

Factors Influencing the Prevalence of Pulmonary Nodules in Lung Cancer Screening Trials: Re-evaluation of a CT Study

Tapio Vehmas

Finnish Institute of Occupational Health, Helsinki, Finland

Abstract

Numerous false positive findings are a problem in computed tomography based lung cancer screening trials. The potential patient-related variables that could predict the existence of such lung nodules were studied. 526 construction workers (age 38–81 yrs.) previously screened with spiral computed tomography were evaluated. Background features (age, body mass index, stature, sex, C-reactive protein, erythrocyte sedimentation rate, asbestos exposure and smoking history), reported symptoms (general condition, cough, mucous production, dyspnoea, chest pain) and findings in high resolution CT were related to the existence of nodules with logistic regression. There were 107 patients with one or more nodules recorded at least by two of the three observers. Advancing age (OR = 1.042/year, 95% CI = 1.000–1.085, $p = 0.048$) and dyspnoea symptom ($p = 0.014$) were positively associated with the existence of nodules, while smoking, asbestos exposure history and other studied parameters were not. Nodules ≤ 5 mm (50 patients) were inversely associated with the maximal thickness of pleural plaques (OR = 0.384, 95% CI = 0.169–0.873, $p = 0.022$). No variables helpful to sample subjects for lung cancer screening studies to reduce the number of false positive findings were found. Poor inspiration or associated pathology such as thick pleura may hamper nodule detection. Further studies should focus especially on the possible effect of computer tomography technology on finding nodules.

Introduction

Lung cancer screening with spiral computed tomography (CT) has been increasingly used for the early detection of this severe malignancy. A recent paper showed that cancers found in such screening have a favourable prognosis [1]. One of the major limitations of CT screening is the large number of non-specific lung nodules, ranging from 6.7 % or 14 % [2–4] in baseline screening up to 74 % among those repeatedly screened [5]. These findings cause a great burden, because their benign nature has to be confirmed with extra studies. Such nodules present a great challenge not only for the medical staff but also for the patients, who often need to be followed up for months or even for years with repeat CT studies. Sometimes more invasive procedures, such as fine-needle aspiration biopsies, bronchoscopies or even thoracotomies are needed with potential iatrogenic hazards.

Reducing the number of these false positive findings while not compromising with the sensitivity of finding cancer would therefore greatly help future screening protocols.

Keywords: Coin lesion, pulmonary; False positive reactions; Lung cancer; Mass screening; Tomography, spiral computed

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While the aetiology of lung cancer has been intensively studied, little is known about factors affecting the population prevalence of non-specific nodules detected by CT.

The purpose of the study is to find out associations between the existence of non-specific pulmonary nodules as well as subjects' background data, symptoms and their high-resolution computed tomography (HRCT) findings. The latter procedure produces less radiation burden than screening CT and may have been performed for other indications previously. Thereby it might be possible to define future lung cancer screening samples in a way to minimise false positive findings thus increasing the specificity of screening.

Methods

Patients

Data were reanalyzed from the previous ASBE-project [6], a series of studies aiming to explore early chest changes, including lung cancer, among asbestos-exposed workers. Construction workers suffering from occupational disease (asbestosis or bilateral pleural plaques) and living close to Helsinki were identified based on previous studies. 602 out of 642 invited were willing to participate. Due to lacking data in one or several parameters to be studied the current analysis had to be restricted to a subsample of 526 subjects (517 men, 9 women). Of these, there were 107 subjects (20.3 %) with one or more lung nodules found at least by two of three observers and 419 subjects without such finding. The patients filled a questionnaire on occupational and health data, gave a blood sample and were imaged with spiral and high-resolution CT. The mean age of the sample was 63 (range 38–80) years, mean duration of asbestos exposure 26 years (2–48), smoked pack-years 24 (0–88), body mass index 27 (17–40) kg/m², stature 174 (153–196) cm, serum C-reactive protein (CRP) content 11 mg/l (10–71) and the erythrocyte sedimentation rate (ESR) 17 (1–110) mm. All were construction workers, 293 with professional training regarded as skilled workers while the rest 233 were semi-skilled. The study was accepted at the local ethics committee and the participants gave their written informed consent.

The health questionnaire, modified form Medical Research Council [7] included questions about occupational history, smoking and respiratory symptoms:

- dyspnoea: 0 = no, 1 = yes while hurrying or walking in gentle uphill, 2 = has to walk slower than people of the same age, 3 = has to stop to breath while walking on flat country
- prolonged cough at least for three months yearly (yes/no)
- increased mucus production while coughing at least for three months yearly (yes/no)
- chest pain (yes/no)
- general performance status: 0 = normal, 1 = subnormal, 2 = unable to work, 3 = unable to care for self

The distribution of the categorical independent variables is given in Table 1.

Table 1. Characteristics of the participants: categorical data

Variable	Coding	Frequency
Sex	female	9
	male	517
Occupational category	semi-skilled	233
	skilled	293
Smoking	never	16
	ex	366
	current	144
Dyspnoea	0	208
	1	160
	2	129
	3	29
General condition	0	6
	1	449
	2	68
	3	3
Prolonged cough	no	352
	yes	174
Mucus production	no	301
	yes	225
Chest pain	no	405
	yes	121

Imaging and image interpretation

A Picker PQ 2000 CT scanner was used. Unenhanced single-slice spiral scanning (10 mm slices, pitch 1.5, 140 kV, 125 mA) with the patients lying supine and in full inspiration was performed from the lung apices to bases. 4–7 additional HRCT images (1.5 mm cuts, 130 kV, 200 mA) with the patient lying prone were also exposed. Images were read by three observers independent from each other and blinded for the clinical information.

The radiological signs below were subjectively scored according to their severity/extent and the average score of both sides was used for the calculations. 0 indicated no pathological changes and the maximum score indicated most severe changes:

- fibrosis score [8] consisting of several items (subpleural irregular and ground glass opacities, septal lines, curvilinear opacities, parenchymal bands and hon-

- eycombing) typical for interstitial lung fibrosis: 0–5
- ground glass opacities: 0–5
- total emphysema score (sum of centrilobular, panlobular, paraceptal and bullous emphysema scores; each scored 0–5): 0–20
- bronchiectasis: 0–3
- pleural plaque maximal thickness: 0–5 mm, 5–10 mm, > 10 mm
- pleural plaque extent (cm²): estimated sum of plaque extent in each continuous 10 mm slice [9]
- pleural plaque calcification score: 0–3

Statistical methods

Logistic regression was used to explore the relations between the continuous and categorical independent variables and the outcome variable (participant either having nodule(s) or not). Besides the enter method with all independent variables included in the model also forward selecting and backward eliminating models (likelihood ratio) were computed. Models were also computed to study the predictors for the existence of small nodules (participant having nodule of 0–5 mm in diameter) only, because they are most likely to be the irrelevant ones. SPSS 14.0 software (SPSS Inc, Chicago, Ill, USA) was used.

Results

There were 107 patients (20 %) with one or more nodules recorded at least by two out of three observers. In 50 patients, the largest nodule measured up to 5 mm, in 53 5–15 mm and in the rest 4 more than 15 mm. Out of the nodules 5 lung cancer were found in follow-up examinations and in other cases malignancy was excluded. The relations between independent variables and lung nodules are given in Table 2. Advancing age of the participant (OR = 1.042/year, 95% CI 1.00–1.085, $p = 0.048$) and dyspnoea as a symptom ($p = 0.014$) were positively associated with the existence of nodules. The latter association persisted even when patients with lung cancer ($n = 5$) were excluded from the analysis. Stepwise methods did not bring essential new information on the relations between variables in Table 2. Nodules ≤ 5 mm were inversely associated with the maximal thickness of pleural plaques (OR = 0.384, 95% CI = 0.169–0.873, $p = 0.022$). Neither the smoking history nor asbestos exposure nor any other background, health-related or radiological variables had significant associations with the nodule findings.

Discussion

Out of several studied background, symptom and radiological variables studied, only participants' age and dyspnoea symptom were significantly associated with

Table 2. Relations between background variables and the existence of lung nodules. The categorical variable status (in brackets) is compared to zero status or to the alternative status.

Variable	OR	95% C.I. for OR		p-value
		Lower	Upper	
Background				
Age	1.042	1.000	1.085	0.048
Sex (male)	1.004	0.164	6.143	0.996
Occupational group (skilled)	0.950	0.604	1.496	0.826
Asbestos exposure years	0.992	0.966	1.019	0.545
Smoking status (all)				0.540
Smoked pack-years	0.985	0.967	1.002	0.088
BMI (kg/m ²)	1.018	0.954	1.085	0.593
Stature (cm)	1.015	0.979	1.052	0.433
S-CRP (mg/l)	1.004	0.965	1.045	0.836
B-ESR (mm)	1.008	0.990	1.025	0.400
Symptoms				
Dyspnoea (all)				0.014
Dyspnoea (mild)	1.973	1.115	3.491	0.020
Dyspnoea (moderate)	1.571	0.826	2.988	0.168
Dyspnoea (severe)	4.404	1.624	11.944	0.004
General condition (all)				0.760
Mucus production (yes)	0.574	0.308	1.069	0.080
Chest pain (yes)	0.604	0.337	1.080	0.089
Prolonged cough (yes)	1.226	0.635	2.368	0.544
Radiological				
Lung fibrosis score	0.987	0.794	1.226	0.903
Ground glass opacities	1.026	0.347	3.033	0.963
Emphysema sum score	1.069	0.930	1.228	0.350
Bronchiectasis	1.771	0.782	4.014	0.171
Pleural plaque thickness	0.803	0.455	1.417	0.449
Pleural plaque extent	1.001	0.995	1.008	0.730
Pleural plaque calcification	1.266	0.924	1.734	0.141

Footnote: OR = odds ratio, C.I. = confidence interval, BMI = body mass index, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate.

the nodules. Nodules ≤ 5 mm were inversely associated with the maximal thickness of pleural plaques.

This series was conducted with single equipment and three experienced radiologists classified the nodules and radiological findings. Technical heterogeneity in CT studies (all performed with the same equipment and image parameters) or the observer factor (same radiologists interpreted all images) did not disturb the current analysis. Most of the subjects were ex- or current smokers and all had been exposed to asbestos, because a high-risk sample for lung cancer was originally selected.

Both background and symptom variables were included in the models, because these variables could easily be explored before CT imaging. Patients may also have previous chest x-rays or HRCT studies available before the intended cancer screening and therefore also some common lung and pleural findings were selected as potential predictors for the existence of nodules.

Advanced age is a well known risk factor for lung cancer and dyspnoea is its symptom and these variables cannot therefore be used to exclude patients from screening trials in order to avoid excessive benign nodules. Ageing increases the probability of exposure to infections with resultant pulmonary scars. The association between the dyspnoea symptom and lung nodules lacks an explanation. Poor inspiration leads to inferior CT image quality, difficult interpretation and probably even to false positive nodule findings. Subjects with lung nodule(s) may also have occult lung diseases other than cancer. The current analyses were controlled for C-reactive protein and erythrocyte sedimentation rate, however.

The inverse association between the maximum pleural thickness and the existence of small nodules is surprising with no plausible biological explanation either. Probably this coexisting pleural pathology has made the detection of small nodules more difficult. Tobacco smoking and asbestos exposure history did not have any significant effect on the existence of nodules. The current findings conflict somewhat with those of Fasola et al., who found no relation between age or asbestos exposure and nodules, but instead found smoking in excess of 25 pack-years as a positive predictor for nodules [10]. Due to the small number of women the potential sex effect could not reliably be explored in this material.

Several other potential predictors for the existence of lung nodules may exist. There may be an observer effect so that some observers, as found in the primary study [6], simply find more nodules than others. It is likely that this effect becomes accentuated when very small lesions are concerned. Whether other health questions or laboratory tests might be more useful to select suitable candidates for lung cancer screening remains to be studied.

A second possible predictor for the existence of nodules is the history of old infections (such as tuberculosis) that may cause permanent scars. Unfortunately, such events were not systematically recorded. This may be one reason for the different prevalence of nodules in CT studies around the world.

Third, CT technology (e.g. slice thickness, current and voltage) may have effects on nodule detection. This matter is especially relevant since it can easily be controlled. According to the Fleischner society nodules ≤ 4 mm in low-risk patients

need no follow-up due to their benign nature [11]. Very small nodules are usually false negative findings. Although not proven, such nodules may be best found with multi-slice CTs by using thin cuts. In a multi-slice CT study with 0.75 mm collimation, 1 mm slice reconstruction and 0.5 mm increment 163 screened persons out of 187 (87 %) had one or more nodules, out of which 75 % fell in the smallest category, 3–5 mm in size [12]. All lung cancer in their series had a diameter of 15 mm or more. The original study, in which this reanalysis is based, was imaged with 10 mm slice thickness and found and at least one nodule among 111 patients (five had cancer) out of 602 (18 %). A check at the Finnish cancer registry 3 years later did not find screen-missed lung cancers [6]. It is therefore questionable whether the new multi-slice CT technology with thin cuts produces benefit when compared to the “old-fashioned” single-slice CT with thicker slices.

Concluding from our results it seems that false positive nodule findings in CT screening cannot be avoided by using the studied variables to assign the study sample. While all the above observer-related, geographical and technical parameters are hard to be included in a single study, a systematic literature review, a meta-analysis of the current literature or a multi-centre study might help to answer these questions.

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Corresponding author:

Tapio Vehmas
Finnish Institute of Occupational Health,
Topeliuksenkatu 41 a A,
FI-00250 Helsinki, Finland.
E-mail: tapio.vehmas@ttl.fi