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Low-dose computed tomography screening for lung cancer in people with workplace exposure to asbestos

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A R T I C L E I N F O

Keywords:
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Low-dose chest CT
Asbestos-exposed
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Pleural thickening
Meta-analysis

A B S T R A C T

Objectives: Smoking is the main risk factor for lung cancer, but environmental and occupational exposure to carcinogens also increase lung cancer risk. We assessed whether extending low-dose computed tomography (LDCT) screening to persons with occupational exposure to asbestos may be an effective way reducing lung cancer mortality.
Materials and methods: We conducted a nested case-control study within the COSMOS screening program, assessing past asbestos exposure with a questionnaire. LDCT scans of asbestos-exposed participants were reviewed to assess the presence of pulmonary, interstitial and pleural alterations in comparison to matched unexposed controls. We also performed an exhaustive review, with meta-analysis, of the literature on LDCT screening in asbestos-exposed persons.
Results: Exposure to asbestos, initially self-reported by 9.8% of COSMOS participants, was confirmed in 216 of 544 assessable cases, corresponding to 2.6% of the screened population. LDCT of asbestos-exposed persons had significantly more pleural plaques, diaphragmatic pleural thickening and pleural calcifications, but similar frequency of parenchymal and interstitial alterations to unexposed persons.

From 16 papers, including this study, overall lung cancer detection rates at baseline were 0.81% (95% CI 0.50–1.19) in asbestos-exposed persons, 0.94% (95% CI 0.47–1.53) in asbestos-exposed smokers (12 studies), and 0.11% (95% CI 0.00-0.43) in asbestos-exposed non-smokers (9 studies).
Conclusion: Persons occupationally exposed to asbestos should be monitored to gather more information about risks. Although LDCT screening is effective in the early detection lung cancer in asbestos-exposed smokers, our data suggest that screening of asbestos-exposed persons with no additional risk factors for cancer does is not viable due to the low detection rate.

1. Introduction

Recent estimates from the International Agency for Research on Cancer (IARC) indicate cancer as one of the most important cause of death worldwide, accounting for about 9.6 million deaths in 2018 with incidence estimated at 18 million new cases per year [1]. Cancer is

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caused by genetic and external factors that exert their effects concurrently or sequentially [2]. Annually, approximately 20% of cancers are estimated to be caused by environmental factors where the environment is defined by the World Health Organization as "all the physical, chemical and biological factors external to a person, and all related behaviours, but excluding those natural environments that cannot reasonably be modified" [3]. This definition includes occupational risk factors.

Already in 1981, Doll and Peto estimated that 4% of all cancer deaths were work-related [4]. However because of the increasing numbers of substances or processes now recognized carcinogenic (202 agents are currently classed as known or probable human carcinogens − Groups 1 and 2 A − by the IARC), Doll and Peto's figure is likely an underestimate. In fact global data elaborated by the International Labour Organization in 2014 indicated that about 666,000 fatal work-related cancers occur every year [5]. And in the European Union, occupational cancers are estimated responsible for about 102,500 deaths annually [6]. Exposure to occupational carcinogens is responsible for a wide range of cancers, but 54–75% of occupational cancers are lung cancers, and 17–29% of lung cancers in men are due to occupational exposure [7,8].

Multicentre studies have shown that screening high-risk groups (mainly heavy smokers over 50 years) with low-dose computed tomography (LDCT) can detect early lung cancer that can be effectively treated by surgery to reduce mortality [9–15]. The 2015 Consensus Report on asbestos and cancer also recommended that asbestos-exposed adults should be considered for admission to LDCT screening programs [16].

Although it is unclear how tobacco smoke and asbestos fibre interact to increase lung cancer risk it has been estimated that exposure to 25 asbestos fibres per year doubles the risk of lung cancer in smokers [16]. Most lung cancer risk models factor in asbestos exposure when estimating risk [17–19]. Although primary prevention is desirable, extending secondary prevention (LDCT screening) to persons at high risk for occupational exposure to asbestos may be an effective way reducing lung cancer mortality, particularly since pleural plaques (asbestos-related radiological signs) seem to be a risk factor for lung cancer mortality and can be detected by LDCT [20].

In the present study we aimed to: (a) assess occupational exposure to asbestos in high-risk smokers/former smokers recruited to the COSMOS 1 and 2 LDCT screening programs at the European Institute of Oncology Milan (IEO); (b) assess the impact of asbestos exposure on risk of lung cancer; (c) perform a case-control study to compare the presence of pleural plaques, pleural thickening and other CT findings in asbestos-exposed COSMOS participants with those in non-exposed participants; and (d) perform a meta-analysis of published data on LDCT screening (for lung cancer) in asbestos-exposed workers. The ultimate goal in this field is to define a surveillance strategy for occupational exposed individuals, in particular asbestos, both smokers or never smoked.

2. Materials and methods

2.1. Epidemiology study

The epidemiological study was nested within the cohorts of the single-centre COSMOS-1 study, carried out at the IEO Milan, and the IEO section of the multicentre COSMOS-2 study. COSMOS 1 and 2 were prospective single-arm observational studies that used LDCT screening to detect lung cancer in high-risk volunteers (smokers or former smokers, over 50 years). Screened persons completed a self-reported questionnaire that enquired about exposure to asbestos and other carcinogenic substances. Persons who indicated exposure were contacted later by an IEO researcher who assessed exposure guided by questionnaire (Appendix A). Researcher training on questionnaire administration was provided by an expert from the Italian National Insurance Institute for Workplace Injuries (INAIL). The questionnaire contained 27 questions in 7 sections: (a) Personal data and work status; (b) Asbestos: domestic exposure; (c) Asbestos: environmental exposure; (d) Asbestos: hobby exposure; (e) Asbestos: work exposure; (f) Exposure to chemicals at work; and (g) Employer compliance with legal obligations relating to exposures.

The names of persons confirmed as exposed as a result of the interview were forwarded to IEO radiologists who reviewed the LDCT scans.

2.2. Case-control study

This involved retrospective re-evaluation of the LDCT scans by two senior radiologists experienced in lung cancer screening, of the 216 persons (cases) considered asbestos-exposed as a result of the questionnaire-guided interview, in comparison with the scans of 216 COSMOS participants (controls). Controls were chosen from the whole cohort excluding the 544 who reported some kind of exposure at baseline. Cases and control were matched for age, sex and smoking history.

The presence of pulmonary, interstitial and pleural alterations considered related to asbestos exposure was assessed, as was the quality of images to assess whether asbestos exposure had an effect on image quality and interpretability for lung cancer detection.

Radiological findings potentially related to asbestos exposure, including septal and intralobular lines, lung nodules ground-glass opacities, honeycombing, parenchymal bands, round atelectasis, bronchial wall thickening, emphysema, pleural thickening and pleural plaques (site, calcifications) (Fig. 1), were compared with CT scans from matched non exposed subjects. Most LD-CT scans were obtained with 16, 32 or 64 detector-row machines (GE Healthcare) using a low-dose protocol (100kVp, 30 mA, 0.5 s) with no contrast and slice thickness 1.25 mm.

2.3. Meta-analysis

A literature search using PubMed, without language or other restrictions, was performed to retrieve papers on lung cancer, asbestos exposure, CT, and CT screening, using the following query: *("tomography" [all fields] AND ("lung" [MeSH term] OR "lung" [all fields]) AND ("nodules" [all fields] OR ("neoplasms" [mesh term] OR "neoplasms" [all fields] OR "cancer"[all fields])) AND (("diagnosis"[subheading] OR "diagnosis" [all fields] OR "screening"[all fields] OR "mass screening" [MeSH term] OR ("mass" [all fields] AND "screening" [all fields]) OR "mass screening" [all fields] OR "screening" [all fields] OR "early detection of cancer" [MeSH term] OR ("early" [all fields] AND "detection" [all fields] AND "cancer" [all fields]) OR "early detection of cancer" [all fields]) AND ("asbestos" [MeSH term] OR "asbestos" [all fields]))) AND (1900/01 [EDAT] : 2018/04 [EDAT])*.

Only studies fulfilling the following criteria were included in the meta-analysis.

- Original article.
- Availability of information making it possible to estimate baseline lung cancer detection rate.
- All participants exposed to asbestos.
- For multiple publications on a single population, the most recent or most informative report was used to extract the lung cancer detection rate.

2.4. Statistical analysis

For the case-control study, logistic regression models were used to assess differences in radiologic findings between participants exposed to asbestos and controls.

For the 216 asbestos-exposed persons and their controls, mean

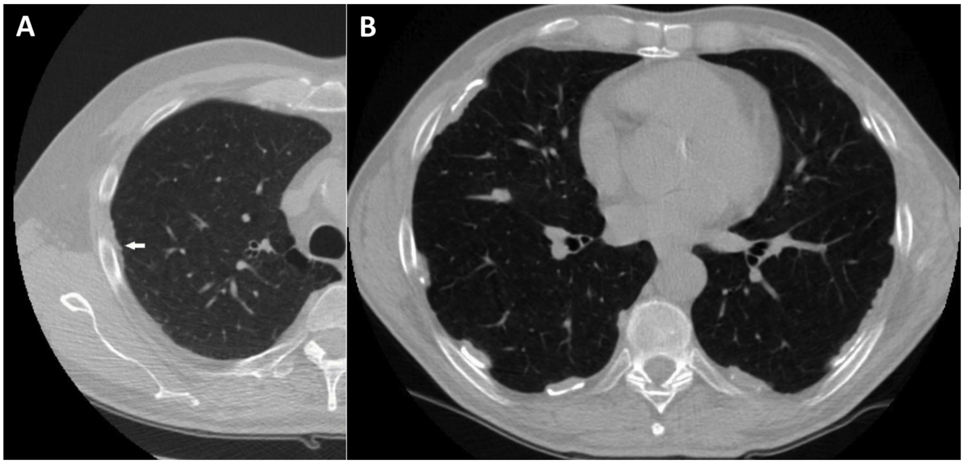

Fig. 1. Low-dose CT scan findings.
Footnote.
A) Pleural thickening. Axial low-dose CT scan of a subject not exposed to asbestos shows a focal, irregular thickening (white arrow) of the right pleura.
B) Pleural plaques. Axial low-dose CT scan of an asbestos-exposed subject. Presence of bilateral, partially calcified, pleural plaques.

annual lung cancer detection rates over the 10-year COSMOS follow-up were calculated by dividing the number of lung cancers detected by the person-years of follow-up accumulated. Baseline detection rates in the same groups were calculated dividing the number of lung cancers detected at baseline LDCT by the number of screened participants. The lung cancer rate in asbestos-exposed persons was incorporated into the meta-analysis of published papers dealing with LDCT screening of asbestos-exposed persons (see below).

Random effects models, with maximum likelihood estimates, were applied to the data extracted from the published studies included in the review/meta-analysis (and the present study) to estimate lung cancer detection rates in asbestos-exposed persons at baseline screening for each study, with 95% confidence intervals (CIs), and also for ever smokers and never smokers separately. In these models the Freeman-Tukey double arcsine transform method was used to stabilize variances. Between study heterogeneity was assessed by the I^2 statistic. P values for heterogeneity (Cochran's Q) are also provided. For studies with no lung cancer cases (zero detection), a 0.5 continuity correction was added to the cancer cases and non-cases to allow calculation of study weightings and variances.

Forest plots are used to illustrate lung cancer detection rates at baseline screening in asbestos-exposed persons in the 15 eligible studies plus the present study. SAS software version 9.4 (Cary, NC) and Open Meta-Analyst [21] were used for the statistical analyses. All P-values are two-sided.

3. Results

A total 785 COSMOS participants indicated they were exposure to environmental carcinogens (other than smoking) on the baseline questionnaire: 544 (69.3%) of these were interviewed between February and November 2014. The remaining 241 (30.7%) were not interviewed for the following reasons: no signed inform consent for scientific research (n = 54), not reachable (n = 170), refused (n = 10), dropped-out from COSMOS (n = 4), died (n = 3). Most (517, 95.0%) interviews were conducted by telephone; 27 (5.0%) were conducted face-to-face; 261 interviewees were from COSMOS-1 (261/5203), and 283 from COSMOS 2 (283/3107). Most (87%) interviewees lived in northern Italy, 6.5% were from central Italy, and 6.5% were from southern Italy/islands.

As shown in Table 1A, 59 (10.7%) interviewees reported exposure to asbestos at home, 16 (2.9%) reported environmental exposure to asbestos (metallurgical plants, asbestos deposits or asbestos quarries), 5 (0.9%) reported asbestos exposure linked to hobbies or do-it-yourself,

Table 1
(A) Home, environmental and occupational exposures to asbestos as reported by 544 COSMOS participants interviewed February-November 2014. Occupational exposures are categorized according the industry worked in. (B) Workplace exposures to noxious substances as reported by 544 COSMOS participants interviewed February-November 2014.

(A) Source of Asbestos Exposure	N
Home exposure to asbestos	58/544 (10.7%)
Environmental exposure to asbestos	16/544 (2.9%)
Asbestos exposure from hobby/do-it-yourself	5/544 (0.9%)
Occupational exposure to asbestos	216/544 (39.7%)
Shipbuilding/ shipping	24/216 (11.1%)
Railway	29/216 (13.4%)
Construction	18/216 (8.3%)
Iron and steel	11/216 (5.1%)
Automotive– mechanical	10/216 (4.6%)
Manufactures for plumbing-hydraulic and electrical sectors	9/216 (4.2%)
Metalworking / tube manufacturing / metallurgy	7/216 (3.2%)
Production of asbestos cement	2/216 (0.9%)
Production of building materials	3/216 (1.4%)
Automotive - body shop	1/216 (0.5%)
Other	102/216 (47.2%)

(B) Substance	N* (% of 544)
Asbestos	216 (39.7%)
Aluminum	98 (18.0%)
Sulfuric acid mist	81 (14.9%)
Silicon dust	82 (15.1%)
Lead	75 (13.8%)
Benzene	69 (12.7%)
Chrome	66 (12.1%)
Ether	69 (12.7%)
Wood dust	66 (12.1%)
Coal	32 (5.9%)
Mercury	28 (5.1%)
Aromatic amines	27 (5.0%)
Manganese	23 (4.2%)
Cadmium	15 (2.8%)
Ceramic fibers	9 (1.7%)
Leather dust	7 (1.3%)
Beryllium	4 (0.7%)
Nitrogen mustard	5 (0.9%)
Other dusts	90 (16.5%)
Other substances	317 (58.3%)

* Sum exceeds 544 because multiple exposures reported by several participants.

and 216 (39.7%), 208 males (96.3%), reported occupational exposure to asbestos, three of whom were still exposed to asbestos at the time of the interview.

Those occupationally exposure to asbestos constituted 2.6% of the COSMOS population considered in this study, among whom exposure occurred mainly in the shipbuilding (11%), railway (13%) and construction (8%) industries. Mean exposure time was 19.8 years, standard deviation 10.8, range 1–54 years.

Only 26 (12.0%) of asbestos-exposed interviewees were informed by their employers about the workplace asbestos hazard. However, 137 (63%) interviewees had periodic medical check-ups at the workplace, while 79 (36%) did not undergo such check-ups. Twenty-five (12%) received a copy of their medical report, and 17 had a medical check-up on leaving employment. Table 1B lists other exposures elicited from the questionnaire: 82 (15.1%) interviewees reported exposure to silicon dust.

3.1. Case-control study

LDCT findings in the 216 asbestos-exposed participants were compared to those in a matched control group of 216 without asbestos exposure. The presence of pleural plaques was detected in 22 (10.2%) participants in the exposed group against 2 (0.9%) in the unexposed group (P = 0.001). The frequencies of diaphragmatic pleural thickening (7.9% vs. 1.4%, OR = 5.67; 95% CI 1.66–19.3; P = 0.006) and pleural calcifications (7.9% vs. 3.2%, OR = 2.43; 95% CI 1.03–5.86; P = 0.048) were significantly higher in asbestos-exposed participants than controls (Table 2). Most person with diaphragmatic pleural thickening (19/20, 95.0%) also had parietal pleural thickening. There were no differences between cases and controls for frequencies of pleural effusions, mono or bilateral pleural thickening, septal/intralobar lines, ground-glass opacities, number of parenchymal nodules, honeycombing, parenchymal bands, rounded atelectases, bronchial thickenings, emphysema, or lymph nodes.

Table 3
Characteristics of 216 asbestos-exposed cases and 216 unexposed controls, together data on lung cancers diagnosed during screening.

	Cases N‡	Controls* N‡
Age (years)		
50-54	39	38
55-59	75	78
60-64	62	60
65-69	30	28
70+	10	12
Sex		
Male	208	208
Female	8	8
Smoking status		
Ex-smoker	102	102
Current smoker	114	114
Pack-years		
<40	73	72
40-60	88	89
≥60	55	55
Person-years of follow-up	1299	1159
Lung cancers	8	9
Lung cancer detection rate (per 100 person-years)	0.6	0.8
Lung cancers at baseline CT	1	4
Prevalence rate	0.5%	1.8%

* Controls chosen from non-interviewed participants individually matched to cases for age, sex, and smoking status including pack-years.
‡ Except where indicated.

3.2. Lung cancer detection

During 2458 person-years of observation (10-year screening period) 17 of the 432 asbestos-exposed cases and non-exposed controls were diagnosed with primary lung cancer (14 adenocarcinomas, 1 squamous

Table 2
Baseline LDCT findings in 216 cases (asbestos-exposed) and 216 controls (unexposed).*

	Cases N (%)	Controls N (%)	Odds ratio‡(95% CI)	P-value
Pleural thickening/nodule: any location	46 (21.3)	45 (20.8)	1.03 (0.65-1.64)	0.91
Mediastinum	4 (1.9)	2 (0.9)	0.61 (0.08-4.48)	0.63
Diaphragm	17 (7.9)	3 (1.4)	6.51 (1.55-27.4)	**0.01**
Parietal	37 (17.1)	27 (12.5)	0.94 (0.49-1.77)	0.84
Fissure	11 (5.1)	19 (8.8)	0.61 (0.29-1.32)	0.21
Pleural thickening/nodule: number of locations				
None	170 (78.7)	171 (79.2)	1.00	
Single location	27 (12.5)	40 (18.5)	0.71 (0.42-1.21)	0.21
Multiple locations†	19 (8.8)	5 (2.4)	3.51 (1.30-9.48)	**0.01**
Pleural thickening:				
None	170 (78.7)	171 (79.2)	1.00	
Diaphragmatic + parietal	17 (8.0)	2 (0.9)	7.83 (1.80-34.1)	**0.006**
Any other location	29 (13.4)	43 (19.9)	0.71 (0.42-1.19)	0.19
Pleural plaques	22 (10.2) §	2 (0.9) ¥	11.0 (2.59-46.8)	**0.001**
Pleural calcifications	17 (7.9)	7 (3.2)	2.43 (1.03-5.86)	**0.048**
Pleural effusion	0 (0.0)	0 (0.0)	–	–
Septal or intralobar lines	6 (2.8)	2 (0.9)	3.00 (0.61-14.9)	0.18
Ground-glass opacity	32 (14.8)	33 (15.3)	0.97 (0.58-1.61)	0.90
Honeycombing	0 (0.0)	0 (0.0)	–	–
Parenchymal bands	33 (15.3)	36 (16.7)	0.91 (0.55-1.50)	0.70
Round atelectasis	2 (0.9)	0 (0.0)	–	0.50
Bronchial wall thickening	9 (4.2)	9 (4.2)	1.00 (0.38-2.66)	1.00
Emphysema	46 (21.3)	45 (20.8)	1.03 (0.64-1.65)	0.90
Nodule ≥10 mm	10 (4.6)	10 (4.6)	1.00 (0.42-2.40)	1.00
Nodule <10 mm	125 (57.9)	126 (58.3)	0.98 (0.67-1.43)	0.92

* Controls were individually matched for age, sex, smoking status and smoking pack-years.
† 19 of 24 patients with pleural thickening in multiple locations had diaphragmatic and parietal involvement.
‡ 7 of the exposed subjects had only parietal pleural plaques, 15 had diaphragmatic and parietal pleural plaques, 2 had diaphragmatic, parietal and mediastinal pleural plaques and 1 had fissural, diaphragmatic, parietal and mediastinal pleural plaques. § 2 of the exposed subjects had diaphragmatic and parietal pleural plaques but did not reported past exposure to asbestos or other noxious substances. ‡ Odds-ratios with 95% confidence intervals obtained from logistic regression modelling.

Table 4
Summary description of 15 studies providing information on lung cancer detection by spiral LDCT among asbestos-exposed subjects.

Author	Country	N	Mean age (range)	Asbestos exposure	Smoking history	Lung cancers detected at baseline screening (%)	Other cancers
Lynch et al. [30] 1988	USA	260	63	Exposure in shipyard or construction work for more than 10 years	Not available	Overall: 2 (0.77%)	1 mediastinal tumor
Tiitola et al. [31]2002	Finland	602	63 (38–81)	Construction work for more than 20 years (mean 26 years)	Smokers ≥10 years Mean 24 pack-years	Ever smoker: 5 (0.83%)	
Minniti et al. [32]2005	Italy	1512	60	Occupational exposure for at least 5 years and a mean duration of 19 years	No 39% Yes 61%	Overall: 4 (0.26%)	1 colorectal cancer metastasis
Das et al. [33] 2007	Germany	187	66.6(45-75)	Occupational exposure for a mean duration 29.7 years (range 16-45 years)	Never 2 (1%) Former 19 (10%) Current 166 (89%)	Overall: 9 (4.81%) Never smoker: 0 (0.00%) Ever smoker: 9 (4.86%)	
Fasola et al. [34] 2007	Italy	1045	58 (40–75)	Exposed workers and former workers for a median duration of 30 years	Never 360 (34.4%) Former 527 (50.4%) Current 160 (15.3%) Median 18.5 pack-years	Overall: 9 (0.86%) Never smoker: 1 (0.28%) Ever smoker: 8 (1.16%)	1 thymic carcinoid tumor
Vierikko et al. [35] 2007	Finland (Helsinki, Tampere, Turku	633	64.5 (45–86)	Heavy occupational exposure (index > 70) or workers with asbestosis or asbestos related pleural findings	Never 137 (22.0%) Former 361 (58.0%) Current 124 (19.9%) Median 18.8 pack-years	Overall: 5 (0.79%) Never smoker: 0 (0.00%) Ever smoker: 5 (1.03%)	
Mastrangelo et al. [36] 2008	Italy	1119	57.1	Occupational exposure for a mean duration of 17.7 years	Never 392 (35.0%) Former 528 (47.2%) Current 199 (17.8%)	Overall: 5 (0.45%) Never smoker: 0 (0.00%) Ever smoker: 5 (0.69%)	
Clin et al. [37]2009	France, Caen	972	61.3(50-75)	High and continued occupational exposure for more than 1 year, or high and discontinued for more than 10 years	Never (32.0%) Ever (68.0%)	Overall: 13 (1.34%)	7 additional lung cancers detected at subsequent screening + 5 mesotheliomas
Roberts et al. [38]2009	Canada, Ontario	516	60(32-83)	Occupational exposure for more than 20 years or documented pleural plaques	Never 121 (23.4%) Former 291 (56.4%) Current 104 (20.2%) Mean 23.4 pack-years	Overall: 6 (1.16%) Never smoker: 0 (0.00%) Ever smoker: 6 (1.52%)	4 mesotheliomas
Pira et al. [39]2010	Italy	149	57(46-75)	Occupational exposure for a mean duration of 12.3 years	No 56 (37.6%) Yes 93 (62.4%)	Overall: 0 (0.00%) Non smoker: 0 (0.00%) Smoker: 0 (0.00%)	
Clin et al. [40]2011	France	5662	63	Occupational exposure assessed by questionnaire and categorized as low (passive), low-intermediate, high-intermediate or high	Never 1474 (26.0) Former 3369 (59.5) Current 400 (7.1) Missing 419 (7.4)	Overall: 50 (0.88%)	11 mesotheliomas
Brims et al. [41]2015	Australia	906	68.8	Occupational exposure for a mean duration of 12.4 years	Mean 17.1 PYs Never 325 (36.4%) Former 511 (57.2%) Current 58 (6.5%)	Overall: 7 (0.77%) Never smoker: 2 (0.62%) Ever smoker: 5 (0.88%)	4 mesotheliomas
Lee et al. [42] 2015	Korea	35	68.5 (48-82)	Environmental exposure around a mine for more than 10 years	No 20 Yes 15	Overall: 0 (0.00%) Never smoker: 0 (0.00%) Ever smoker: 0 (0.00%)	1 suspicious mesothelioma
Schaal et al. [43] 2016	France	55	55.7	Occupational exposure for at least 15 years	No 28 (51%)) Yes 27 (49%)	Overall: 0 (0.00%) Non smoker: 0 (0.00%) Smoker: 0 (0.00%)	
Kato et al. [44]2018	Japan	2132	76.1(51-101)	asbestos-product manufacturing for more than 1 year or other industries related to asbestos exposure for more than 10 years or pleural plaques	Never 452 (21.2%) Ever1680 (78.8%)	Overall: 45 (2.11%) Never smoker n/a (0.7%) Ever smoker: n/a (2.5%)	

cell carcinoma, 2 small-cell lung cancers).

Detection rates were similar in the two groups: 0.6/100 person-years for cases (8 cancers 1299 person-years of follow-up) and 0.8/100 person-years for controls (9 cancers 1159 person-years of follow-up) (Table 3). Cancer detection frequencies at baseline were 0.5% in the exposed group (1 case) and 1.8% in the control group (4 cases).

3.3. Meta-analysis

A total of 210 studies published up to 31 st April 2018 were retrieved by our pre-defined PubMed search. Following evaluation of titles and abstracts, the full texts of 31 of these studies were obtained. Full texts of 3 other studies, identified from other sources (mainly citations in reviews) were obtained. All 34 studies were assessed for inclusion in the meta-analysis. Ten were excluded for absence of original data and 9 were excluded after further review: 3 for small or undefined proportions of asbestos-exposed patients [22–24], 2 for failure to state number of lung cancers diagnosed at baseline LDCT screening [20,25], and 4 because original findings were inextricably mixed with data from other studies [26–29] (Supplementary Table 1). Summary data from the 15 studies that satisfied our eligibility criteria are shown in Table 4 [30–44].

Fig. 2 presents lung cancer detection rates and numbers of cancer cases and screened persons, together with Forest plots of the data for the 15 eligible studies plus the present study. The overall lung cancer detection rate at baseline LDCT screening for all 16 studies was 0.81% (95% CI 0.50–1.19), based on 161 lung cancers diagnosed in 16,001 screened persons We found that I^2 was 71.1% (Cochran's Q $P < 0.0001$) providing strong evidence for between heterogeneity with particularly high detection rates for the studies of Das et al. [33] (4.81%, 95%CI, 2.14–8.41) and Kato et al. [44] (2.11; 95%CI, 1.54–2.77).

When the analysis was restricted to ever smokers (12 studies including the present study the detection rate was 0.94% (95% CI 0.47–1.53), again with I^2 (58.0%, Cochran's Q $P = 0.003$) indicating marked between study heterogeneity, which again was largely due to the studies of Das et al. (4.81%, 95% CI 2.14–8.41) and Kato et al. (2.50; 95% CI 1.80–3.30). When the analysis was restricted to asbestos-exposed non-smokers (9 studies) the detection rate was low (0.11%, 95%CI, 0.00-0.43) and the studies were markedly homogeneous ($I^2 = 0\%$). Cancer detection rates for the individual studies, with the weightings applied for the random effects models are shown in Supplementary Table 2.

4. Discussion

Although carcinogen exposure was self-reported by 785 (9.4%) of the COSMOS population considered in this study, we administered our questionnaire-guided interview to only 544 participants, all of whom who had self-reported asbestos exposure at baseline. From interview responses, we determined that 216 (39.7%) persons were exposed to asbestos, 2.6% of the COSMOS population considered in this study. Thus, the questionnaire-guided interview proved effective in identifying occupational exposures and this is important as it is not easy to establish past exposure to asbestos, and whether such exposure was occupational or otherwise. Several factors, including long disease latency and the large variety of occupations giving rise to exposure, make it difficult to reliably reconstruct exposure histories [45]. Use of structured questionnaires or checklists, administered by trained interviewers, is a recognized means ascertaining employment history and occupation exposure to asbestos [16,46].

Our questionnaire-driven interviews revealed that 79/216 (36%) of those exposed did not undergo periodic company-sponsored medical check-ups; that 72 (92%) of these did not receive a medical check-up on leaving the job in which they were exposed; and that 190/216 (88%) reported that employers did not inform them of the risks associated with their workplace exposure to asbestos. Most respondents in fact reported they were unaware of the risks associated with their asbestos exposure.

This lack of information and awareness is worrying because it suggests that many of those exposed to asbestos will seek medical help only when symptoms appear – typically decades later when treatments are largely ineffective. The 2014 Helsinki recommendations emphasized the long tradition of follow-up of asbestos-exposed works that is mandatory in many countries [16]. Although follow-up protocols vary, they usually include history-taking and exposure assessment, lung function tests and chest x-ray. The Helsinki recommendations also indicated that CT scans are useful for the diagnosis of asbestos-related diseases [16].

Our findings indicate that asbestos exposure seems not to affect the accuracy of LDCT for lung cancer detection and or to increase the risk of false positive or false negative findings on LDCT as number of subjects with ground-glass opacities, and parenchymal nodules was similar in the two groups.

LDCT was able to detect pleural plaques in 10% of asbestos-exposed participants, which is in agreement with previous studies [20,47,48]. This relatively low frequency may be attributable to the fact that participants to the COSMOS screening were asymptomatic heavy smokers, not selected for their exposure to asbestos. Of interest, pleural plaques were also detected in two of the participants who did not report any past exposure to asbestos, but who leaved in areas known for potential environmental exposure attributed to asbestos-related industries. Our case control study also revealed that LDCT scans of asbestos-exposed participants had significantly higher frequencies of diaphragmatic pleural thickening and pleural calcifications than non-exposed controls, but no differences in terms of parenchymal or interstitial alterations. These findings indicate that pleural thickening is readily detected by LDCT. Because these abnormalities are a marker of asbestos exposure and may be an independent risk factor for pleural mesothelioma and lung cancer [16,25,49–52], LDCT screening of selected high-risk populations of asbestos-exposed persons suggests itself as a way of reducing lung cancer mortality in this subgroup, as also proposed by the 2014 Helsinki recommendations [16].

However, evidence that LDCT screening is effective in asbestos-exposed persons is limited. Our literature search identified only 15 independent studies providing data on lung cancer detection at baseline LDCT in persons exposed to asbestos. The overall detection rate (0.81%, 95% CI 0.50–1.19, including the present study) was similar to that for lung cancer screening trial participants not exposed to asbestos. In particular baseline detection rates in the US National Lung Screening Trial were 0.68% (168 lung cancers) among the 24,715 randomized to LDCT [9], and 1.1% (55 lung cancers) among the 5203 heavy smokers [11]. Detection rates were significantly higher in the studies of Das et al. [33] and Kato et al. [44] (4.81% and 2.11% respectively) however the former study [33] enrolled participants at particularly high risk of lung cancer, while in the latter study [44] participants were old (mean 76.1 years, range 51–101 years).

When we stratified study cases according to smoking status, the lung cancer detection rate was higher for asbestos-exposed ever-smokers (0.94%, 95% CI 0.47–1.53) than non-smokers (0.11%, 95% CI 0.00-0.43), and only 6 persons with lung cancer (in 9 studies) were identified among the 1891 asbestos-exposed non-smokers. These data suggest that LDCT screening is probably not effective in asbestos-exposed non-smokers and thus contributes to the current controversy as whether LDCT screening in asbestos-exposed persons may be useful for early lung cancer detection. This controversy is in part fuelled by the lack of evidence that radiographic and spirometric surveillance of asbestos-exposed persons reduced mortality is useful [16].

5. Conclusion

Although LDCT screening is effective in detecting lung cancer in ever-smokers exposed to asbestos, we have found the screening for

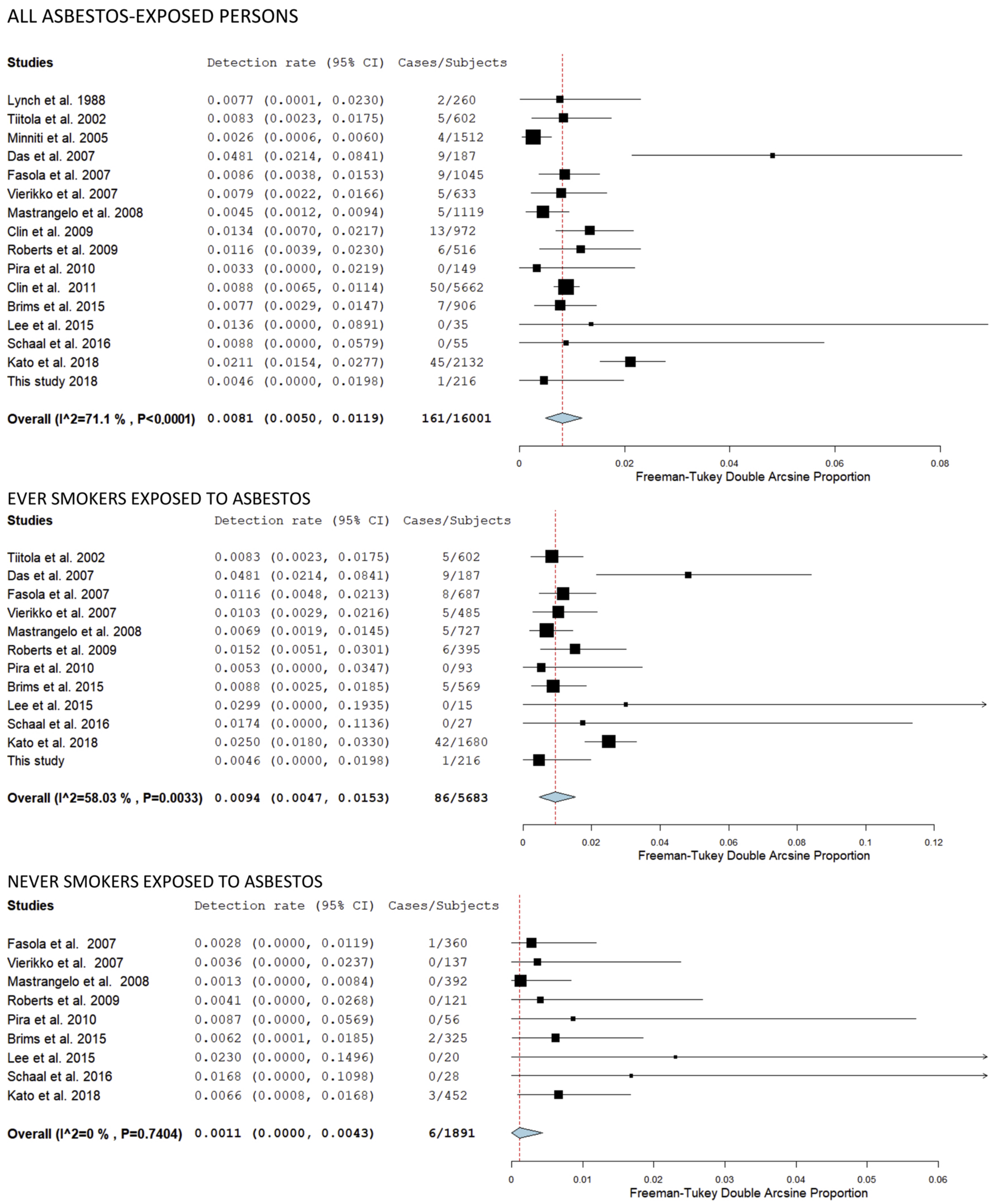

Fig. 2. Forest plots showing lung cancer detection rates at baseline LDCT screening for asbestos-exposed persons in 16 studies (including the present study). Random effects models were used to produce the lung cancer detection rates as explained in the text.
Footnote: Detection rates, 95% confidence intervals (CIs) using the Freeman-Tukey double arcsine method, and total sample size (Cases/Subjects) are provided for each study. The area of each square in the plot is proportional to the study's weight in the meta-analysis. The overall estimated effect and its 95% CIs is represented by a diamond, and as a dashed vertical line. The amount of variability among studies, along with p value testing for heterogeneity (Cochran's Q) are provided. For studies with no lung cancer cases (zero detection), a 0.5 continuity correction.

asbestos-exposed persons with no additional risk factors for cancer does not appear viable due to the low cancer detection rate.

Conflict of interest

Giulia Veronesi has financial relationships with Medtronic, Abmedica and Versurgical for consultation and proctoring. All other authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.03.003.

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