Impact of low-dose computed tomography screening on lung cancer mortality among asbestos-exposed workers

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Abstract

Background: We previously showed that low-dose computed tomography (LDCT) screening in asbestos-exposed workers is effective in detecting lung cancer (LC) at an early stage. Here, we evaluate whether LDCT screening could reduce mortality from LC in such a high-risk population.

Methods: Within a cohort of 2433 asbestos-exposed men enrolled in an Occupational Health surveillance programme, we compared mortality between the participants in the ATOM002 study (LDCT-P, $N = 926$) and contemporary non-participants (LDCT-NP, $N = 1507$). We estimated standardized mortality ratios for the LDCT-P and LDCT-NP populations using regional and national rates (SMR_FVG and SMR_ITA, respectively). We compared survival for all causes, all neoplasms, LC and malignant neoplasm of pleura (MNP) between LDCT-P and LDCT-NP using Cox proportional hazard models adjusted for age, smoking history, asbestos exposure level and comorbidities.

Results: A reduction in mortality from LC was observed in the LDCT-P group compared with regional and national figures (SMR_FVG = 0.55, 95% confidence interval (CI) 0.24-1.09; SMR_ITA = 0.51, 95% CI 0.22-1.01); this was not the case for the LDCT-NP group (SMR_FVG = 2.07, 95% CI 1.53-2.73; SMR_ITA = 1.98, 95% CI 1.47-2.61). A strong

reduction in LC mortality was observed for the LDCT-P compared with the LDCT-NP [hazard ratio (HR) = 0.41, 95% CI 0.17-0.96]. Mortality was also reduced for all causes (HR = 0.61, 95% CI 0.44-0.84), but not for all neoplasms (HR = 0.97, 95% CI 0.62-1.50) and MNP (HR = 0.86, 95% CI 0.31-2.41) within the LDCT-P population.

Conclusions: In our cohort, participation in the LDCT screening study was associated with reduced mortality from LC. This finding supports the use of LDCT in surveillance programmes for asbestos-exposed workers.

Key words: Lung cancer, screening, low-dose computed tomography (LDCT), mortality, asbestos

Key Messages

- Over 125 million people around the world are still exposed to asbestos in the workplace.
- Asbestos-related diseases are a global health care issue, and this will be the case for many years.
- To date, no surveillance approach has proven effective in reducing mortality in an asbestos-exposed population.
- In our cohort of asbestos-exposed subjects, participation in the low-dose computed tomography (LDCT) screening study was associated with reduced mortality from lung cancer.
- Our finding supports the use of LDCT in surveillance programmes for asbestos-exposed workers.

Introduction

Despite bans in most industrialized countries, over 125 million people around the world are still exposed to asbestos in the workplace[1]; and there are millions of people who are no longer exposed to asbestos but had significant past exposure. As a result, asbestos-related diseases are a global health care issue, and this will be the case for many years. In 2015, there were an estimated 180 000 deaths worldwide due to occupational asbestos exposure (from lung, larynx and ovarian cancer and mesothelioma).[2,3] One in three deaths from occupational cancer is attributable to asbestos.[1] Lung cancer (LC) is the most common asbestos-related malignancy,[3,4] followed by pleural mesothelioma. Overall, there were an estimated 36 551 asbestos-related LC deaths in the European Union in 2015.[5]

Despite the magnitude of this problem, there is currently no established standard for the surveillance of subjects with a history of occupational asbestos exposure. Surveillance programmes in place at local occupational health units to monitor these subjects vary widely across and within countries, with protocols usually including periodic medical review but not always a chest X-ray (CXR).[1,6–12] Indeed, to date no surveillance approach has proven effective in reducing mortality in asbestos-exposed people.

By contrast, the randomized U.S. National Lung Screening Trial recently showed a 20% reduction in LC mortality for high-risk current or former smokers with annual low-dose computed tomography (LDCT) screening.[13] Based on this finding, many oncology professional organizations now recommend annual LDCT screening in subjects aged 55–80 years and with a $\geq$ 30 pack-year smoking history.[14–18] Given the synergistic carcinogenic effect of cigarette smoking and asbestos exposure in causing LC, the U.S. National Comprehensive Cancer Network recommends LDCT screening also for subjects aged $\geq$50 years with a $\geq$ 20 pack-year smoking history and occupational exposure to carcinogens, including asbestos. However, to date no randomized trial has confirmed a reduction in LC mortality from LDCT screening of asbestos-exposed subjects.

In the early 2000s, we conducted the ATOM002 study, a prospective, non-randomized study to assess the feasibility and utility of LDCT screening of asbestos-exposed subjects for the early detection of LC and malignant neoplasm of pleura (MNP).[19] The ATOM002 study population comprised 1045 subjects identified among asbestos-exposed workers and former workers already under surveillance at the Monfalcone Occupational Health Unit in the Friuli Venezia Giulia (FVG) region of north-east Italy. With a population of 30 000, the town of Monfalcone still is one of the most important shipbuilding centres in Europe. Large quantities of asbestos were used in local shipyards for many decades until 1992, when the use of asbestos in workplaces was banned by Italian law.[20,21] The Monfalcone public health surveillance programme for individuals with a history of occupational asbestos exposure was established in 1994 at the local Occupational Health Unit. Since then, a dedicated outpatient clinic has been running for asbestos-exposed workers and their spouses,

with the option of self-referral. Routine surveillance investigations include physical examination, spirometry, carbon monoxide diffusing capacity and CXR.

When the ATOM002 study started in 2002, there were around 2500 asbestos-exposed individuals in the surveillance programme. Chest computed tomography scans were not used routinely, but could be performed as a second-level investigation. In the absence of a surveillance protocol, the frequency of clinic review and the type and frequency of investigations were not standardized. Eligibility criteria for the ATOM002 study included definite exposure to asbestos, age 40–75 years, no previous cancer (except non-melanoma skin cancer), no severe comorbidities, no clinical suspicion of LC or MNP and no chest CT scan during the previous 2 years; both smokers and non-smokers were eligible. After the ATOM002 trial opened in February 2002, participation in the study was offered to all eligible subjects enrolled in the Monfalcone surveillance programme when they were next reviewed at the occupational health unit. The ATOM002 statistical design required accrual of at least 832 evaluable subjects; 1045 subjects were enrolled. ATOM002 participants underwent baseline CXR and LDCT. Those with positive findings on baseline imaging underwent high-resolution CT scan (HRCT) and further workup; those with negative findings underwent another screening LDCT 1 year later. The baseline LDCT identified nine subjects with LC (eight stage I and one stage IIA non-small cell lung cancers) and one with thymic carcinoid, which had not been detected on CXR; all these patients underwent surgery with curative intent. No MNP was diagnosed.[19]

Here, we report a cohort mortality study of asbestos-exposed subjects from the Monfalcone surveillance programme. We focused on overall and cause-specific mortality among the ATOM002 participants (LDCT-P) who underwent chest LDCT screening, and compared this with mortality figures for contemporary subjects enrolled in the same surveillance cohort but who did not take part in the ATOM002 study (ATOM002 non-participants, LDCT-NP). We expected to observe reduced mortality from lung cancer in the LDCT-P when compared with the LDCT-NP as a result of an early diagnosis. To put our findings into a broader context, we also performed external comparisons with the general regional population and the whole country.

Methods

Study population

Our study population comprised individuals who were enrolled in the Monfalcone Occupational Health surveillance programme for asbestos exposure and resident in the FVG region in early 2002. Exclusion criteria included: (i) individuals with a cancer diagnosis on enrolment; (ii) individuals whose records could not be linked with the regional health database; (iii) individuals lost to follow-up; (iv) women, as only less than 4% of the subjects in the surveillance programme were female (these were mainly asbestos-exposed workers' wives, who had handled and washed their husbands' asbestos-contaminated work clothes).

The final study population comprised two sub-cohorts: (i) the LDCT-P sub-cohort including the men who entered the ATOM002 LDCT screening study, which was open for accrual between February 2002 and October 2003; and (ii) the LDCT-NP sub-cohort including the contemporary men enrolled in the same Occupational Health Surveillance programme, who did not enter the ATOM002 study. The flow diagram of cohort selection is reported in Figure 1. This study was approved by the local ethics committee of the Monfalcone Hospital, Gorizia, Italy.

Data collection

We extracted demographics and work history information from the Monfalcone Occupational Health surveillance programme database. An experienced Monfalcone occupational health physician assessed the type and duration of asbestos exposure based on subjects' work history and other accessible records, including employment record books, confirmation of exposure by the Italian Workers Compensation Authority (INAIL) and information obtained from individual subjects and colleagues during interviews. A semi-quantitative estimate of the level of asbestos exposure was assessed as follows:

- high when there was evidence of contact with friable material containing asbestos in confined spaces;
- medium when the subject had had occasional contact with friable materials, worked with compact material containing asbestos or used continuously substrates containing asbestos; and
- low when the subject had had occasional exposure to environmental materials containing asbestos.

Information on smoking habits (i.e. never, former, current smoker) was available in the Monfalcone Occupational Health surveillance programme database. Details on medical visits and diagnostic procedures performed within the surveillance programme were also retrieved from the database, including date, type and relevant findings.

The Charlson-Quan comorbidity index was calculated for each subject using methods reported elsewhere.[22] We identified all hospital admissions in the 10 years before the

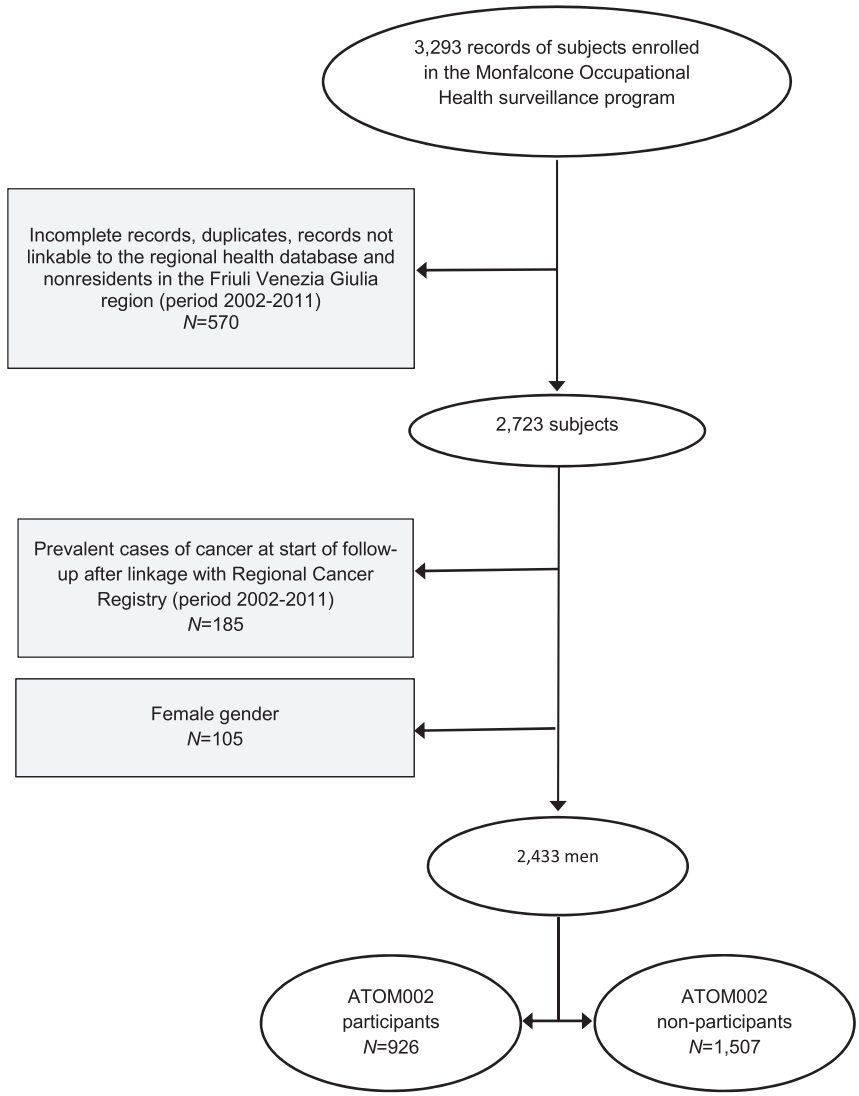

Figure 1. The flow diagram of cohort selection. The figure shows the steps used in the selection of the cohorts. (A) Monfalcone, a town located in the coastal area of north-east Italy, is one of the most important shipbuilding centres in Europe. (B) ATOM002 participants: subjects enrolled in the Monfalcone Occupational Health surveillance programme who participated in the Alpe-Adria Thoracic Oncology Multidisciplinary Group Study (ATOM002 study) (Fasola *et al.,* 2007). (C) ATOM002 non-participants: contemporary subjects enrolled in the Monfalcone Occupational Health surveillance programme who did not participate in the ATOM002 study (Fasola *et al.,* 2007).

start of follow-up through record linkage with the regional health database; the comorbidities reported in the discharge summary, coded according to the International Classification of Diseases (ICD) Ninth edition (ICD-9), were used.

The individuals' residence history in the FVG region, vital status and any occurrence of cancer were assessed through record linkage with the regional health database, using a unique identifier. Incident cases and causes of death were coded according to international rules. Cases of cancer were confirmed through the regional cancer registry, which was active for the period 1995–2009. Incident cases were coded according to the ICD-10. Mortality information, available in the region for the period 1989–2011, included the date of death and underlying and contributing cause(s) of death. Causes of death were coded according to the ICD-9.

The follow-up start date was the date of enrolment in the ATOM002 study for the LDCT-P subjects and the date of the first surveillance examination for LDCT-NP subjects after 1 February 2002. For cancer incidence in both sub-cohorts, the end date of follow-up was the date of cancer diagnosis, end of residence in the FVG region or 31 December 2009, whichever came first. For mortality in both sub-cohorts, the end date of follow-up was the date of death, end of residence in the FVG region or 31 December 2011, whichever came first.

Statistical analysis

We calculated standardized incidence ratios (SIRs) and standardized mortality ratios (SMRs), along with 95% confidence intervals (95% CIs).[23] The expected number of incident cases, based on regional rates specific for calendar year and age, was calculated for: all cancers (ICD10 C00-C43/C45-C96); malignant neoplasm of trachea, bronchus and lung (LC) (ICD10 C33-34); andmesothelioma (ICD10 C45). SIR was calculated as the ratio of the number of incident cases in the cohort to the number expected among the general population of the FVG region (SIR_FVG), given the lack of reliable figures for the whole Italian population. The age-specific incidence rates for all cancers, LC and mesothelioma for the FVG region (years 1995–2009) were provided by the Italian Association of Cancer Registries.[24]

Expected number of deaths, based on both national and regional rates, specific for calendar year and age, was calculated for: all causes (ICD9 001–999); all neoplasms (ICD9 140–239); LC (ICD9 162); and malignant neoplasm of pleura (MNP) (ICD9 163). To conduct sensitivity analyses using two external standards, SMRs were calculated as the ratio of the number of deaths observed (O) in the cohort to the number expected (E) on the basis of rates among the general population of the FVG region (SMR_FVG) and Italy (SMR_ITA). For mortality from all causes and all neoplasms, excluding MNP, we used the age-specific mortality rates reported by the Italian National Institute of Health.[25] With regards to MNP, we used the mortality data provided by the Italian National Institute of Statistics (ISTAT) for the FVG region and Italy (years 2002–11).

Cox proportional hazard models were used in internal analyses to compare incidence and mortality between LDCT-P and LDCT-NP.[26] Univariate, bivariate and multivariate analyses were conducted. Final models included the following explanatory variables (predictors) with a *P*-value <0.2 in the univariate and bivariate analyses[26,27]: smoking habits, sector of employment, level of asbestos exposure and Charlson-Quan comorbidity index.[22] Each final model was adjusted for age at start of follow-up. We used time-on-study as the time scale (i.e. time since the start of follow-up), with age at start of follow-up (continuous in years) included as a covariate in the bivariate and multivariate analyses. All analyses were performed using SAS software, Version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

The characteristics of the study cohort and the LDCT-P and LDCT-NP sub-cohorts are reported in Table 1.

Table 1. Characteristics of the study cohort, at start of follow-up

	LDCT-P[a]		LDCT-NP[b]	
	N	%	*N*	%
Total	926	100.0	1507	100.0
Age (years)				
<55	246	26.6	480	31.9
55-59	293	31.6	255	16.9
60-64	218	23.5	238	15.8
65-69	121	13.1	216	14.3
70-74	48	5.2	159	10.6
75+	–	–	159	10.6
Median (IQR)	58.0 (9.00)		60.0 (16.0)	
Smoking habits				
Never	309	33.4	546	36.2
Former	473	51.1	200	13.3
Current	144	15.5	761	50.5
Asbestos exposure level				
Low	82	8.9	380	25.2
Medium	704	76.0	958	63.6
High	140	15.1	169	11.2
Ch-Q Comorbidity Index				
0	877	94.7	1379	91.5
1	29	3.1	43	2.9
2	18	1.9	64	4.3
3	2	0.2	14	0.9
4-8	–	–	7	0.5
Follow-up (person-years)				
Total	8045.5		11 617.8	
Mean (SD)	8.7 (1.3)		7.7 (2.5)	

IQR, interquartile range; SD, standard deviation.
[a]ATOM002 study participants sub-cohort.
[b]ATOM002 study non-participants sub-cohort.

LDCT-P were younger; although the proportion of never-smokers was similar, LDCT-P were more likely to have quit smoking. Medium and high asbestos exposure categories were more highly represented in LDCT-P. The comorbidity index was slightly higher in LDCT-NP. The whole cohort included 2433 men, with 926 in the LDCT-P sub-cohort and 1507 in the LDCT-NP sub-cohort. Among LDCT-P, 913 (98.6%) subjects had a second LDCT: 126 within 1 year and 787 within 2 years of the baseline LDCT.

The number of observed and expected incident cancer cases and SIRs, by ATOM002 participation, are presented in Table 2. A total of 105 incident cases of cancer were observed in the LDCT-P (SIR_FVG = 1.05, 95% CI 0.86-1.28), and 171 were observed in the LDCT-NP (SIR_FVG = 1.15, 95% CI 0.99-1.33). Incident cases of LC by age, smoking and asbestos exposure are presented in Supplementary Table 1, available as Supplementary data at *IJE* online. Compared with the standard population, the LDCT-P group showed a weak increase in incidence in LC

Table 2. Standardized incidence ratios of cancer based on Friuli Venezia Giulia region rates among the ATOM002 study participants (LDCT-P) and non-participants (LDCT-NP). Follow-up period: 2002–09

Friuli Venezia Giulia region rates											
		LDCT-P (N = 926)					LDCT-NP (N = 1507)				
Cancer	ICD10	P-Y	O	E	SIR_FVG	95% CI	P-Y	O	E	SIR_FVG	95% CI
All cancers	C00-C43/C45-C96	6051.24	105	99.90	1.05	0.86-1.28	8702.58	171	148.88	1.15	0.99-1.33
Mouth	C03-C06	6310.59	2	1.02	1.97	0.24-7.11	9075.23	2	1.32	1.51	0.18-5.47
Oesophagus	C15	6305.11	3	1.78	1.68	0.35-4.92	9079.44	1	2.41	0.41	0.01-2.31
Stomach	C16	6305.72	8	4.28	1.87	0.81-3.68	9044.91	10	7.22	1.38	0.66-2.55
Colorectal	C18-C21	6263.94	21	13.47	1.56	0.96-2.38	9033.23	19	21.14	0.90	0.54-1.40
Liver	C22	6318.18	3	4.66	0.64	0.13-1.88	9068.34	9	7.03	1.28	0.59-2.43
Pancreas	C25	6317.46	4	2.88	1.39	0.38-3.55	9076.82	5	4.33	1.16	0.37-2.69
Larynx	C32	6318.67	0	2.67	–	–	9055.27	5	3.41	1.47	0.48-3.42
Lung	C33-C34	6264.21	16	12.61	1.27	0.73-2.06	9044.34	38	20.30	1.87	1.34-2.55
Mesothelioma	C45	6308.23	8	1.20	6.65	2.87-13.11	9065.41	13	1.60	8.11	4.31-13.86
Prostate	C61	6255.01	28	29.28	0.96	0.64-1.39	8929.19	51	40.45	1.26	0.94-1.66
Bladder	C67	6312.13	3	7.82	0.38	0.08-1.12	9070.96	3	13.12	0.23	0.05-0.67
Kidney	C64	6308.99	2	4.51	0.44	0.05-1.60	9066.95	6	6.60	0.91	0.30-1.98
CNS	C71	6313.87	3	1.43	2.10	0.43-6.12	9079.37	1	1.83	0.55	0.01-3.04
Leukemia	C91-C95	6316.91	1	1.42	0.70	0.02-3.91	9079.55	1	2.51	0.40	0.01-2.22

P-Y, person-years; O, observed; E, expected; CNS, central nervous system.

(SIR_FVG = 1.27, 95% CI 0.73-2.06) and a marked increase in mesothelioma (SIR_FVG = 6.65, 95% CI 2.87-13.11). Of the 16 incident cases of LC among LDCT-P, nine were ascertained on baseline and seven during follow-up. The LDCT-NP group also showed an increase in LC (SIR_FVG = 1.87, 95% CI 1.34-2.55) and mesothelioma (SIR_FVG = 8.11, 95% CI 4.31-13.86) (Table 2).

Mortality from all causes was reduced in comparison with both the regional and the national general population in the LDCT-P, but not in the LDCT-NP (Tables 3, 4). We found a trend towards reduction in mortality from all neoplasms in the LDCT-P in comparison with the regional spopulation (SMR_FVG = 0.76, 95% CI 0.56-1.02) (Table 3). Neither the LDCT-P nor the LDCT-NP had reduced mortality from all neoplasms, compared with the national population (Table 4).

The distribution of deaths from LC by age, smoking and asbestos exposure is presented in Supplementary Table 1, available as Supplementary data at *IJE* online. A total of 58 LC deaths were observed between 2002 and 2011 (LDCT-P, O = 8; LDCT-NP, O = 50) (Tables 3 and 4). The SMRs_FVG for LC deaths were 0.55 (95% CI 0.24-1.09) and 2.07 (95% CI 1.53-2.73), respectively for the LDCT-P and LDCT-NP populations (Table 3). The corresponding LC SMRs_ITA were 0.51 (95% CI 0.22-1.01) and 1.98 (95% CI 1.47-2.61) in the LDCT-P and LDCT-NP populations, respectively (Table 4). A total of 17 MNP deaths were observed (LDCT-P, O = 6; LDCT-NP O = 11). We found no reduction in MNP mortality, regardless of ATOM002 study participation, compared with either the national or the regional standard population (LDCT-P: SMR_FVG = 4.85, 95% CI 1.59-10.57; SMR_ITA = 9.54, 95% CI 3.12-20.80; LDCT-NP: SMR_FVG = 5.81, 95% CI 2.90-10.41; SMR_ITA = 11.79, 95% CI 5.89-21.11) (Tables 3, 4).

Adjusted Cox proportional hazard models showed a non-reduced incidence for LC, with an HR close to 1 in the LDCT-P sub-cohort compared with the LDCT-NP sub-cohort (Table 5). Results did not vary by smoking habits. Multivariate Cox proportional hazards models showed reduced mortality in the LDCT-P sub-cohort for all causes, but not for all neoplasms compared with the LDCT-NP sub-cohort. The LDCT-P sub-cohort had strongly reduced mortality from LC (HR = 0.41, 95% CI 0.17-0.96), whereas there was no difference in MNP mortality (Table 6). Such reduced mortality in the LDCT-P sub-cohort was confirmed across smoking strata.

Discussion

In this cohort mortality study of asbestos-exposed subjects under surveillance at the Monfalcone occupational health unit, we report a marked 59% reduction of LC mortality associated with LDCT screening compared with surveillance with clinic review and CXR. This result is independent of comorbidities and smoking history. Notably, we

Table 3. Standardized mortality ratios (SMR_FVG) based on Friuli Venezia Giulia region rates among ATOM002 study participants (LDCT-P) and non-participants (LDCT-NP). Follow up period: 2002–11

Friuli Venezia Giulia region Rates

		LDCT-P (P-Y = 8045.51)				LDCT-NP (P-Y = 11 617.75)			
Cause of death	**ICD9**	**O**	**E**	**SMR_FVG**	**95% CI**	**O**	**E**	**SMR_FVG**	**95% CI**
All causes	001-999	70	116.27	0.60	0.47-0.76	256	248.79	1.03	0.91-1.17
All neoplasms	140-239	44	57.53	0.76	0.56-1.02	98	100.68	0.97	0.80-1.19
Oesophagus	150	2	1.71	1.17	0.14-4.23	2	2.38	0.84	0.10-3.04
Stomach	151	7	3.66	1.91	0.77-3.94	3	6.90	0.43	0.09-1.27
Colorectal	153-154; 159.0	5	6.17	0.81	0.26-1.89	4	11.14	0.36	0.10-0.92
Liver	155.0-155.1	3	4.75	0.63	0.13-1.84	3	7.46	0.40	0.08-1.17
Pancreas	157	3	3.55	0.84	0.17-2.47	6	5.48	1.09	0.36-2.39
Larynx	161	0	0.92	–	–	0	1.49	–	–
Lung	162	8	14.50	0.55	0.24-1.09	50	24.21	2.07	1.53-2.73
Malignant neoplasm of pleura	163	6	1.24	4.85	1.59-10.57	11	1.89	5.81	2.90-10.41
Prostate	185	0	2.81	–	–	1	6.95	0.14	0.00-0.80
Bladder	188	1	1.42	0.70	0.02-3.93	1	3.08	0.32	0.01-1.81
Kidney	189	0	1.41	–	–	2	2.25	0.89	0.11-3.22
Central nervous system	191	3	1.36	2.21	0.45-6.44	0	1.82	–	–
Leukaemia	204-208	0	1.20	–	–	2	2.28	0.88	0.11-3.17
Mental disorders	290-303; 305-319	0	1.25	–	–	3	4.44	0.68	0.14-1.97
Diseases of nervous system and sense organs	320-389	2	2.85	0.70	0.08-2.53	5	6.82	0.73	0.24-1.71
Diseases of digestive system	520-579	0	6.97	–	–	21	12.44	1.69	1.05-2.58
Diseases of genitourinary system	580-629	0	1.13	–	–	5	3.08	1.62	0.53-3.78
Symptoms, signs and ill-defined conditions	780-799	1	1.11	0.90	0.02-5.01	3	2.10	1.43	0.29-4.17
Injury and poisoning	800-999	1	4.84	0.21	0.01-1.15	10	9.54	1.05	0.50-1.93
Diseases of circulatory system	390-459	20	28.96	0.69	0.42-1.06	79	77.77	1.02	0.81-1.27
Diseases of respiratory system	460-519	1	5.24	0.19	0.00-1.06	24	18.22	1.32	0.84-1.96

P-Y, person-years; O, observed; E, expected.

did not observe any reduction in MNP mortality. LDCT screening has been proven effective in detecting LC at an early stage in asbestos-exposed subjects.[19,28] Although a corresponding reduction in LC mortality remains to be confirmed in randomized trials, many professional organizations around the world already recommend LDCT-based screening for workers with asbestos exposure and an estimated risk level of LC equal to that in the eligibility criteria of the National Lung Screening Trial study.[14,17] Given that a randomized controlled trial may prove challenging due to the recommendations already in place, an international group of experts has recently called for the collection of standardized data in an international setting to gain the necessary evidence to validate and refine these recommendations.[29]

In this scenario our findings are of paramount importance, providing the best evidence currently available, in the absence of randomized controlled trial results in support of the effectiveness of LDCT screening in reducing LC mortality among subjects with a history of asbestos exposure. Although not randomized, an internal comparison assessed mortality between the LDCT-P sub-cohort who underwent LDCT screening and contemporary subjects,, enrolled in the same surveillance programme at the local occupational health unit, who did not take part in the ATOM002 LDCT screening study. For external comparisons, as a form of sensitivity analysis we used both regional and national Italian rates. Regional rates reflect the underlying morbidity and mortality from cancer due to factors other than asbestos exposure, and national rates represent baseline rates (particularly of LC and MNP) not influenced by the asbestos experience of the index population. Of course, in no way do SMRs or SIRs represent direct comparisons between the LDCT-P and LDCT-NP groups. The direct comparisons between participants and non-participants are described by HRs from COX regression models. The sensitivity analysis confirmed a highly consistent reduction in LC deaths in the screened population. An interesting finding is that the LDCT-P sub-cohort had more LC incident cases than deaths (16 vs 8), whereas the LDCT-NP sub-cohort had more deaths from LC (38 vs 50).

Table 4. Standardized mortality ratios (SMR_ITA) based on Italian rates among ATOM002 study participants (LDCT-P) and non-participants (LDCT-NP). Follow-up period: 2002–11

		Italian rates							
		LDCT-P (P-Y = 8045.51)				LDCT-NP (P-Y = 11 617.75)			
Cause of death	ICD9	O	E	SMR_ITA	95% CI	O	E	SMR_ITA	95% CI
All causes		70	108.44	0.65	0.51-0.82	256	239.54	1.07	0.94-1.21
All neoplasms	140-239	44	51.52	0.85	0.62-1.14	98	91.40	1.07	0.88-1.31
Esophagus	150	2	0.89	2.25	0.27–8.12	2	1.32	1.51	0.18-5.46
Stomach	151	7	3.12	2.24	0.90-4.62	3	5.66	0.53	0.11-1.55
Colorectal	153-154; 159.0	5	5.08	0.98	0.32-2.29	4	9.28	0.43	0.12-1.10
Liver	155.0-155.1	3	3.72	0.81	0.17-2.36	3	6.01	0.50	0.10-1.46
Pancreas	157	3	2.96	1.01	0.21-2.96	6	4.61	1.30	0.43-2.84
Larynx	161	0	0.94	–	–	0	1.51	–	–
Lung	162	8	15.54	0.51	0.22-1.01	50	25.26	1.98	1.47-2.61
Malignant neoplasm of pleura	163	6	0.63	9.54	3.12-20.80	11	0.93	11.79	5.89-21.11
Prostate	185	0	2.33	–	–	1	6.50	0.15	0.00-0.86
Bladder	188	1	1.80	0.56	0.01-3.09	1	3.95	0.25	0.01-1.41
Kidney	189	0	1.14	–	–	2	1.93	1.04	0.13-3.74
Central nervous system	191	3	1.20	2.49	0.51-7.28	0	1.64	–	–
Leukaemia	204-208	0	1.46	–	–	2	2.79	0.72	0.09-2.59
Mental disorders	290-303; 305-319	0	0.73	–	–	3	2.96	1.01	0.21-2.96
Diseases of nervous system and sense organs	320-389	2	2.85	0.70	0.08-2.53	5	7.35	0.68	0.22-1.58
Diseases of digestive system	520-579	0	5.25	–	–	21	10.14	2.07	1.28-3.17
Diseases of genitourinary system	580-629	0	1.25	–	–	5	3.82	1.31	0.42-3.05
Symptoms, signs, and ill-defined conditions	780-799	1	0.87	1.14	0.03-6.37	3	2.36	1.27	0.26-3.72
Injury and poisoning	800-999	1	4.01	0.25	0.01-1.39	10	8.33	1.20	0.58-2.21
Diseases of circulatory system	390-459	20	30.03	0.67	0.41-1.03	79	81.22	0.97	0.78-1.22
Diseases of respiratory system	460-519	1	5.21	0.19	0.00-1.07	24	17.54	1.37	0.88-2.04

P-Y, person-years; O, observed; E, expected.

Table 5. ATOM002 Study participation and incidence for all cancers, lung cancer and mesothelioma

	LDCT-P	LDCT-NP				
	N incident cases (P-Y)	*N* incident cases (P-Y)	Crude HR[a]	95% CI	Adjusted HR[a]	95% CI
All cancer sites	105 (6051.24)	171 (8702.58)	0.90	0.70-1.15	1.11	0.82-1.50
All cancer sites except lung	89 (6103.61)	133 (8735.64)	0.97	0.74-1.27	1.13	0.81-1.57
Lung cancer	16 (6264.21)	38 (9044.34)	0.63	0.35-1.13	1.02[b]	0.50-2.09
Never smokers[c]	1 (2123.92)	5 (3267.66)	0.32	0.04-2.77	0.83[d]	0.08-8.91
Former smokers[c]	8 (3212.24)	3 (791.15)	0.75	0.19-2.96	1.02[d]	0.23-4.52
Current smokers[c]	7 (928.05)	30 (4985.53)	1.31	0.57-2.99	1.53[d]	0.66-3.55
Mesothelioma	8 (6308.23)	13 (9065.41)	0.96	0.40-2.35	1.15[e]	0.42-3.17

P-Y, person-years of follow-up;
[a]HR, hazard ratio from Cox proportional hazard models.
[b]Adjusted for age at start of follow-up, smoking and asbestos exposure level.
[c]Cox proportional hazard models for lung cancer stratified by smoking levels.
[d]Adjusted for age at start of follow-up.
[e]Adjusted for age at start of follow-up and industrial sector of employment.

Table 6. ATOM002 Study participation and mortality for all causes, all cancers, lung cancer and malignant neoplasm of pleura

	LDCT-P (P-Y = 8045.5) *N* deaths	LDCT-NP (P-Y = 11 617.8) *N* deaths	Crude HR[a]	95% CI	Adjusted HR[a]	95% CI
All causes	70	256	0.39	0.30-0.51	0.61[b]	0.44-0.84
All causes (except accidents and lung cancer)	61	196	0.45	0.36-0-60	0.70[b]	0.50-1.00
All neoplasms	44	98	0.63	0.44-0.90	0.97[b]	0.62-1.50
All neoplasms except lung	36	48	1.08	0.70-1.67	1.46[b]	0.84-2.52
Lung cancer	8	50	0.22	0.10-0.46	0.41[b]	0.17-0.96
Never smokers[c]	1	6	0.25	0.03-2.08	0.48[d]	0.05-4.58
Former smokers[c]	3	5	0.16	0.04-0.68	0.29[d]	0.06-1.47
Current smokers[c]	4	39	0.50	0.18-1.40	0.63[d]	0.22-1.77
Malignant neoplasm of pleura	6	11	0.79	0.30-2.14	0.86[e]	0.31-2.41

P-Y, person-years of follow-up.

[a]HR, hazard ratio from Cox proportional hazard models.

[b]Adjusted for age at start of follow-up, Charlson-Quan comorbidity index, smoking and asbestos exposure level.

[c]Cox proportional hazard models for lung cancer stratified by smoking levels.

[d]Adjusted for age at start of follow-up.

[e]Adjusted for age at start of follow-up, Charlson-Quan comorbidity index and industrial sector of employment.

Mortality from all causes in the LDCT-P sub-cohort was reduced when compared both externally with the two general reference populations (Tables 3 and 4) and, more importantly, internally with the LDCT-NP sub-cohort (HR = 0.61) (Table 6). Our results are in line with previous findings in a surveillance cohort of 576 German workers heavily exposed to asbestos, who underwent high-resolution chest CT in 1993–97 and were followed for up to 14 years.[30] In that cohort, participants were identified from the 74 106 asbestos-exposed subjects registered with the German Central Registration Agency for Employees, for whom relevant information on job activities and duration of asbestos exposure was available. Mortality from LC was reduced in the HRCT cohort (SMR = 0.39, 95% CI 0.17-0.77), supporting a role for HRCT in the surveillance of these subjects. The SMR for pleural mesothelioma of 28.1 (95% CI 15.73-46.36) was in keeping with heavy asbestos exposure. Indeed, the HRCT-screened subjects in the German study had a higher asbestos exposure than our LDCT-P population in which only 15% of subjects had had a high level of asbestos exposure. The reduction in LC mortality observed in our study confirms, therefore, the effectiveness of LDCT not only in heavily exposed subjects but also in our less selected population.

The main limitation of our study is that there was no randomization to address the possibility of selection bias. In addition, the study was not powered to compare mortality for outcomes other than LC. Another limitation is the lack of data on LC stage. The identification of cancer cases was based on the regional cancer registry, which unfortunately does not include information on cancer stage, so we could not compare LC stage by LDCT participation. A further limitation is the inability to fully evaluate possible effect modification between smoking and LDCT screening participation. Specifically, our study does not include a quantitative exposure assessment of asbestos and cigarette smoking, because of the common limitation of many Italian health surveillance programmes in not estimating the concentration of asbestos fibres in the workplace nor quantifying the intensity and duration of cigarette smoking. Our measures of association may, therefore, be affected by residual confounding by the level of asbestos exposure and cigarette smoking and by an interaction between asbestos exposure and smoking. However, the results we report in Tables 5 and 6, which include stratification by smoking status, are consistent with the interpretation that LDCT participation may have reduced mortality in the intervention group.

Nevertheless, these findings may be at least partially explained by a 'healthy study participant' effect, a variation of the 'healthy worker effect' previously reported for occupational epidemiology studies.[31] Subjects enrolled in the ATOM study were likely to be healthier, not only than their contemporaries enrolled in the same surveillance programme but also than the general population, as confirmed by the Charlson-Quan comorbidity index distribution. Study participants also had to fulfill the eligibility criteria for the ATOM study, including no history of cancer or severe concomitant conditions and age <75 years. Notably, LDCT-P subjects were younger and had quit smoking more frequently than LDCT-NP subjects. Finally, it has been reported that cancer screening programmes may

facilitate the identification of both malignant and non-malignant conditions,[32,33] and have an impact on life expectancy.

It is, however, not plausible that the reduction in LC mortality associated with LDCT is fully explained by such biases. First, the LDCT-P sub-cohort had a smoking distribution (never, former, current) that was similar to that described for the same age group in the general regional population.[34] This supports the validity of the reduced SMR for LC that we obtained when LDCT-P were compared with the FVG and national general population. Further, not only were the sensitivity analyses (regional and national comparison groups) highly consistent, but also mortality from all neoplasms excluding lung was increased in the LDCT-P sub-cohort compared with the LDCT-NP sub-cohort (HR = 1.46, Table 6). Our results comparing cancer incidence in LDCT participants and non-participants (Table 5), also showed no differences for all cancers, all cancers excluding LC and LC.

Another potential criticism of our LC mortality results comes from the observation of reduced mortality for causes of death other than accidents and LC (HR = 0.70, Table 6), mainly vascular conditions. Indeed, assessment of cigarette smoking was incomplete in our study and as a result, our analyses did not include, for example, adjustment for intensity, duration, dose (pack-years) nor years since cessation of smoking. However, information about smoking cessation available for the LDCT-P sub-cohort (and not for LDCT-NP sub-cohort) shows that 40% of LDCT-P former smokers quit smoking less than 15 years since screening programme enrolment. A study conducted previously in this population area,[35] has shown that smoking cessation does not correlate with a significant reduction in LC mortality within the first 15 years since quitting. In contrast, some evidence among insulators who were also smokers has shown a steep mortality reduction even within 10 years of smoking cessation.[36] Further, clear evidence exists of reduced mortality from vascular events by time since smoking cessation even within 3–5 years of quitting[37] and even among older adults.[38] Hence, it is likely that our estimates of HR (LDCT-P sub-cohort vs LDCT-NP sub-cohort) for all causes of death except accidents and LC may indeed be affected by residual confounding due to the absence of adjustment for years since smoking cessation. Instead, our estimates of HR for LC mortality were much less affected, if at all, because of the longer latency of the preventive effect of smoking cessation on LC mortality. Finally, it should not be forgotten that a strong reduction of all-cause mortality has been demonstrated following improvements in cardiovascular treatments and influenza vaccination in the elderly.[39] We can hypothesize that, because of the adherence to the ATOM002 intervention, participants may have also obtained other effective preventive and treatment benefits which impacted on cardiovascular and other mortality but did not alter LC mortality, consistent with the literature. Therefore, this observation supports the interpretation of a specific, causal preventive role of LDCT screening in LC in asbestos-exposed subjects, and lowers the plausibility of alternative explanations, such as potential selection bias among screening participants or residual confounding by carcinogens such as cigarette smoking, that would have affected all neoplasms along with LC.

In summary, the hard reality that our LDCT programme was not associated with reduced MNP mortality indicates that approaches other than LDCT screening should be pursued for the early diagnosis of MNP. Our findings support LDCT screening for LC in asbestos-exposed subjects. Many issues remain to be addressed, including the optimum screening interval, cost-effectiveness and overall affordability. Nevertheless, the fact that annual LDCT has been adopted for high-risk current or former smokers in many places, on the basis of a much lower reduction in LC cancer mortality, strongly suggests that screening of asbestos-exposed workers should be considered.

Supplementary Data

Supplementary data are available at *IJE* online.

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