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

Giuseppe Mastrangelo¹, Maria Nicoletta Ballarin², Ernesto Bellini³, Rosanna Bizzotto⁴, Federica Zanolli⁵, Francesco Giovine⁶, Mario Gobbi⁷, Gianna Tessadri⁸, Luciano Marchiori⁹, Gianluca Marangi⁵, Saviero Bozzolan⁵, John H. Lange¹⁰, Flavio Valentini¹¹ and Paolo Spolaore¹²

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: (i) plaques of any size in patients with a history of asbestos exposure and (ii) plaques of any size in patients with a history of asbestos exposure and (iii) widespread plaques involving the greater part of a hemithorax [7]. A subject was referred to a respiratory physician in the presence of: (i) plaques of any size in patients with a history of asbestos exposure and (ii) plaques of any size in patients with a history of asbestos exposure and (iii) widespread plaques involving the greater part of a hemithorax [7]. A subject was referred to a respiratory physician in the presence of: (i) plaques of any size in patients with a history of asbestos exposure and (ii) plaques of any size in patients with a history of asbestos exposure and (iii) widespread plaques involving the greater part of a hemithorax [7].

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 analysis, 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.

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics of 1119 male asbestos workers included in the statistical analysis: mean and SD of interval variables and percentage (%) of the frequency variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at screening (years)</td>
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<tr>
<td>Years elapsed from first exposure</td>
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<tr>
<td>Years elapsed from last exposure</td>
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<tr>
<td>Duration of exposure (years)</td>
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<td>Intensity of exposure (fibers/ml)</td>
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<tr>
<td>Cumulative exposure (fibers/ml × years)</td>
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<tr>
<td>Non-smokers</td>
</tr>
<tr>
<td>Former smokers</td>
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<td>Current smokers</td>
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</tbody>
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SD, standard deviation.
Table 2. Main characteristics of the five screen-detected primary lung cancer cases

<table>
<thead>
<tr>
<th>Cases</th>
<th>Age</th>
<th>Smoking</th>
<th>Cumulative asbestos exposure (fibres/ml × years)</th>
<th>TSFE, TSLE (years)</th>
<th>Asbestosis, pleural plaques</th>
<th>Date of diagnosis</th>
<th>Histology</th>
<th>TNM classification and stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61</td>
<td>ExS</td>
<td>13.6</td>
<td>18, 15</td>
<td>A0, P0</td>
<td>April 2005</td>
<td>AC</td>
<td>T2/N1/M0 Stage III</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>ExS</td>
<td>182</td>
<td>May 2002 and February 2005</td>
<td>A1, P0</td>
<td>September 2002</td>
<td>NSCCb</td>
<td>Advanced</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>ExS</td>
<td>108</td>
<td>June 2002 and June 2002</td>
<td>A1, P0</td>
<td>July 2003</td>
<td>AC-SC0</td>
<td>T1/N2/M0 Stage III</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>CS</td>
<td>4.0</td>
<td>October 2001 and November 2004</td>
<td>A0, P0</td>
<td>July 2002</td>
<td>AC</td>
<td>T1/N2/M0 Stage III</td>
</tr>
<tr>
<td>5</td>
<td>52</td>
<td>CS</td>
<td>35.0</td>
<td>December 2004 and December 2004</td>
<td>A0, P1</td>
<td>March 2005</td>
<td>SC</td>
<td>T1/N0/M0 Stage IA</td>
</tr>
</tbody>
</table>

aAge 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, NCN); histology (AC, adenocarcinoma; SC, squamous cell carcinoma; NSCC, non-small cell carcinoma); TNM classification and stage.

bCytologic not histologic diagnosis.
cTwo primary lung tumors: AC at inferior lobe (\(C176\)) and SC at superior lobe (\(C176/C176\)) of the right lung.

discussion

The incidence rate of lung cancer was 154 per 100 000 (males, age group 55–59 years) reported by Veneto Tumour Registry (accessed at http://www.registrotumoreveneto.it/) from 1998 to 2001 was applied to the time period 2003–05, then, the incidence rate ratio should be 1.00 (\(=148.9/148.7\)).

According to Hauptmann et al. [8], the risk of lung cancer increases soon after asbestos exposure, with its maximum effect at 12 years after the exposure was the 1119 workers were screened in July 2002 and followed up for 3 years until July 2005.

Passive surveillance through the regional archive of hospital discharge records demonstrated that no lung cancer cases were missed. Furthermore, there were no false-negative cases (no lung cancer cases were observed after initial negative CT scans), while false-positive cases were 11 (difference between 16 biopsies and 5 lung cancer cases diagnosed at biopsy/cytology). Therefore, sensitivity was 100% (\(=5/5\)), specificity 99% (\(=1114 - 11)/1114\)), while the positive predictive value was as low as 31% (\(=5/16\)).

Since 1012 of 5379 asbestos workers were not found in the regional Register of Residents, the number in the overall cohort reduced to 4367, among whom 47 new lung cancer cases were found from 1999 to 2005 (7 years). Therefore, incidence for lung cancer was 154 per 100 000 (\(=47/(4367 \times 7)\)) in the whole cohort, close to 149 per 100 000 observed in the screened sub-cohort of 1119 workers.

With reference to the cost analysis, we considered a pilot study where 837 subjects accepted the invitation to undergo examinations. The overall cost of screening was €892 778 consisting of €42 225 for the first process, €1276 for the second process (fixed cost corresponded to €43 501 = 42 225 + 1 276) and €849 276 for the third process (variable cost). The cost of the third process made up of €67 245 (8%) for organizational–administrative activities: €394 842 (46%) for baseline and follow-up CT scanning and other testing and €387 189 (46%) for the medical staff directly involved in the screening programme (including estimating exposure) and nursing. Therefore, the cost per unit screened was €1014 (\(=€849 276/837\)). We actually examined 1165 workers instead of 837. On the basis of the results of the pilot study, the cost of the third process was estimated to be €1 181 310 (\(=€1014 \times 1165\)) resulting in an overall cost of €1 224 811 (\(=€1 181 310 + €43 501\)). Lastly, the cost for screen-detected lung cancer case was therefore €244 962 (\(=€1 224 811/5\)).
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%. The 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


