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CHEST

Lung cancer risk and cancer-specific mortality in subjects undergoing routine imaging test when stratified with and without identified lung nodule on imaging study

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Abstract

Objectives To assess the risk of lung cancer and specific mortality rate in patients with and without solitary pulmonary nodules (SPN) on chest radiograph and CT.

Methods This prospective study included 16,078 patients ≥35 years old (893 of them had an SPN detected with either chest radiograph or CT) and 15,185 without SPN. Patients were followed up for 18 months or until being diagnosed with lung cancer. Risk and mortality lung cancer were calculated in both groups with Poisson regression.

Results In patients with SPN, incidence of lung cancer was 8.3 % (95 % CI 6.0–11.2) on radiograph and 12.4 % (95 % CI 9.3–15.9) on CT. A chronic obstructive pulmonary disease in patients with radiographs (odds ratio 2.62; 95 % CI 1.03, 6.67) and smoking habit (odds ratio 20.63; 95 % CI 3.84, 110.77) in patients with CT were associated with a higher probability of lung cancer. Large nodule size and spiculated edge were associated with lung cancer on both CT and radiograph. Lung cancer-specific mortality was lower in patients with SPN than in those without SPN (1.73/1000 person-years, 95 % CI 1.08–2.88 vs. 2.15/1000 person-years, 95 % CI 1.25–3.96).

Conclusions The risk of lung cancer for patients with SPN is higher in clinical populations than in screening studies. Moreover, patients with SPN showed lower mortality than those without SPN.

Key Points

- *Lung cancer risk is 8 % for SPN detected on routine radiographs.*
- *Lung cancer risk is 12.4 % for SPN detected in routine chest CT.*
- *Smoking, COPD, SPN diameter and edge were predictors of malignancy.*
- *Lung cancer risk of SPN in routine practice seems higher than in screening.*

Keywords Solitary pulmonary nodule (SPN) · Lung neoplasm · General population · Diagnostic imaging · Mortality

Introduction

A solitary pulmonary nodule (SPN), defined as a pulmonary opacity up to 30 mm in diameter, is a frequent finding in imaging chest tests in both asymptomatic and symptomatic patients in clinical practice. Moreover, most nodules are detected when having both chest radiograph and CT [1].

To support clinicians in the management of these findings, the American College of Chest Physicians established several recommendations [2, 3] based on patient and nodule characteristics that are associated with a higher probability of lung cancer. However, most of the available evidence supporting these recommendations is based on screening studies [4, 5], which only include CT performed on a population with high risk of cancer (individuals aged between 50 and 75 years with at least a 30-pack-year smoking history). Moreover, according to previous studies [1], nodules detected in screening studies tend to be

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different from those detected in clinical practice (smaller nodules, prevalence of malignant nodules is much lower, and the growth of the malignant nodule is usually longer). Therefore, the models developed using data from screening studies for predicting the probability of lung cancer in pulmonary nodules could not be applied to other clinical populations [6]. Figures derived from screening trials may not accurately estimate the absolute risk of cancer in clinical populations in whom SPN has been detected. However, we lack data on the risk of lung cancer in clinical populations with SPN.

Furthermore, it will be useful to stratify risk according to the patient and nodule characteristics, for both chest radiograph and CT. In order to complete the information required for appropriate clinical decision-making, beyond knowledge of the risk of cancer for those people with SPN, the information about the risk in the absence of SPN is also relevant. Following a cohort of patients without SPN will enable us to obtain a reference risk with which to compare the risk observed in patients with a detected SPN. The reference cohort is important to assess the need for clinical interventions. If the risk of lung cancer in patients with SPN is equal to the risk in patients without SPNs then no additional clinical work-up is needed. In fact, subjects later diagnosed with lung cancer in screening trials had previously shown a normal imaging test [7].

Our group performed a multicentre cohort study in which we showed in the baseline data [8] the prevalence and associated characteristics of SPN in a general clinical population undergoing chest imaging (chest radiograph and CT). According to these results, the prevalence of SPN was lower than seen in previous screening studies [9]; hence, the probability of cancer and the variables associated in this population could also be different.

Thus, the aim of this study was to assess the risk of developing lung cancer and the lung cancer-specific mortality rate at 18 months in a cohort of patients with and without SPN in chest imaging test (chest radiograph and CT) performed in the routine practice of radiology departments.

Materials and methods

Patients

Prospective cohort study of patients≥35 years referred for thoracic imaging evaluation in two hospitals in the Valencian Community (Spain) were evaluated during the years 2010 and 2011. San Juan Hospital (Alicante) and Dr Peset Hospital (Valencia) are two tertiary centres with a catchment population of 234,424 and 377,780 people, respectively. All patients referred to the radiology department from other hospital services and those referrals from primary health care centres were included. Lung cancer screening is not implemented in our area. All patients with an imaging test (chest radiograph or CT) during the period of study were included. Those patients who first had a chest radiograph where the SPN was detected, and subsequently had a CT, were categorized as having had a chest radiograph. Thus, only those patients who first had a CT were categorized as CT.

Patients previously diagnosed with lung cancer and patients who were not resident in the Valencian Community were excluded.

The baseline data were previously published [8] and show the prevalence of an SPN in the 25,529 consecutive patients included. Here we present the follow-up of 893 patients with SPN and of 15,185 patients without SPN (Fig. 1). We limited the follow-up to 61.6 % of 24,636 patients without SPN detected in an imaging test initially included because of logistic reasons as data were unavailable in one of the study hospitals.

Imaging

Chest radiographies were obtained with the standard technique in digital format (CR Philips at one hospital and CR Agfa the other). The CT technique varied according to the study that was being performed which included non-contrast CT, contrast CT, CT angiography and high resolution CT. Most chest CTs were obtained with a slice thickness of 1.25 mm (CT images were obtained with slice thicknesses of 3 mm or less (2, 1.5 and 1.25 mm) according to the different clinical situations and the equipment used), 120 kVp and variable mAs according to the patient's body weight. The nodules were measured using calipers in the PACS workstations in their largest diameter in the posteroanterior and lateral radiograph. In CT, lung window settings (1550/−600) were used to measure nodule size in the largest diameter. Mediastinal window settings (350/50) were also used to further detect calcification or fat within the nodule.

Institutional review board approval (University Miguel Hernandez Committee Ref DSP-BLL-001-10) was obtained. Given that the study uses only routine data and no additional interventions, informed consent was not sought from the patients.

Data collection

Detection and description of the SPN

Eight expert chest radiologists (all of them with more than 10 years of experience) from both hospitals determined the presence of SPN in the thoracic study of all patients included. They used the glossary for chest radiology to describe SPN characteristics [9], which defines SPN as a pulmonary opacity up to 30 mm in diameter. We limited our study to nodules between 3 and 30 mm. Intrapulmonary lymph nodes were excluded. Pseudolesions, when detected (nipples, warts, rib

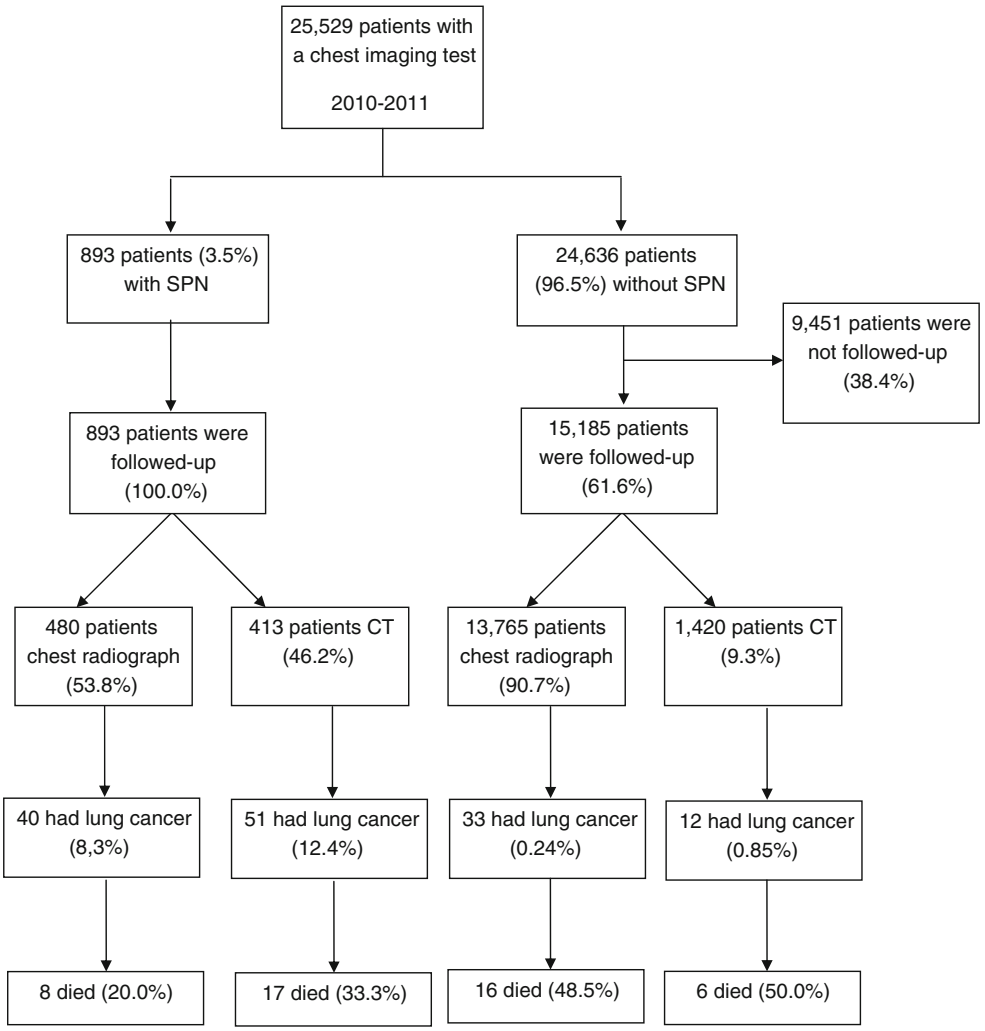

Fig. 1 Flow diagram showing the follow-up of the study participants

fractures, external objects, hair and so on), were excluded from our study. In chest radiographs, nipple markers were used to differentiate true nodules from the nipples. Inter- and intraobserver agreement were examined through a validation study previously published [8].

In patients with SPN, the radiologists described nodule characteristics in a form predesigned by the researchers consisting in (a) size, expressed in millimetres, and also expressed as mean (SD) in diameter; (b) nodule shape, smooth or irregular (lobular or speculated); (c) location, upper, middle or lower lobes; and (d) for those patients who underwent a CT, nodule appearance (solid, partially solid, ground glass or calcified). This form was completed by the radiologists simultaneously with the radiology report, in order to standardize the information.

Patients' characteristics

In all patients, selected variables were collected from the radiological register: type of test performed (CT or radiograph); department that ordered the test; care setting (inpatient or outpatient); reason for test (respiratory, non-respiratory, preoperative, neoplasm or not specified) and patient characteristics (age, sex).

In the 893 patients with SPN, we collected extra information from the medical records: smoking habit (non-smokers, current or former smokers), previous neoplasm, presence of a respiratory disease (and specifically, the presence of COPD) and respiratory symptoms (haemoptysis, dyspnoea, cough).

Diagnostic work-up

All participants were followed up for 18 months from their entry in the study:

- The 893 patients presenting with SPN were followed up through the revision of their medical records including the ascertainment of lung cancer diagnosis and the specific death.

- To determine the frequency of lung cancer among the 15,185 patients not presenting with SPN, we linked our database with the Hospital Minimum Basic Data Set (MBDS), which registers all clinical interventions performed and diagnosis in patients who have been admitted to the hospital. In those patients where a confirmed diagnosis or suspicion of lung or thoracic cancer appeared in the MBDS, medical records were cross-checked to confirm the diagnosis of lung cancer, the exact date of the diagnosis and the specific cause of death.

The lung diagnosis was made according to the established clinical guidelines [10], by histopathological examination of resection specimens or cytopathological examination of needle-aspiration biopsy samples. There were some cases where no histology data were available, but the patients had radiotherapy for high-risk PET-positive nodules. There were 11 such cases out of 91 (four cases in patients who had a radiograph and seven cases in those having a CT), which were diagnosed with lung cancer. Lung cancer-specific mortality during the follow-up period was collected from medical records.

Statistical analysis

All data was computerized and checked to discard errors. Statistical precision was determined through the calculation of 95 % confidence intervals using the appropriate method according to the type of measurement and the available data. All analyses were carried out with the statistical programme Stata 8 (Stata Corp., College Station, Texas, USA).

Descriptive analysis was carried out using frequency distribution or median and interquartile range (IQR) when appropriate. Age was transformed in quartiles because the equal variance and normal distribution were rejected.

We estimated the risk of lung cancer during the 18-month follow-up period for both patients with and without SPN and the confidence intervals. Multivariable logistic-regression models were prepared to estimate the risk of lung cancer associated with sociodemographic and clinical variables and nodule characteristics (the model only included predictors that reached statistical significance; $p<0.05$). Multivariate Poisson regression was used to estimate the impact of SPN on lung cancer mortality (mortality rates were assessed from the lung cancer diagnosis date until the date of death). In multivariate analysis, odds ratio (OR) of nodule size shows the risk for each increase of 1 mm in size. Likelihood ratio tests were used to derive p values.

Results

Patients with SPN in chest radiograph or CT (893 patients)

Results on risk of lung cancer are presented first for SPNs detected through chest radiograph and then for those patients whose SPN was detected through CT.

Chest radiograph

Patients' characteristics (Table 1) Forty of the 480 patient with SPN detected through chest radiograph were diagnosed with lung cancer (8.3 %; 95 % CI 6.0, 11.2). Subjects aged 50–60 years old showed the highest risk, but the difference with other age groups of patients was not significant. Current and former smokers had a greater risk of lung cancer than non-smokers (12.7 %; 95 % CI 9.0, 17.3 and 2.0 %; 95 % CI 0.2, 7.1, respectively; $p<0.001$). Lung cancer was more frequently observed among patients with a diagnosis of COPD than among patients without COPD (13.2 %; 95 % CI 7.8, 20.6 and 6.4 %; 95 % CI 4.1, 9.5).

Nodule characteristics (Tables 2 and 3)
Patients with a spiculated nodule had a higher risk of lung cancer than patients with other types of nodule edges (44.0 %; 95 % CI 30.0, 58.7, $p<0.001$).

The mean nodule diameter was 11.6 mm (SD 6.7). The mean diameter of the nodules detected in patients who were diagnosed with lung cancer was higher than in those not diagnosed with lung cancer (mean 20.2, SD 7.5 and mean 10.7, SD 6.1, respectively, $p<0.001$). The relationship between nodule size and risk of cancer is shown in Table 3. Patients with nodules between 3 and 4 mm did not develop lung cancer during the follow-up period; the risk of lung cancer in patients with nodules between 4 and 8 mm was 1.5 % (95 % CI 0.2, 5.3) and in patients with nodules between 8 and 12 mm it was 3.4 % (95 % CI 1.1, 7.7). There was a relevant increase of lung cancer risk in nodules larger than 8 mm (P for trend <0.001) (Fig. 2).

Multivariate analysis In multivariable analysis, patients diagnosed with COPD had a higher risk of lung cancer (OR 2.62, 95 % CI 1.03, 6.67, $p=0.044$). The risk of cancer was higher in smokers and former smokers than in non-smokers although the association was not significant (OR 4.05, 95 % CI 0.82, 20.01, $p=0.086$). Moreover, patients with spiculated nodules were more likely to develop lung cancer than patients with smooth border nodules (OR 11.69, 95 % CI 2.20, 62.04, $p=0.004$). Nodule size was associated with a higher risk of lung cancer (OR 1.13, 95 % CI 1.07, 1.20, $p<0.001$) (data not shown).

Table 1 Frequency of lung cancer and its distribution according to patients' characteristics in the 893 patients with SPN, for both chest radiograph and CT

Variables *N* (%) (95 % CI)	Chest radiograph				CT			
	Total 480 (100)	No cancer 440 (91.7)	Cancer 40 (8.3) (6.0–11.2)	*p*	Total 413 (100)	No cancer 362 (87.7)	Cancer 51 (12.4) (9.3–15.9)	*p*
Gender				0.078				0.002
Male	285 (100)	256 (89.8)	29 (10.2) (6.9–14.3)		261 (100)	219 (83.9)	42 (16.1) (11.9–21.1)	
Female	195 (100)	184 (94.4)	11 (5.6) (2.8–9.9)		152 (100)	143 (94.1)	9 (5.9) (2.7–10.9)	
Age (years)				0.211				0.936
<50	76 (100)	73 (96.1)	3 (3.9) (0.8–11.1)		50 (100)	45 (90.0)	5 (10.0) (3.3–21.8)	
50–59	85 (100)	74 (87.1)	11 (12.9) (6.6–22.0)		87 (100)	76 (87.4)	11 (12.6) (6.5–21.5)	
60–69	133 (100)	121 (91.0)	12 (9.0) (4.7–10.2)		126 (100)	111 (88.1)	15 (11.9) (6.8–18.9)	
≥70	186 (100)	172 (92.5)	14 (7.5) (4.2–12.3)		150(100)	130 (86.7)	20 (13.3) (8.3–19.8)	
Setting				0.044				0.019
Inpatient	51 (100)	43 (84.3)	8 (15.7) (7.0–28.6)		86 (100)	69 (80.2)	17 (19.8) (12.0–29.8)	
Outpatient	429 (100)	397 (92.5)	32 (7.5) (5.2–10.4)		327 (100)	293 (89.6)	34 (10.4) (7.3–14.2)	
Reason for requesting imaging test				0.467				0.699
Respiratory	86 (100)	76 (88.4)	10 (11.6) (5.7–20.3)		79 (100)	66 (83.5)	13 (16.5) (9.1–26.5)	
Non-respiratory	135 (100)	125 (92.6)	10 (7.4) ()3.6–13.2)		86 (100)	75 (87.2)	11 (12.8) (6.6–21.7)	
Extrapulmonary neoplasm	102 (100)	91 (89.2)	11 (10.8) (5.5–18.5)		108 (100)	95 (88.0)	13 (12.0) (6.6–19.7)	
Preoperative	50 (100)	47 (94.0)	3 (6.0) (1.3–16.5)		51 (100)	45 (88.2)	6 (11.8) (4.4–23.9)	
Not available	107 (100)	101 (94.4)	6 (5.6) (2.1–11.8)		89 (100)	81 (91.0)	8 (9.0) (4.0–16.9)	
Smoking habit				0.000				0.000
No	99 (100)	97 (98.0)	2 (2.0) (0.2–7.1)		92 (100)	90 (97.8)	2 (2.2) (0.3–7.6)	
Former and current	275 (100)	240 (87.3)	35 (12.7) (9.0–17.3)		252 (100)	203 (80.6)	49 (19.4) (14.7–24.9)	
Not specified	106 (100)	103 (97.2)	3 (2.8) (0.6–8.0)		69 (100)	69 (100.00)	0 (0.00) (–)	
Previous malignancy				0.285				0.914
No	313 (100)	290 (92.7)	23 (7.3) (4.7–10.8)		286 (100)	250 (87.4)	36 (12.6) (9.0–17.0)	
Yes	167 (100)	150 (89.8)	17 (10.2) (6.0–15.8)		126 (100)	111 (88.1)	15 (11.9) (6.8–18.9)	
Not available	–	–	–		1 (100)	1 (100)	0 (0.00) (–)	
COPD				0.000				0.006
No	358 (100)	335 (93.6)	23 (6.4) (4.1–9.5)		292 (100)	262 (89.73)	30 (10.27) (7.0–14.3)	
Yes	121 (100)	105 (86.8)	16 (13.2) (7.8–20.6)		120 (100)	100 (83.3)	20 (16.7) (10.5–24.5)	
Not available	1 (100)	0 (0.00)	1 (100.00) (–)		1 (100)	0 (0.00)	1 (100.00) (–)	
Respiratory symptoms				0.719				0.823
No	404 (100)	370 (91.6)	34 (8.4) (5.9–11.6)		344 (100)	301 (87.5)	43 (12.5) (9.2–16.5)	
Yes	52 (100)	47 (90.4)	5 (9.6) (3.2–21.0)		57 (100)	51 (89.5)	6 (10.5) (4.4–23.9)	
Not available	24 (100)	23 (95.8)	1 (4.2) (0.1–21.1)		12 (100)	10 (83.3)	2 (16.7) (2.1–41.4)	

Table 2 Frequency of lung cancer according to the SPN characteristics in the 893 patients with SPN, for both chest radiograph and CT

Variables *N* (%) (95 % CI)	Chest radiograph				CT			
	Total 480 (100)	No cancer 440 (91.7)	Cancer 40 (8.3) (6.0–11.2)	*p*	Total 413 (100)	No cancer 362 (87.7)	Cancer 51 (12.4) (9.3–15.9)	*p*
Diameter (mm), mean (SD)	11.6 (6.7)	10.7 (6.1)	20.2 (7.5)	0.000	10.5 (6.8)	9.43 (6.1)	17.6 (7.7)	0.000
Localization				0.018				0.035
Upper lobe	263 (100)	232 (88.2)	31 (11.8) (8.2–16.3)		200 (100)	169 (84.5)	31 (15.5) (10.8–21.3)	
Middle lobe	38 (100)	38 (100.0)	0 (0.00) (–)		50 (100)	49 (98.0)	1 (2.0) (0.05–10.6)	
Lower lobe	161 (100)	153 (95.0)	8 (5.0) (2.2–9.6)		150 (100)	131 (87.3)	19 (12.7) (7.8–19.1)	
Not available	18 (100)	17 (94.4)	1 (5.6) (0.1–27.3)		13 (100)	13 (100.0)	0 (0.0) (–)	
Border				0.000				0.000
Smooth border or well-defined border	127 (100)	125 (98.4)	2 (1.6) (0.2–5.6)		88 (100)	83 (94.3)	5 (5.7) (1.9–12.8)	
Irregular or not well defined	145 (100)	111 (76.5)	34 (23.5) (16.8–31.2)		152 (100)	116 (76.3)	36 (23.7) (17.2–31.3)	
Spiculation	50 (100)	28 (56.0)	22 (44.0) (30.0–58.7)		67 (100)	41 (61.2)	26 (38.8) (27.1–51.5)	
Lobulation	33 (100)	28 (84.8)	5 (15.2) (5.1–31.9)		41 (100)	34 (82.9)	7 (17.1) (8.7–37.9)	
Other irregular	62 (100)	55 (88.7)	7 (11.3) (4.7–21.9)		44 (100)	41 (93.2)	3 (6.8) (1.4–18.7)	
Not available	208 (100)	204 (98.1)	4 (1.9) (0.5–4.9)		173 (100)	163 (94.2)	10 (5.8) (2.8–10.4)	
Opacity on CT								0.195
Solid					225 (100)	202 (89.8)	23 (10.2) (6.6–14.9)	
Ground glass					14 (100)	12 (85.7)	2 (14.3) (1.8–42.8)	
Partly solid					16 (100)	16 (100.0)	0 (0.0) (–)	
Calcification					25 (100)	20 (80.0)	5 (20.0) (6.8–40.7)	
Not available					133 (100)	112 (84.2)	21 (15.8) (10.0–23.2)	

Table 3 Lung cancer risk according to nodule size in the 893 patients with SPN, for both chest radiograph and CT

Variables *N* (%) (95 % CI)	Chest radiograph				CT			
	Total 480 (100)	No cancer 442 (92.1)	Cancer 38 (7.9) (5.7–10.7)	*p*	Total 413 (100)	No cancer 361 (87.4)	Cancer 52 (12.6) (9.5–16.2)	*p*
Diameter (mm)				0.000				0.000
3–4	34 (100)	34 (100.00)	0 (0.00) (–)		47 (100)	47 (100.0)	0 (0.00) (–)	
>4–8	134 (100)	132 (98.5)	2 (1.5) (0.2–5.3)		165 (100)	157 (95.2)	8 (4.8) (2.1–9.3)	
>8–12	149 (100)	144 (96.6)	5 (3.4) (1.1–7.7)		76 (100)	70 (92.1)	6 (7.9) (3.0–16.4)	
>12–16	59 (100)	51 (86.4)	8 (13.6) (6.0–25.0)		41 (100)	32 (78.1)	9 (21.9) (10.6–37.6)	
>16–20	21 (100)	17 (81.0)	4 (19.0) (5.5–41.9)		28 (100)	20 (71.4)	8 (28.6) (13.2–48.7)	
>20–24	15 (100)	11 (73.3)	4 (26.7) (7.8–55.1)		16 (100)	9 (56.3)	7 (43.7) (19.8–70.11)	
>24–28	30 (100)	20 (66.7)	10 (33.3) (17.3–52.8)		19 (100)	10 (52.6)	9 (47.4) (24.4–71.1)	
>28	13 (100)	8 (61.5)	5 (38.5) (13.9–68.4)		8 (100)	5 (62.5)	3 (37.5) (8.5–75.5)	
Not available	25 (100)	23 (92.0)	2 (8.0) (1.0–26.0)		13 (100)	12 (92.3)	1 (7.7) (0.2–36.0)	

CT

Patients' characteristics (Table 1) Fifty-one out of 413 patients with SPN detected by CT were diagnosed with lung cancer (12.4 %, 95 % CI 9.3, 15.9). The risk was greater in men than in women (16.1 %; 95 % CI 11.9, 21.1 and 5.9 %; 95 % CI 2.7, 10.9, respectively, $p=0.002$). Current or former smokers had a greater risk of lung cancer than non-smokers (19.4 %; 95 % CI 14.7, 24.9 and 2.2 %; 95 % CI 0.3, 7.6, respectively, $p<0.001$). Risk of lung cancer was higher in patients with COPD than in patients without it (16.7 %; 95 % CI 10.5, 24.5 and 10.3; 95 % CI 7.0, 14.3, respectively, $p=0.006$).

Nodule characteristics (Tables 2 and 3) Patients with a spiculated nodule had a higher frequency of lung cancer than patients with other types of nodule edges (38.8 %, 95 % CI 27, 51.5, $p<0.001$).

The mean nodule diameter was 10.5 mm (SD 6.8) and was greater among patients with lung cancer compared to those without lung cancer (mean 17.6, SD 7.7 and mean 9.4, SD 6.1, respectively, $p<0.001$). The relationship between nodule size and risk of cancer is shown in Table 3. Patients with nodules between 3 and 4 mm did not develop lung cancer during the follow-up period; the frequency of lung cancer in patients with nodules between 4 and 8 mm was 4.8 % (95 % CI 2.1, 9.3) and in patients with nodules between 8 and 12 mm it was 7.9 % (95 % CI 3.0, 16.4). The frequency of lung cancer progressively increased when nodule size was over 8 mm (*P* for trend <0.001) (Fig. 2).

Multivariate analysis Results in patients whose SPN was detected by CT showed that the risk of cancer was higher in smokers and former smokers than in non-smokers (OR 20.63; 95 % CI 3.84, 110.77, $p<0.001$). Nodule size was associated with a higher risk of lung cancer (OR 1.18; 95 % CI 1.11, 1.25, $p<0.001$). Patients with spiculated nodules showed a nearly significant association with lung cancer incidence in comparison with patients with smooth border nodules (OR 3.37, 95 % CI 0.94, 12.14, $p=0.063$) (data not shown).

Patients without SPN in chest radiograph or CT (15,185 patients)

Out of 24,636 patients without SPN detected in the imaging test, 15,185 (61.6 %) patients were included in the follow-up; there were no differences between those patients included in the follow-up (15,185; 61.6 %) and those who were not (9451; 38.4 %): 7617 (50.16 %) men and 7568 (49.84) women and the median age was 67 years (IQR 54, 88; range 35–104). Most patients had chest radiograph (13,765, 90.65 %) and 1420 (9.35 %) had a CT.

During the follow-up period, 45 (0.30 %) patients developed lung cancer: the risk of lung cancer in patients who first underwent a chest radiograph was 0.24 % (95 % CI 0.17, 0.34) and 0.85 % (95 % CI 0.44, 1.47) in those who first had a CT.

Time to diagnosis and lung cancer-specific mortality

Time to diagnosis varied according to the presence or absence of SPN in the imaging test (Fig. 3). In patients with SPN found on chest radiograph the median time until the lung cancer diagnosis was 46.5 days (IQR 20, 144); in those without SPN after chest radiograph, the median time was 368 days (IQR 83, 470).

In patients who were found to have SPN in CT, the median time until the lung cancer diagnosis was 28 days (IQR 12, 96.5); in patients without SPN the median time was 355.5 days (IQR 101, 444.8).

Out of 91 patients with SPN and a diagnosis of lung cancer, 25 (27.5 %, 95 % CI 19.36, 37.41) died. Of the 45 patients without SPN and a diagnosis of lung cancer, 22 (48.89, 95 % CI 34.96, 63.00) died. The lung cancer-specific mortality rate was lower in patients with SPN than in those without (1.733/1000 person-years; 95 % CI 1.077, 2.788 vs 2.145/1000 person-years; 95 % CI 1.245, 3.965; $p<0.001$).

Discussion

This multicentre prospective study shows a considerably high risk of lung cancer in patients having a chest SPN detected by radiograph (8.3 %) or CT (12.4 %), during an 18-month follow-up. In comparison with our study, screening studies have shown a lower frequency of cancer in patients with SPN (PanCan study 1.46 % and BCCA cohort 0.84 %, during 3.1 and 8.6 years of follow-up, respectively [8]). The National Lung Cancer Screening Trial [4] also showed a lower cancer probability: 2.4 % for CT and 4.4 % for chest radiography, despite including a high-risk population, some patients with more than one nodule and a longer follow-up period (5 years). If we limit our data to those patients between 55 and 89 years old (patients with similar age to those patients included in screening studies), the risk of lung cancer is still higher in our study than in screening studies (31/311, 9.9 % in radiograph and 38/295, 12.8 % in CT).

The baseline data of this study [8] showed a lower prevalence of SPN than in previous screening studies for both patients having CT and chest radiograph (for CT, 73.7 % in the PanCan Study [3] and 27.9 % in the National Lung Screening Trial [4] vs 17.0 % in our study; and for chest radiography, 6.2 % in the National Lung Screening Trial [4] vs 2.1 % in our study). Thus, despite the lower prevalence of SPN, this study shows a higher frequency of malignancy. Our study was carried out in a routine clinical population undergoing imaging tests for any reason, including both symptomatic and asymptomatic patients. The inclusion of symptomatic patients is the likely explanation of why the risk of lung cancer we observed was higher than that observed in the screening studies, where only asymptomatic people are included. Although patients with previous malignancy were also included in our study, there were no differences in the risk of lung cancer between these patients and others with different levels of diagnostic suspicion.

In contrast, the probability of cancer in our study was lower than shown in previous clinic-based studies [11, 12], where the percentage of malignancy was more than 50 %, but these observational studies included only CT as an imaging test, retrospective data and had a small sample size.

Adjusting for the different related variables, COPD, nodule size and spiculated edge were associated with a high risk of lung cancer in those patients presenting with an SPN in chest radiographs. In patients showing SPN in CT, the risk of cancer was associated with smoking habit and nodule size, and the spiculated edge was nearly significant. Previous studies showed a high risk of lung cancer according to sex, nodule size, nodule location and presence of spiculation; however, these screening studies only included smokers. Nevertheless, we found no relationship between sex and lung cancer in the multivariate analysis. The higher risk observed in men is explained by smoking habit and characteristics of the nodules detected; once taken into account in multivariate analyses, sex is no longer associated with the risk of cancer.

In the present study a higher risk of lung cancer was detected in patients with larger nodules (over 4 mm). In our study, a linear relationship was found between nodule size and risk of lung cancer. In contrast, in previous studies such as the National Lung Cancer Screening Trial [3], the highest risk of cancer for patients undergoing either x-ray or CT was found in nodules between 4 and 10 mm in size. Some authors argue that the nodule size cannot be used as a risk predictor factor because it may vary depending on the appearance of the nodule (solid, partly solid, etc.) [4]; thus, the nodule morphology could be a more useful parameter. However, although pure ground-glass opacity nodules are frequently associated with malignancy [13], we did not find differences between the types of nodules detected. Twenty per cent of the partly solid and 14.3 % of the ground-glass nodules progressed to lung cancer, but the difference was not significant. Nevertheless, the results could not be conclusive because of the small sample size.

This is the first study to assess the risk of lung cancer for patients without SPN for both chest radiograph and CT in a clinical setting. Only 0.24 % of the patients that did not show an SPN on chest radiograph and 0.85 % of the patients without an abnormality in CT developed lung cancer in the following 18 months. Therefore, the absence of an SPN in imaging tests

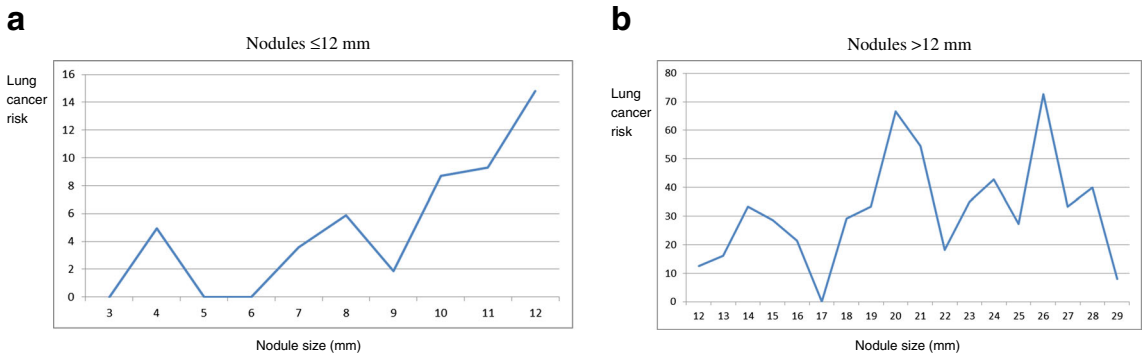

Fig. 2 Relationship between nodule size (**a** ≤12 mm, **b** >12 mm) and lung cancer risk for both chest radiograph and CT

has a very low risk of cancer. However, in contrast with patients showing SPN in the imaging test, the time to diagnoses was longer and the mortality higher. Thus, the presence of SPN in an imaging test could be a positive predictor in the survival of patients; however, longer follow-up is needed to establish which part of this better survival could be attributed to timely diagnosis and earlier treatment or to overdiagnosis.

We have to address several limitations. The lack of electronic medical records meant that we were unable to retrieve complete information for a relatively high proportion of cases in some categories. Incomplete information in some patients' data such as smoking habit, or respiratory symptoms, could lead to information bias. We have dealt with these missing values as an additional category. We acknowledge that missing values could bias results if missing data is related to other variables. However, there were no significant differences with respect to other patient characteristics (such as age, sex, diagnostic test, reason for test or nodule characteristics) between patients with the available data and those without. We limited follow-up to 18 months; hence, we could have underestimated the risk of cancer because some lesions are slow growing. We assume that the standard recommendations to follow up the lesions are a minimum of 3 years; however, these preliminary results are relevant for the high risk of cancer presented in this short period of time. We only included data of patients without SPN from one of the two hospitals included in the study. This centre has an electronic medical record, which facilitates the collection of information. This fact might have introduced a selection bias in the population studied in the two participating hospitals. However, there were no statistical differences between patients included in the follow-up and those who were not according to the main variables included in the study. To determine the frequency of lung cancer among patients without SPN in the imaging study, we linked our database with the MBDS, restricted to hospitalized patients. However, we do not think our data are affected by this, because patients who are going to have a biopsy are usually admitted to hospital. Some of the patients with SPN might have undergone evaluation in other health centres, leading to an underestimation of lung cancer diagnosis. However, we were able to check the diagnostic procedure carried out and the outcome in each patient included in the study during the whole follow-up period. On the other hand, when a patient decided to move to a different medical centre or area, he/she usually asks for his/her medical data and this process is documented in his/her medical record. Moreover, both hospitals included in the study are public tertiary centres, where all health care is free of charge and designated as the reference hospital in their areas.

Our population reflects a general clinical setting, including symptomatic patients (more of them were initially studied with CT) and asymptomatic patients; thus, our results could be applied to other similar clinical settings. Future research is focused on the development and validation in a different cohort of patients of models for predicting the probability of lung cancer in pulmonary nodules based on the variables included in this study. Moreover, we are evaluating how potentially malignant pulmonary nodules are evaluated in a clinical setting, in order to assess the benefit–risk of the nodule management.

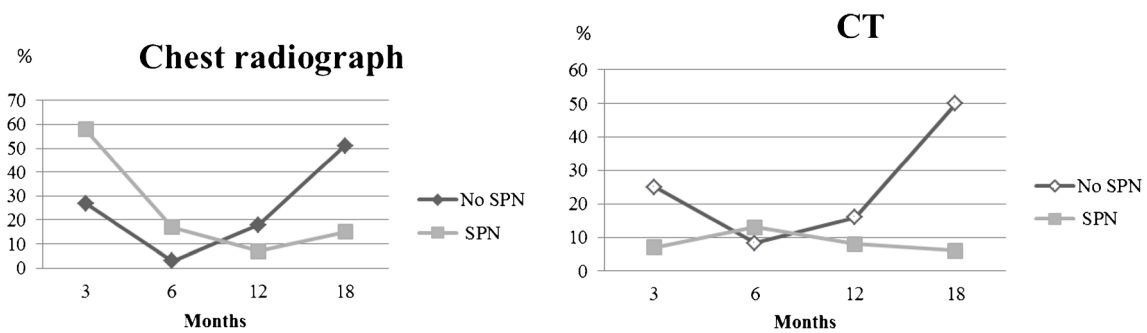

Fig. 3 Time to diagnosis of lung cancer in patients with SPN detected in an imaging test and without SPN, for both chest radiograph (**a**) and CT (**b**)

In conclusion, we showed a high risk of lung cancer in patients with SPN detected when undergoing thoracic imaging tests for any reason in a routine clinical population. Size and shape of the nodule, COPD and smoking habit were the only predictors of lung cancer among patients with SPN. Considering the different time to diagnoses and mortality in patients with and without SPN, the presence of SPN in an imaging test could be a predictor of survival. Given the differences in the risk of lung cancer and the associated variables between our results and those from screening studies, clinicians should value the presence of SPN in an imaging study according to the positive predictive value observed in a routine clinical care.

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Institutional review board approval was obtained: the ethical committee of the Miguel Hernandez University approved the study protocol (ref. DSP-BLL-001-10). Written informed consent was not required for this study because only secondary data were included. Methodology: cohort study, multicenter study

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