestos workers with their contact details and development of software for data entry and (iii) carrying out screening: organizational and administrative tasks (reception of subjects, preparation of medical reports, management of the follow-up, etc.) and diagnostic
work-up. Each process was broken down into its component activities, identifying a time for each activity (duration of use of medical equipment, and time spent by administrative and medical staff). The cost of processes 1 and 2 was sustained only once during the set-up of the screening (fixed cost). The cost of process 3 (variable cost) was estimated as sum of products (time × standard cost of each activity × number of subjects to be examined), separately for internal resources and services 'acquired' outside, from organizational units not directly involved in the screening programme. The average 'cost per unit screened' was the ratio between variable cost and number of screened subjects.

Results

Out of 2000 workers invited, 1165 (58%) agreed to undergo examinations (1129 males and 36 females) between January 2000 and July 2003. After excluding women because of low numbers and 10 men with missing data, 1119 male asbestos workers were included in the study.

Table 1 shows the baseline characteristics of these workers: age, years elapsed from hire to the date of the first medical examination, years elapsed from last exposure to end of follow-up, length of exposure in years, maximum intensity of exposure to asbestos ever reached during working career and historical cumulative asbestos exposure. It can be seen that these workers experienced a heavy exposure to airborne asbestos, and that, although their mean age was relatively young, the latency period (years elapsed from first exposure to occurrence of an asbestos-related disease) was high.

We found 361 cases of asbestos pleural plaques (APPs) in the screened population, a prevalence of 32%, and 242 cases of lung NCNs (any diameter), a prevalence of 21%.

In order to detect a growth of the lesion before performing a biopsy, 338 subjects (29%) with suspect NCNs and/or APPs were included in the radiological follow-up that led to 25 biopsies: 13 of lung, 9 of pleura and 3 of both. Out of 16 lung biopsies, 5 were lung cancer: 4 primary (see below) and 1 secondary lung cancer. An additional primary lung cancer was diagnosed by sputum cytology. The five screen-detected primary lung cancer cases are shown in Table 2 and described in the text box.

Case 1 had low asbestos exposure and time since first exposure (TSFE) of <20 years. NCN was <1 cm in diameter at the first and second CT and therefore the radiologist did not suggest further examinations. Repeat CT scan was requested 24 months later to determine whether interim growth has occurred but was delayed due to intercurrent illnesses when NCN was found to have a diameter higher than 1 cm and at biopsy the disease stage was quite advanced.

Case 2 had high asbestos exposure and many years since first exposure. There were signs of asbestosis and a NCN of ~2 cm at the first CT scan. The subject did not undergo surgical resection because of advanced stage lung cancer and the presence of other diseases. The lung cancer diagnosis was based on bronchial washing cytology.

Case 3 had high asbestos exposure and many years since first exposure. CT scan showed radiological signs of asbestosis. Two primary lung tumours were found: an adenocarcinoma in the lower lobe and a squamous cell carcinoma of the upper lobe of the same lung. Only one NCN of <1 cm in diameter was observed on the initial CT scans. After 7 months, CT was repeated and a lung biopsy was performed immediately confirming advanced stage lung cancer.

Case 4 had low exposure and high TSFE. Initial CT found a lung NCN of ~1 cm and 7 months later. Positron emission tomography was then carried out which was positive with advanced stage lung cancer.

Case 5 had low exposure and high TSFE. CT was repeated and a lung biopsy was performed immediately confirming advanced stage lung cancer.

In order to determine whether interim growth had occurred, the patient was invited for repeat CT scan in November 2004, when the NCN became larger than 1 cm in diameter. At biopsy, the stage was IA.

Cumulative incidence of lung cancer was 0.4% (= 5/1119) in the whole population and 0.69% (= 5/727) in the subgroup of smokers or ex-smokers (all cases were current or former smokers). The incidence of lung cancer was 149 per 100 000 (= 5/(1119×3)), assuming that all...
Table 2. Main characteristics of the five screen-detected primary lung cancer cases<sup>a</sup>

<table>
<thead>
<tr>
<th>Cases</th>
<th>Age, smoking</th>
<th>Cumulative asbestos exposure (fibres/ml × years)</th>
<th>TSFE, TSLE</th>
<th>Asbestosis, pleural plaques</th>
<th>First CT: date and Ø of NCN</th>
<th>Last CT: date and Ø of NCN</th>
<th>Histology</th>
<th>TNM classification and stage</th>
<th>Date of diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61, ExS</td>
<td>13.6</td>
<td>18, 15</td>
<td>A0, P0</td>
<td>May 2002 and Ø &lt; 1 cm</td>
<td>February 2005 and Ø &gt; 1 cm</td>
<td>AC</td>
<td>T2/N1/M0 Stage IIB</td>
<td>April 2005</td>
</tr>
<tr>
<td>2</td>
<td>65, ExS</td>
<td>182</td>
<td>50, 17</td>
<td>A1, P0</td>
<td>June 2002 and Ø = 2 cm</td>
<td>Advanced</td>
<td>NSCC&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Stage Advanced</td>
<td>September 2002</td>
</tr>
<tr>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>63, ExS</td>
<td>108</td>
<td>25, 11</td>
<td>A1, P0</td>
<td>September 2002 and Ø &lt; 1 cm</td>
<td>May 2003 and Ø = 1.5 cm&lt;sup&gt;o&lt;/sup&gt;</td>
<td>AC&lt;sup&gt;c&lt;/sup&gt;</td>
<td>SC&lt;sup&gt;c&lt;/sup&gt; Stage IIIA</td>
<td>July 2003</td>
</tr>
<tr>
<td>4</td>
<td>56, CS</td>
<td>4.0</td>
<td>25, 13</td>
<td>A0, P0</td>
<td>October 2001 and Ø = 1 cm</td>
<td>April 2002 and Ø = 1 cm</td>
<td>AC</td>
<td>T1/N2/M0 Stage IIIA</td>
<td>July 2002</td>
</tr>
<tr>
<td>5</td>
<td>52, CS</td>
<td>35.0</td>
<td>36, 17</td>
<td>A0, P1</td>
<td>December 2001 and Ø &lt; 1 cm</td>
<td>November 2004 and Ø &gt; 1 cm</td>
<td>SC</td>
<td>T1/N0/M0 Stage IA</td>
<td>March 2005</td>
</tr>
</tbody>
</table>

<sup>a</sup>Age at diagnosis (years); smoking habits (CS, current smokers; ExS, ex-smokers); exposure (fibres/ml × years); TSFE (years); TSLE (time since last exposure, years); radiological asbestosis (A1, yes; A0, no) and pleural plaques (P1, yes; P0, no); history of screening with low dose computed tomography (month and year of executing CT; diameter of non-calcified nodule, Ø NCN); histology (AC, adenocarcinoma; SC, squamous cell carcinoma; NSCC, non-small cell carcinoma); TNM classification and stage.

<sup>b</sup>Cytologic not histologic diagnosis.

<sup>c</sup>Two primary lung tumors: AC at inferior lobe (\(\frac{5}{16}\)) and SC at superior lobe (\(\frac{5}{16}\)) of the right lung.
received, and then declines. Under this model, there is a shorter latency period than previously assumed, especially for high intensity of exposure [8]. Since in our workers the average time from last exposure was 16 years and the average time since first exposure was 31 years, the timing of asbestos exposure could explain why in workers with a high historical asbestos exposure lung cancer risk was not increased relative to the general population: the most exposed and susceptible workers could have died from lung cancer before the beginning of this study.

A total of 835 (42%) asbestos workers refused the invitation to participate in the screening programme. The high default rate is one of the major limitations of our study, but also represents a practical concern in any screening programme. Although we did not know the reasons for refusing, the equal lung cancer incidences (149 per 100 000 in the screened workers and 154 per 100 000 in the total cohort) suggest no major differences in the distribution of risk factors.

As shown in a recent review study [9], Henschke et al. reported 22/27 CT screening-detected lung cancer cases in Stage I [4], Swensen et al. 13/21 [10], Diederich et al. 5/11 [11], Sone et al. 21/22 [12], Nawa et al. 28/36 [13] and Sobue et al. 1/13 [14]. Tiitola et al. [15] observed no Stage I lung cancer case in 602 subjects (97% smokers) with asbestos diseases. In our study, only one of five cases of lung cancer was detected in stage I.

On the other hand, the cumulative incidence of lung cancer (0.4% in the whole population and 0.69% in smokers or ex-smokers) was lower than the 2.7% found by Henschke et al. [4], 1.73% reported by Swensen et al. [10] and 1.35% observed by Diederich et al. [11], but slightly higher than 0.4% by Sone et al. [12] 0.45% by Nawa et al. [13]. In 602 former asbestos workers, mostly smokers (97%), with asbestosis and/or bilateral pleural plaques, Tiitola et al. [15] found five CT screen-detected lung cancer cases, an incidence of 0.8%. This latter figure was 1.3% (=3/230) in our subjects with similar characteristics (smokers or ex-smokers with APPs and/or asbestosis).

Radiation dose has been estimated to range from 0.3 to 0.55 mSv with low-dose CT and 3–27 mSv using conventional CT [16]. Given that ~20% of our workers required at least two additional low-dose CTs and about 5–10% of them required one conventional CT, the total dose delivered to 1119 individuals at the first round of screening could be close to 1000 mSv, an average of ~1 mSv per examined subject and ~220 mSv per screen-detected lung cancer case. Therefore, any long-term effect could occur in some subjects as a result of the screening examination [17]. On the other hand, in our screening programme, the overall cost was €1 224 811. Since we detected only one treatable cancer (Case 5), saving one life required the total cost of the whole programme of screening.

In conclusion, lung cancer screening with CT had a low uptake among members of the target population, the frequency of lung cancer detection was low, the cost in time, money and radiation exposure were high and lung cancer incidence in asbestos workers was equal to that in the general male population of the same age (it could have peaked in the past). The screening programme was not demonstrated as cost-effective from the perspective of the government as a third-party funding agency.

**Key points**
- Screening with low-dose CT for early diagnosis of lung cancer in former asbestos workers was unsatisfactory because of low adherence, low yield of cases detected, high cost and radiation dose delivered to healthy subjects.
- As no advantage concerning prevention could be achieved in the target group, the screening programme was discontinued.
- Our findings do not support testing for early lung cancer detection in asymptomatic individuals previously exposed to lung carcinogens.

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**Conflicts of interest**

None declared.

**References**


