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ORIGINAL ARTICLE

Lung and pleural CT signs predict deaths: 10-year follow-up after lung cancer screening of asbestos-exposed workers

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Abstract
Purpose To work out the predictive value of pathological (HR)CT signs concerning long-term mortality among those screened for lung cancer.
Methods Five hundred and eighty four construction workers (574 males, 10 females) were originally screened for lung cancer and found negative. Their images were also scored for several lung and pleural signs. Mortality data were checked from the National Registry of Causes of Death. Cox regression adjusted for age, sex, smoking, BMI, and asbestos exposure was used to explore the relations between the radiological signs and deaths. The mean follow-up time was 10.53 years (0.56–12.98 years) and a total of 6,150 person years were followed up.
Results Altogether, 185 deaths occurred (64 cardiovascular, 51 cancer, 24 non-cancer respiratory deaths, and 46 deaths from other causes). All studied emphysema signs were significant predictors of all-cause deaths as were most fibrosis signs (subpleural nodules, septal lines, parenchymal bands, and honeycombing), ground-glass opacities, thickened bronchial walls, pleural plaque extent, and adherences. Cardiovascular deaths were significantly associated with paraseptal emphysema and bullae. Several lung/pleural signs also predicted cancer and respiratory deaths.
Conclusion Pathological lung/pleural CT signs found in screening seem to predict deaths in long term, which may require more careful medical surveillance of such individuals. Further studies are needed to generalize the present findings to general population.

Keywords CT · Lung · Mortality · Pleura

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Introduction

Computed tomography (CT) is increasingly used not only to diagnose symptomatic patients but also to screen populations at risk of lung and colon cancers, coronary heart disease, occupational lung disease, etc. The average annual number of CT examinations in Switzerland in 1998 was 46.3/1,000 population, with an annual increase in hospital use from 8 to 18% (Midez et al. 2006). In France, an estimated 4.2–6 million CT procedures were performed in 2002 (Scanff et al. 2008). This vast number of CT examinations contains a lot of incidental findings, which may cause problems as well during clinical examinations as in screening studies. In a systematic review, 7.7 and 14.2% of patients undergoing either coronary artery disease or lung cancer screening with CT were found to have clinically significant incidental findings requiring additional investigations (Jacobs et al. 2008). It may be difficult to judge what findings are really important, i.e., the information gained by using expensive technology and considerable patient irradiation cannot be optimally used.

Pathological lung and pleural high-resolution CT signs, irrespective in what context they are found, may indicate poor health prospects for the future. Little is known about the long-term mortality related to such signs among screened populations or symptomatic patients. By using a

previous material of asbestos-exposed workers screened with CT for lung cancer in 1996–1997, we carried out a follow-up study. We made benefit from the National Register of Causes of Death and checked the all-cause and cause-specific mortalities, which were associated with several pathological lung and pleural signs found in the screening study.

Materials and methods

Study population

We used a previous material consisting of asbestos-exposed construction workers originally screened for lung cancer with CT (Tiitola et al. 2002a). The screened persons were originally recognized with the aid of previous studies and trade union registers. Invitations were submitted to those living in the Helsinki area ($n = 642$) and 602 participated. Among those, there were 85 asbestosis diagnoses and 601 cases of bilateral pleural plaques. Smoking ($\geq$10 pack-years) was an inclusion criterion for the patients without asbestosis diagnosis. Besides a CT study, they underwent a health examination and a survey.

In this follow-up study, sufficient data were available for 590 of the screened ones. Five cases with a screen-detected lung cancer and a single mesothelioma were excluded leaving thus 584 subjects (10 women, 574 men) left with no screen-detected malignancy. Their mean age at the time of the CT study was 63 years (range 38–81 years), body mass index (BMI) 27 kg/m^2 (17–40), and the duration of asbestos exposure 26 years (2–48). There were 18 never smokers, 405 ex-smokers, 159 current smokers, and 2 persons with no smoking data available. Those with data available ($n = 582$) had smoked 24 pack-years on an average (0–84).

All patients gave a written informed consent at the time of the primary study, and the study plan was accepted by the local ethics committee. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Imaging and image interpretation

All patients underwent chest spiral CT (Picker PQ 2000 scanner, Picker International, Cleveland, Ohio) in supine position with full inspiration. All patients were first imaged supine by single-slice spiral mode at full inspiration (10 mm slice reconstructions, 125 mA, 140 kV, 10 mm collimation, pitch 1.5). Thereafter, the first subjects were imaged prone with four thin section cuts (1.5-mm slices, 130 kV, 200 mA, algorithm: sharp) equally spaced from tracheal bifurcation to lung bases and most subjects thereafter with seven such cuts from the aortic arch to lung bases. The combination of these two methods is later referred as (HR)CT. All images were printed as hard copies with lung and pleural window settings and inspected on lighted view boxes. Lungs were scored (integers only) independently by three experienced radiologists for the following:

- existence/absence of pulmonary nodules (0 or 1)
- subpleural curvilinear opacities (score 0–5: 0 indicating a clear finding and 5 maximum pathology as judged according to severity and extent)
- subpleural septal lines (score 0–5)
- parenchymal bands (score 0–5)
- subpleural nodules (score 0–5)
- honeycombing (score 0–5)
- emphysema (score 0–5) categorized as centrilobular, paraseptal and panlobular as well as bullae
- subpleural dependent opacities (score 0–5)
- ground-glass opacities (score 0–5)
- thickness of bronchial walls (score 0–3)
- bronchiectasis (score 0–3).

Pleura was scored by the following:

- slice-by-slice estimated total plaque extent (cm^2)
- the maximum thickness of plaques (<5 mm, 5–10 mm, >10 mm)
- calcification score (score 0–3)
- pleural adherences: at diaphragms or sinuses, converging adherences, and other adherences (sum score 0–9)
- rounded atelectases: 1–2 recordings (sum score 0–6)

All radiologists worked independently and blinded. Zero score indicated normal finding and the maximal score (5 or 3 depending on the sign) the most advanced possible pathological finding. The lung findings were defined according to the textbook by Webb et al. (1996), and the scoring system and the consistency of readings have been described in detail (Tiitola et al. 2002b; Huuskonen et al. 2001, 2004). The bilateral average scores of signs given by the three radiologists were used.

Follow-up

Permission for the follow-up study was given by the institutional board and by Statistics Finland. A patient register report required by the national legislation was made. No additional ethics committee permission was required at this stage. Mortality dates and the underlying causes of death according to the International Classification of Diseases (ICD-10 by the World Health Organization) were checked from the National Register of Causes of Death (Statistics Finland) by using the participants' unique personal identification codes. The follow-up covered comprehensively

deaths between the baseline examination and the end of 2007, about 94% of deaths during 2008 and less comprehensively deaths until April 13, 2009. The mean follow-up time was 10.53 years (range 0.56–12.98 years) and a total of 6,150 person years were followed up.

Statistical methods

The Cox proportional hazards model was used (first with the enter method). Age, sex, body mass index, pack-years of smoking, and asbestos exposure years were adjusted for by using them as covariates (no correlation coefficient between the continuous covariates exceeded 0.5). Occasional lacking covariate data were replaced by the group mean value (pack-years with 3 replacements, asbestos exposure years with 2 replacements, and BMI with 56 replacements). The above regression model was run for each lung and pleural sign separately. The signs were transformed to z-scores due to their differing scales. After computing these models, a backward likelihood ratio (LR) model with all lung and pleural signs and covariates was run. All-cause mortality was first studied. Lung and pleural signs showing any suggestive associations ($P < 0.10$) with mortality were further studied regarding cardiovascular, all cancer, intrathoracic malignant neoplasms, and non-cancer respiratory mortality separately. SPSS 17.0 software (SPSS Inc, Chicago, Illinois) was used. P values < 0.05 were regarded as significant. The underlying causes of death in the national male population aged 60–79 during 1998–2007 were worked out from Statistics Finland (2010).

Results

The (HR)CT signs mostly showed right skew frequency distributions with normal or minor findings predominating and less advanced findings (Table 1).

Altogether, 185 deaths were found. Fourteen deaths occurred within 2 years after the CT study, 27 after 2–4 years, 33 after 4–6 years, 32 after 6–8 years, 33 after 8–10 years, and 46 after more than 10 years. In 64 (34% of all deaths) the underlying cause of death was cardiovascular (ICD-10 codes I00–I99), in 51 (28%) cancer/neoplasm (ICD -10 codes C00–D48), in 24 (13%) non-cancer respiratory (ICD-10 codes J00–J99), in 12 (6%) (K00-93) digestive system, in 10 (5%) death was reported but the code was not available at the time of query, in 8 (4%) central nervous system (G00-99), and in the remaining 16 (9%) cases consisted other reasons. Out of cancer deaths, 22 (12%) were due to intrathoracic malignant neoplasms (ICD codes C30–39), 14 due to alimentary organs (ICD codes C15–26), and the rest 15 being various other cancers. The corresponding national numbers among the general male population aged 60–79 were as follows: total 112,296 deaths, cardiovascular 48,702 (43%), all cancer 25,488 (23%), lung cancer 9,931 (9%), and non-cancer respiratory deaths 8,589 (8%). The present material therefore showed

Table 1 Distribution of (HR)CT signs among the sample

	Score	Minimum	Maximum	Mean	SD
Solitary nodules	0 or 1	0 ($n = 479$)	1 ($n = 111$)		
Subpleural curvilinear opacities	0–5	0.00	2.83	0.32	0.52
Subpleural septal lines	0–5	0.00	2.75	0.64	0.60
Parenchymal bands	0–5	0.00	3.00	0.42	0.51
Subpleural nodules	0–5	0.00	3.50	0.22	0.37
Honeycombing	0–5	0.00	3.33	0.05	0.25
Centrilobular emphysema	0–5	0.00	4.00	0.32	0.69
Paraseptal emphysema	0–5	0.00	4.67	0.19	0.54
Panlobular emphysema	0–5	0.00	4.25	0.24	0.59
Bullae	0–5	0.00	4.17	0.14	0.44
Subpleural dependent opacities	0–5	0.00	2.67	0.16	0.30
Ground-glass opacities	0–5	0.00	2.17	0.08	0.23
Thickened bronchial walls	0–3	0.00	2.67	0.32	0.34
Bronchiectasis	0–3	0.00	2.33	0.15	0.28
Pleural plaque extent	cm^2	4.00	324	83	48
Pleural plaque max. thickness	0–3	1.00	3.00	1.81	0.59
Pleural plaque calcification	0–3	0.00	3.00	1.53	0.90
Pleural adherences	0–9	0.00	6.00	1.23	0.94
Rounded atelectases	0–6	0.00	4.33	0.08	0.30

over represented all cancer (28% vs. 23%), intrathoracic malignant neoplasm (12% vs. 9%), and non-cancer respiratory (13% vs. 8%) deaths.

The association of lung and pleural signs (as separately studied) with all-cause deaths is given in Table 2. All emphysema variables were significant predictors of deaths as were most fibrosis variables, ground-glass opacities, and thickened bronchial walls. Out of pleural variables, the plaque extent and adherences were significant predictors of deaths. When all lung and pleural variables were simultaneously studied in the same backward eliminating model, honeycombing (HR = 1.259; 95% CI = 1.116–1.420, $P < 0.001$), paraseptal emphysema (HR = 1.255; 95% CI = 1.110–1.418, $P < 0.001$), and the extent of pleural plaques (HR = 1.203; 95% CI = 1.046–1.383) remained as the only significant predictors of all-cause mortality.

Cardiovascular deaths were associated with the following signs (as separately studied): paraseptal emphysema (HR = 1.317; 95% CI = 1.112–1.560, $P = 0.001$) and bullae (HR = 1.193; 95% CI = 1.013–1.406, $P = 0.034$). The first one remained significant in the backward eliminated model.

All cancer (excluding respiratory cancer) deaths were predicted by the existence of pulmonary nodules (HR = 3.166, 95% CI = 1.279–7.841, $P = 0.013$).

Significant associations between (HR)CT signs (as separately studied) and respiratory cancer deaths are given in Table 3. Deaths from intrathoracic malignant neoplasms were significantly predicted by fibrosis signs, centrilobular emphysema, ground-glass opacities, thickened bronchial walls, and bronchiectasis. In the eliminated model, these deaths were significantly predicted by subpleural curvilinear opacities and nodules, honeycombing, centrilobular emphysema as well as by the calcification and maximal thickness of pleural plaques.

Significant associations between (HR)CT signs (as separately studied) and non-cancer respiratory deaths are given in Table 4. Deaths were predicted by several fibrotic and emphysema signs as well as by ground-glass opacities, the extent of pleural plaques, and thickness of bronchial walls. When all signs were studied in the same regression model and then backward eliminated, centrilobular emphysema, panlobular emphysema, the extent of pleural plaques, and bronchial wall thickness remained as significant predictors.

Discussion

Several (HR)CT signs predicted significantly all-cause and cause-specific deaths in the present material originally screened for lung cancer. The causality between the detected pleural/lung signs and mortality is obscure, and it is more likely that these signs are manifestations of inflammatory/exposure/autoimmune/genetic or other mostly unknown processes, which are responsible for the deaths. To our

Table 2 Lung and pleural signs predicting all-cause deaths

	HR			Sig.
	Estimate	95% lower	95% upper	*P* value
Solitary nodules	1.058	.731	1.532	.764
Subpleural curvilinear opacities	1.104	.958	1.273	.170
Subpleural septal lines	1.382	1.213	1.574	.000
Parenchymal bands	1.322	1.167	1.496	.000
Subpleural nodules	1.259	1.139	1.391	.000
Honeycombing[a]	1.320	1.212	1.438	.000
Centrilobular emphysema	1.236	1.089	1.404	.001
Paraseptal emphysema[a]	1.257	1.124	1.405	.000
Panlobular emphysema	1.201	1.074	1.344	.001
Bullae	1.160	1.047	1.285	.004
Subpleural dependent opacities	1.082	.965	1.213	.177
Ground-glass opacities	1.184	1.051	1.332	.005
Thickened bronchial walls	1.234	1.081	1.408	.002
Bronchiectasis	.994	.851	1.160	.934
Pleural plaque extent[a]	1.187	1.036	1.360	.013
Pleural plaque max. thickness	1.083	.938	1.250	.279
Pleural plaque calcification	1.012	.866	1.184	.877
Pleural adherences	1.156	1.019	1.311	.024
Rounded atelectases	1.022	0.899	1.163	.737

Cox regression (enter model with signs separately studied) adjusted for sex, age, body mass index, smoked pack-years, and asbestos exposure years

HR hazard ratio/z-score of the radiological sign (with 95% confidence limits)

[a] Variable remains significant in backward eliminated regression model

Table 3 Significant association between lung and pleural signs and respiratory cancer deaths

	HR			Sig.
	Estimate	95% lower	95% upper	*P* value
Subpleural septal lines	3.596	2.002	6.460	.000
Parenchymal bands	3.019	1.651	5.521	.000
Subpleural nodules[a]	3.440	2.175	5.441	.000
Honeycombing[a]	7.016	3.672	13.405	.000
Centrilobular emphysema[a]	1.754	1.118	2.751	.015
Ground-glass opacities	7.597	2.640	21.856	.000
Thickened bronchial walls	3.656	1.356	9.857	.010
Bronchiectasis	3.921	1.427	10.773	.008

Cox regression (enter model with signs separately studied) adjusted for sex, age, body mass index, smoked pack-years, and asbestos exposure years

HR hazard ratio/z-score of the radiological sign (with 95% confidence limits)

[a] Variable remains significant in backward eliminated regression model. Other variables significant in this model are subpleural curvilinear opacities, pleural plaque calcification, and maximal thickness

Table 4 Significant association between lung and pleural signs and non-malignant respiratory deaths

	HR			Sig.
	Estimate	95% lower	95% upper	*P* value
Subpleural septal lines	1.991	1.429	2.776	.000
Parenchymal bands	2.001	1.515	2.643	.000
Subpleural nodules	1.321	1.038	1.682	.024
Honeycombing	1.436	1.190	1.734	.000
Centrilobular emphysema[a]	1.816	1.370	2.406	.000
Paraceptal emphysema	1.438	1.129	1.831	.003
Panlobular emphysema[a]	1.594	1.289	1.972	.000
Ground-glass opacities	1.436	1.106	1.864	.007
Thickened bronchial walls	1.549	1.147	2.090	.004
Pleural plaque extent[a]	1.705	1.230	2.361	.001

Cox regression (enter model with signs separately studied) adjusted for sex, age, body mass index, smoked pack-years, and asbestos exposure years

HR hazard ratio/z-score of the radiological sign (with 95% confidence limits)

[a] Variable remains significant in backward eliminated regression model. A variable also significant in this model is bronchial wall thickness

knowledge, this is the first CT follow-up study not limited to a specific disease entity investigating the association between lung and pleural signs and subsequent mortality.

It is not surprising that signs of emphysema or chronic bronchitis (thickened bronchial walls), even when adjusted for smoking, were associated with deaths. Haruna et al. (2010) could show that the extent of emphysema measured by CT was a good predictor of mortality among patients with COPD and pulmonary emphysema. Previous studies on the relation between radiological signs and mortality have mainly dealt fibrotic lung diseases. Among patients with usual interstitial pneumonia or nonspecific interstitial pneumonia, high fibrotic score (the extent of reticulation plus honeycombing) was associated with increased death risk (Shin et al. 2008). Lung fibrosis at thin-section CT predicted deaths among patients with interstitial lung fibrosis (Gay et al. 1990; Lynch et al. 2005; Best et al. 2008). The 10-year risk of death due to asbestosis rose sharply with increasing interstitial fibrosis as identified on the baseline chest X-ray (Markowitz et al. 1997). Extensive pleural adherences restrict lung function. While diffused ground-glass opacities are associated with widespread inflammatory or infiltrative lung disorders, focal ground-glass opacities, also called non-solid or part-solid nodules, can represent early-stage bronchioloalveolar carcinoma (Infante et al. 2009). This sign has not been associated with long-term increased mortality before. The same applies to the extent of pleural plaques.

Among findings that did not predict deaths in the present material were solitary non-malignant nodules, rounded atelectases, and bronchiectasis. Many nodules represent scars of old infections or intrapulmonary lymph nodes that seem to be harmless regarding mortality. As rounded atelectases may not harm their host, the same does not hold true for bronchiectasis. It is a distinct disease entity unlike some other radiological signs, which we studied. The bronchiectasis patients probably had been well recognized and received adequate medical/surgical treatment, which attenuated their mortality risk. Bronchiectasis was rare with the primary score being ≤ 1 (scale 0–3) in 576 (98%) of the cases, which limited the power of our statistical analysis.

The primary study on lung cancer screening detected 5 lung cancers (Tiitola et al. 2002a). The first register search from the national cancer registry 3 years afterward revealed 2 new lung cancer cases diagnosed 2 years and 2 versus 5 months after the screening. Neither was retrospectively visible on reinspected CT scans. Excluding the screen-detected 5 cancers, 22 new deaths from intrathoracic malignant neoplasms were found at the follow-up. The screen-detected cancers were excluded, because these may cause secondary changes in lung and these would then be interpreted as signs "predicting" cancer, which surely is not the fact. If repeated screening rounds are performed, lung signs predicting future respiratory cancers (Table 4) should be taken into account during the baseline screening round. This information may probably be used to adjust the screen interval shorter or to use other additional screening methods, such as sputum cytology, for those at the greatest risk.

All our volunteers represented blue-collar workers, and major socio-economical differences were unlikely to occur between them. Unfortunately, we did not have information on life habits, blood pressure, cholesterol levels, etc., which thus could not be controlled. Cancer and respiratory deaths were over represented in the present material, most likely due to their lower than average socio-economic position with associated risk factors, asbestos exposure, and smoking. Healthy and risk-free people will not be imaged with CT, and potential pathological signs predicting deaths among them are probably less common and are hard to be investigated due to radiation protection reasons. Unfortunately, more detailed health information on dietary habits, alcohol use, and leisure-time physical activity, etc., was not collected in this study and could not be adjusted for.

Conclusions

We found that several pathological (HR)CT signs in this cohort screened for lung cancer predicted all-cause and cause-specific deaths during long term. CT examinations seem to contain a lot of previously unknown information on health risks. Radiologists reading images should pay attention and report these signs (even if they are incidental findings), since they seem to affect patient prognosis. Further studies among other populations are needed to confirm and to generalize the present results. Efforts to clarify the links between the radiological signs and mortality, so far as still unknown, should be undertaken to find proper preventive measures. CT-screened subjects with positive lung and pleural findings are at a special risk of death and should undergo especially careful health surveillance.

Conflicts of interest The authors declare no conflicts of interest.

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