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Original Article

Lung Cancer Screening: Fourteen Year Experience of the Pamplona Early Detection Program (P-IELCAP)[☆]

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ABSTRACT

Introduction and objectives: European experience regarding lung cancer screening using low-dose chest CT (LDCT) is available. However, there is limited data on the Spanish experience in this matter. Our aim is to present the results from the longest ongoing screening program in Spain.
Methodology: The Pamplona International Early Lung Cancer Detection Program (P-IELCAP) is actively screening participants for lung cancer using LDCT since the year 2000 following the IELCAP protocol, including spirometric assessments. Men and women, ≥40 years of age, current or former smokers with a tobacco history of ≥10 pack-years are included. Results are compared to those from other European trials.
Results: A total of 2989 participants were screened until March 2014 (73% male). A median of 2 (IQR 1–3) annual screening rounds were performed. Sixty lung cancers were detected in 53 participants (73% in Stage I). Adenocarcinoma was the most frequent. The lung cancer prevalence and incidence proportion was 1.0% and 1.4%, respectively, with an annual detection rate of 0.41. The estimated 10-year survival rate among individuals with lung cancer was 70%. Chronic obstructive pulmonary disease and emphysema are important lung cancer predictors.
Conclusions: The experience in Spain's longest lung cancer screening program is comparable to what has been described in the rest of Europe, and confirms the feasibility and efficacy of lung cancer screening using LDCT.

Cribado de cáncer de pulmón: catorce años de experiencia del Programa Internacional de Detección Precoz de Cáncer de Pulmón con TBDR de Pamplona (P-IELCAP)

RESUMEN

Introducción y objetivos: La experiencia europea en relación con el cribado de cáncer de pulmón con tomografía de baja dosis de radiación (TBDR) es amplia. Sin embargo, la evidencia sobre la experiencia en España es limitada. Nuestro objetivo es presentar los resultados del programa de cribado de cáncer de pulmón más largo de España.

Métodos: El Programa Internacional de Detección Precoz de Cáncer de Pulmón con TBDR de Pamplona (P-IELCAP) viene reclutando individuos de manera activa desde el año 2000 siguiendo el protocolo IELCAP. Se incluyen individuos ≥ 40 años de edad, fumadores o ex fumadores (consumo acumulado ≥ 10 paquetes-año). Los resultados se comparan con los de otros estudios europeos.

Resultados: Un total de 2.989 participantes fueron reclutados hasta marzo de 2014 (73% varones), realizando una mediana de 2 (IQR 1-3) rondas de cribado por individuo. Se detectaron 60 cánceres de pulmón en 53 participantes (73% en estadio I). Adenocarcinoma fue el tipo histológico más frecuente. La proporción de prevalencia e incidencia de cáncer de pulmón fue del 1,0 y del 1,4%, respectivamente, con una tasa de detección anual de 0,41. La tasa de supervivencia a 10 años de los pacientes con cáncer de pulmón fue del 70%. La enfermedad pulmonar obstructiva crónica y el enfisema son importantes factores de riesgo para desarrollar cáncer de pulmón.

Conclusiones: La experiencia del programa de cribado de cáncer de pulmón más largo de España es comparable con lo descrito en el resto de Europa y confirma la viabilidad y la eficacia del cribado mediante TBDR.

Introduction

Lung cancer screening studies using low-dose chest computed tomography (LDCT) began almost two decades ago, when initial results suggested that screening was useful in detecting lung cancer at early stages.[1–4] The International Early Lung Cancer Action Program (I-ELCAP), a single arm trial that screened more than 30,000 individuals with LDCT, found that 85% of their lung cancer cases were in clinical stage I, with an estimated 10-year survival rate of 88%.[5] Subsequently, results from the randomized National Lung Screening Trial (NLST) showed a significant reduction in lung cancer-specific mortality in the LDCT screening arm.[6] These studies encouraged the United States Preventive Task Force (USPSTF) to recommend LDCT screening for lung cancer.[7]

Many studies have analyzed the results of lung cancer screening in Europe; initial results from a German cohort were published in 2002, and in 2012 the LUSI (Lung Cancer Screening Intervention trial) study was presented.[2,8] Other European countries, such as the Netherlands,[9] Belgium,[9] France,[10] Denmark,[11] and Italy,[12,13] have also been active in this field with their respective trials [NELSON (NEderlands Leuvens longkanker Screenings ONderzoek),[9] DEPISCAN,[10] DLCST (Danish Lung Cancer Screening Trial),[11] DANTE (Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays)[12] and ITALUNG[13]].

Until recently, when the Institute of Oncology of Valencia (IVO) became an I-ELCAP member site and started recruiting participants into this ongoing lung cancer screening program, experience in Spain was limited to a single center in Pamplona, also part of I-ELCAP,[5] in which lung cancer screening has been ongoing since 2000. Preliminary data from the early years of screening have been described previously, although they focused on the value of emphysema and chronic obstructive pulmonary disease (COPD) as risk factors for lung cancer and the use of F-18-fluorodeoxyglucose positron emission tomography (PET).[14,15] More than a decade later, the number of patients screened and cancers diagnosed has doubled, prompting us to reanalyze the data from our entire cohort to describe the results of the longest ongoing lung cancer screening program in Spain.

Materials and Methods

Participants

Study subjects are participants enrolled in the Pamplona International Early Lung Cancer Detection Program (P-IELCAP), part of the I-ELCAP,[5] between September 2000 and April 2014. Details regarding individual enrollment, LDCT characteristics, lung cancer detection protocol, emphysema and airway obstruction assessments have been described elsewhere.[14,16] Briefly, we included

men and women, 40 years of age or older, who were current or former smokers with a smoking history of ≥10 pack-years, with no lung cancer symptoms. In contrast to our previous study, we expanded our baseline data by including smoking status (current or former smoker), body mass index (BMI, calculated by dividing subjects' weight in kilograms by the square of their height in meters), family history of lung cancer (present or absent), and time since smoking cessation in years.

LDCT and spirometry were performed at baseline and at a follow-up visit up to 1 year later, according to the established I-ELCAP protocol.[16] Participants with no nodules or with non-calcified nodules <5 mm on LDCT were invited to an annual repeat screening. Positive results (non-calcified nodule ≥5 mm) required further study, including any of the following, depending on nodule size and characteristics: PET, antibiotics, three-month repeat LDCT or percutaneous needle or surgical biopsy.[16] Individuals whose tests did not suggest or confirm malignancy were invited to continue annual screening. Participants diagnosed with lung cancer were also followed up annually. There was no limit on the number of screening rounds. Emphysema was measured qualitatively and airway obstruction was determined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations (forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) ratio <70%).[17] The University of Navarra's ethics committee approved the study protocol and all subjects signed an informed consent prior to enrollment.

Data Analysis

Quantitative data with normal distribution is presented as mean±standard deviation (SD), and non-normal data is presented as median and the interquartile range (IQR). Categorical data were described using relative frequencies. Details of measures of inter-reader reliability and the κ coefficient for visual assessment of emphysema by LDCT are described in our previous study.[14]

Lung cancer prevalence and incidence rates were calculated according to whether the diagnosis was based on the results of the baseline evaluation or on one of the follow-up screening rounds, respectively. Calculations were based on the number of individuals diagnosed with lung cancer. The incidence rate divided by the median follow-up time yielded the annual lung cancer detection rate, and the inverse of this rate estimated the number of people who needed to be screened in 1 year to detect 1 case of lung cancer (NND).[18]

The Cox proportional hazards method was used to assess the risk of developing lung cancer using several variables, with special emphasis on COPD and emphysema. Variables used for adjustment in the multivariate analysis included age, sex, pack-years of

smoking, BMI, family history of lung cancer and smoking status at baseline.

Medical records were reviewed to obtain mortality data on patients with lung cancer and a Kaplan–Meier survival curve was constructed.

A P value of less than .05 was considered statistically significant, and all statistical analyses were performed using SPSS Statistics 20.0 for Windows (IBM, Chicago, IL).

Results

A total of 2989 individuals were screened, and their baseline characteristics are shown in Table 1. Participants were predominantly men (73%) with a median age of 55 (49–62). Most were current smokers with a history of 32 (20–46) pack-years. Twenty-five percent of the screened population had COPD, 93% with mild or moderate disease (GOLD grades 1 or 2), and 24% had evidence of emphysema on the baseline LDCT. More than half of the sample underwent 2 or more screening rounds. There were no significant differences in baseline characteristics between participants who underwent 1, 2 or more rounds except for COPD severity distribution (Table 1). Participants who complied with screening had a median follow-up of 42 (22–73) months and 3 (2–5) screening rounds.

A total of 53 participants were diagnosed with lung cancer: 29 on the first screening round (1.0% prevalence), and 24 on subsequent rounds (1.4% incidence). After the baseline round of screening, the annual lung cancer detection rate was 0.41, and the number of individuals needed to be screened in 1 year in order to detect 1 lung cancer was 245. Two synchronous tumors were found in one participant at his eighth annual screening round (squamous cell carcinoma and adenocarcinoma), and 6 individuals with prevalent lung cancers had a new lung cancer diagnosis in one of the follow-up visits (metachronous tumor). The median difference between the two diagnoses was 48 (34–75) months. All of the metachronous tumors had the same histologic pattern and disease stage, except for 2, where more advanced disease was found on the second cancer. Based on the 60 available samples, the great majority of lung cancers were non-small cell lung carcinomas (NSCLC, 92%), where 55% were adenocarcinomas, followed by squamous cell carcinomas (22%). More than one-third of the identified adenocarcinomas had a bronchioloalveolar component. Eighty-two percent were early stage lung cancers (stages I and II) and 7% were in stage IV. Four

of the 5 small cell lung carcinomas (SCLC) were extensive disease. Table 2 shows the lung cancer characteristics of the entire cohort and stratified by screening round.

Differences between individuals with and without lung cancer are shown in Table 3. Those with lung cancer were significantly older (5-year difference, P<.001), had a greater smoking history (20 pack-year difference, P<.001), and a significantly higher proportion of airway obstruction and emphysema. Worse lung function, expressed as a lower percent predicted FEV1 and a lower FEV1/FVC ratio, was also observed in participants who developed lung cancer.

Results from univariate analysis are shown in Table 4A. Age, number of pack-years, COPD, emphysema, and baseline percent predicted FEV1 were significantly associated with lung cancer. On multivariate analysis, after adjusting for age, sex and pack-years of smoking (Model 1), COPD and emphysema were significant risk factors for lung cancer (HR 4.52; 95% CI 2.50–8.18, P<.001; HR 4.52; 95% CI 2.56–7.95, P<.001, respectively). After adding BMI, smoking status at baseline and family history of lung cancer to the previous model, the risk was slightly attenuated without loss of significance. In Model 3, where COPD and emphysema were included in a single model, both were still significant risk factors: HR 3.41; 95% CI 1.85–6.29, P<.001, and HR 3.26; 95% CI 1.82–5.85, P<.001 for COPD and emphysema, respectively (Table 4B).

Twelve patients diagnosed with lung cancer died (23%). Most of them (58%) had advanced disease (lung cancer stages III–IV or extensive disease in SCLC). The 10-year lung cancer survival rate among the 53 individuals with lung cancer was 70%. Considering only those with stage I lung cancer, the 10-year survival rate improved to 80%. Mean survival time was 110 (95% CI 93–127) months and 127 (95% CI 111–143) months for all of the individuals diagnosed with lung cancer and those with stage I disease, respectively (Fig. 1).

Discussion

This study describes the use of LDCT in lung cancer screening in the longest ongoing screening program in Spain, and contributes to European experience in this area.

Our results are comparable to those published in other countries in terms of lung cancer prevalence, incidence, histology and staging. Considering only the baseline screening round, our lung cancer prevalence rate was 1.0%. While in the NLST trial (United States) prevalence was 1.0%,[19] in Europe these rates varied widely

Table 1
Baseline Characteristics of the Study Population.

Characteristic	P-IELCAP	One screening round	Two or more rounds	P
No.	2989	1308	1681	
Age	55 (49–62)	55 (48–62)	55 (50–62)	.22
Men (%)	73	71	74	.05
BMI	28±4	28±5	27±4	.22
Pack-years	32 (20–46)	31 (20–48)	32 (22–46)	.15
Current smoker (%)	64	64	64	.89
Time since last cigarette, years	6 (2–14)	6 (1–13)	7 (2–15)	.048
Follow-up, months	13 (0.1–49)	0.1 (0.1–0.1)	42 (22–73)	<.001
Screening rounds per subject	2 (1–3)	1 (1–1)	3 (2–5)	<.001
Lung cancer family history (%)	19	18	19	.28
Spirometry results				
Airway obstruction (%)	25	23	25	.28
GOLD 1 (%)	56	57	55	.72
GOLD 2 (%)	37	32	40	.04
GOLD 3 (%)	6	10	5	.01
GOLD 4 (%)	1	1	0	.01
Emphysema in LDCT (%)	24	25	23	.32

Abbreviations: P-IELCAP, Pamplona International Early Lung Cancer Detection Program; BMI, body mass index; GOLD, global initiative for chronic obstructive lung disease; LDCT, low-dose chest computed tomography.

Table 2
Characteristics of Lung Cancer Diagnoses.

Variable	Whole cohort	Prevalence round	Incidence rounds
Participants with lung cancer	53	29	24
Histologic distribution, *n*[a]	60	29	31
Adenocarcinoma, n (%)	33(55)	19(66)	14(45)
Squamous, n (%)	13(22)	4(14)	9(29)
Large cell, n (%)	7(12)	3(10)	4(13)
Small cell, n (%)	5(8)	2(7)	3(10)
Others, n (%)[b]	2(3)	1(3)	1(3)
BAC component, n (%)[c]	12(36)	7(37)	5(36)
Staging[a]			
NSCLC, n	55	27	28
Stage I (%)	40(73)	24(89)	16(57)
Stage II (%)	5(9)	1(3.7)	4(14)
Stage III (%)	6(11)	1(3.7)	5(18)
Stage IV (%)	4(7)	1(3.7)	3(11)
SCLC, n	5	2	3
Limited disease	1(20)	1(50)	0(0)
Extensive disease	4(80)	1(50)	3(100)
Deaths, *n* (%)[d]	12(23)	5(17)	7(29)
Early stage (I–II), n (%)	5(42)	4(80)	1(14)
Late stage (III–IV), n (%)	4(33)	0(0)	4(57)
Limited disease	0(0)	0(0)	0(0)
Extensive disease	3(25)	1(20)	2(29)

Abbreviations: BAC, bronchioloalveolar carcinoma; NSCLC, non-small cell lung carcinoma; SCLC, small cell lung carcinoma.
[a] One patient with synchronous and six patients with metachronous tumors are included. The stage and histology of each tumor is counted separately.
[b] Others include carcinoid tumors.
[c] BAC component in adenocarcinomas.
[d] Deaths in participants with lung cancer.

Table 3
Differences in Baseline Characteristics Between Individuals With and Without Lung Cancer.

Characteristic	Lung cancer (n=53)	No lung cancer (n=2936)	P value
Age	60(55–65)	55(49–62)	<.001
Male (%)	83	73	.10
BMI	27±5	28±4	.05
Pack-years	52(37–77)	31(20–46)	<.001
Current smoker (%)	74	64	.24
Time since last cigarette (years)	6(2–18)	6(2–14)	.65
Lung cancer family history (%)	25	19	.28
Spirometry results			
Airway obstruction (%)	66	24	<.001
GOLD 1 (%)	66	55	.22
GOLD 2 (%)	28	37	.30
GOLD 3 (%)	6	7	.81
GOLD 4 (%)	0	1	.62
Emphysema by LDCT (%)	60	23	<.001

Definition of abbreviations: BMI, body mass index; GOLD, global initiative for chronic obstructive lung disease; LDCT, low-dose chest computed tomography. Data are expressed as mean±standard deviation (SD) or median (interquartile range, IQR).

Table 4
Cox Univariate and Multivariate Regression Analysis to Assess Lung Cancer Risk.

Variable	HR (CI 95%)	P value
A. Univariate analysis		
Age	1.06 (1.03–1.09)	<.001
BMI	0.94 (0.88–1.01)	.07
Men	1.65 (0.81–3.39)	.17
Pack-years	1.03 (1.02–1.04)	<.001
Current smoker	1.24 (0.68–2.26)	.49
Family history of lung cancer	1.34 (0.72–2.52)	.35
COPD	6.09 (3.44–10.76)	<.001
Emphysema	5.57 (3.20–9.68)	<.001
% predicted FEV1	0.97 (0.96–0.98)	<.001

Variable	Model 1 HR (CI 95%)	Model 2 HR (CI 95%)	Model 3 HR (CI 95%)
B. Multivariate analysis			
COPD	4.52 (2.50–8.18)	4.42 (2.44–7.99)	3.41 (1.85–6.29)
Emphysema	4.52 (2.56–7.95)	4.20 (2.37–7.44)	3.26 (1.82–5.85)

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; HR, hazard ratio. Adjustment models: Model 1: age, sex, pack-years of smoking; Model 2: age, sex, pack-years, BMI, current smoker and family history of lung cancer; Model 3: age, sex, pack-years, COPD and emphysema.

Table 5

Differences in Lung Cancer Prevalence and Incidence Rates Between Studies.

Cohort	No.	Participants with lung cancer	Prevalence	Stage I (%)
A. Results from baseline screening round.				
P-IELCAP[a]	2989	29	1.0%	89
NLST	26 309	270	1.0%	57
DLCST	2052	17	0.8%	59
NELSON[a]	7557	70	0.9%	64
LUSI	2029	22	1.1%	82
ITALUNG[a]	1406	20	1.4%	50
DANTE[a]	1276	28	2.2%	57
DEPISCAN	336	8	2.4%	38

Cohort	No.	Participants with lung cancer	Incidence	Duration (years)	Annual detection rate	Stage I (%)
B. Results from the second and/or subsequent screening rounds.						
P-IELCAP[a]	1681	24	1.4%	3.5	0.41	57
NLST	24 715	379	1.5%	6.5	0.24	65
DLCST	1976	52	2.6%	4	0.66	73
NELSON[a]	7294	130	1.8%	4	0.45	74[b]
ITALUNG[a]	1263	18	1.4%	4	0.36	76
DANTE[a]	1114	32	2.9%	2.81	1.02	53
LUSI	NA	NA	NA	NA	NA	NA
DEPISCAN	NA	NA	NA	NA	NA	NA

Abbreviations: P-IELCAP, Pamplona Early Lung Cancer Detection Program; NLST, National Lung Screening Trial; DLCST, Danish Lung Cancer Screening Trial; NELSON (NEderlands Leuvens longkanker Screenings ONderzoek; LUSI, German Lung Cancer Screening Intervention trial; DANTE, Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays; NA, data not available for calculation.

[a] These studies include individuals with synchronous or metachronous tumors. The prevalence and incidence rates are based on the number of individuals diagnosed with lung cancer rather than the total number of cancers.

[b] Data only available from the first 54 lung cancers detected in incidence screening rounds.
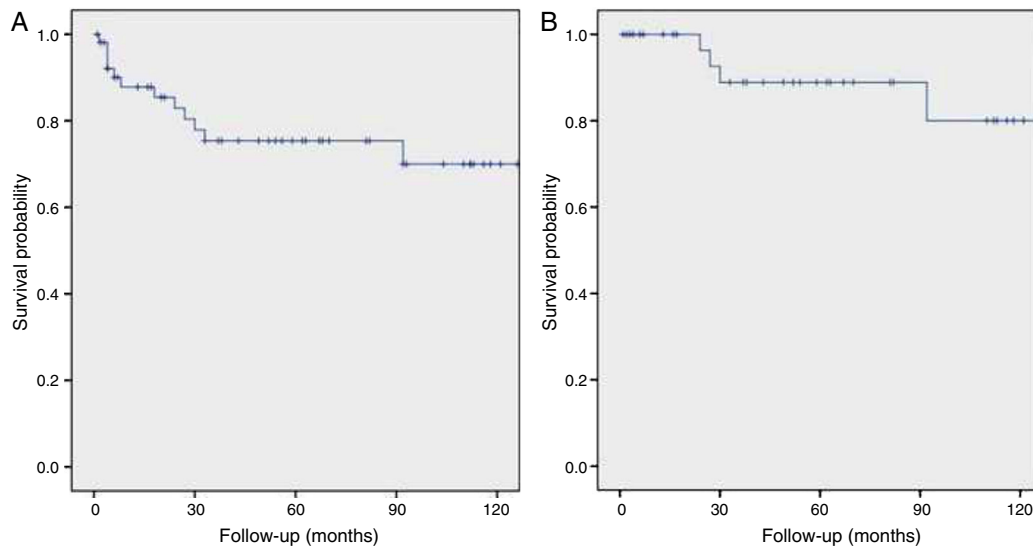
Fig. 1. Kaplan Meier survival curves for (A) the total number of participants with lung cancer, and (B) those with stage I disease.

among studies, from 0.8% in the DLCST up to 2.4% in DEPISCAN[10,11] (Table 5A). P-IELCAP had the highest proportion of stage I lung cancers in the baseline screening round, with a 30% mean difference with respect to the other studies. Only the LUSI trial showed similar results to ours, probably because their evaluation algorithm, like ours, was based on ELCAP, highlighting the value of using a standard protocol.[1,8] Differences in prevalence rates compared to other cohorts could be explained by the inclusion criteria used in each study. For instance, P-IELCAP recruited younger participants with a lower smoking history threshold than other studies.

When considering lung cancer diagnoses during annual screenings, incidence determined from P-IELCAP data was 1.4% (Table 5B). This result was comparable to ITALUNG (1.4%), but much lower than that observed in the DLCST (2.6%) and DANTE (2.9%).[20–22] When incidence rates were adjusted for the duration of each study (annual detection rate), the results were more homogenous. The P-IELCAP annual detection rate (0.41) was comparable to the results from the NELSON (0.45) and ITALUNG trials (0.36),[20,23] while the difference with DLCST was slightly less.[21] Possible explanations for the differences between studies could be related to the inclusion criteria employed in each trial, the methods used for recruitment (such as mass mailing used in other studies), the LDCT protocol (slice collimation and thickness), number of screening rounds and the interval between each round, the pulmonary nodule/lung cancer assessment protocol (nodule diameter or nodule volume and volume-doubling times), among others. Participants' inherent characteristics according to the geographical areas they belong to could also have influenced results.

Adenocarcinoma was the most frequent histological pattern found in our study, consistent with observations from other screening cohorts.[8,10,19–21]

The proportion of stage I lung cancers detected on the incidence rounds decreased significantly in P-IELCAP (from 89% to 57%). From the European studies mentioned here, only the DANTE trial showed similar behavior, but not to the same extent.[22] This trend, however, has also been reported in other studies,[24] such as the Lung Screening Study (53%–25%),[25] the Pittsburgh Lung Screening Study (58%–37%)[26] and a study by Swensen and colleagues (71%–50%).[27] The 57% stage I disease found in P-IELCAP incidence screening rounds is in line with other series, such as DANTE (53%) and the NLST (65%).[22,28]

As previously mentioned, P-IELCAP was one of the many sites involved in the I-ELCAP, and part of our cohort was included in the 2006 article, for which more than 30,000 participants were recruited from sites in North America, Europe and Asia.[5] With only a fraction of participants from the latter (11%), P-IELCAP results were consistent with those from I-ELCAP, especially in the baseline screening round (1.3% prevalence and 85% stage I lung cancer in I-ELCAP, compared to the 1.0% prevalence and 89% stage I lung cancer in P-IELCAP). However, some differences were found in the incidence rounds, where even though the incidence rate was much lower in I-ELCAP (0.3% vs 1.4% in P-IELCAP), a high stage I lung cancer detection was maintained (86% vs 57% in P-IELCAP). In spite of this difference, the 10-year survival rates for patients with stage I disease were comparable in both studies (80% in P-IELCAP and 88% in I-ELCAP, respectively) (Fig. 1B).[5]

These results show that lung cancer screening with LDCT in a Spanish center is feasible and effective. However, this study was performed in a private center and results may not be entirely applicable to public institutions in a country where national health coverage predominates. Costs and resources' utilization would be important limitations in this setting. Regarding cost-effectiveness, an actuarial analysis in a high-risk population in the United States suggested that offering lung cancer screening as an insurance benefit would save lives at relatively low cost.[29] What is clear, and backed by most current guidelines, is that screening targeting a high-risk population should be performed in medical centers where multidisciplinary teams are available.[30,31]

Our study also confirms the value of COPD and emphysema as important risk factors for lung cancer in a screening setting. None of the studies cited previously have made this assessment. However, the NLST and the Pittsburgh Lung Screening Study (PLuSS) have confirmed the value of emphysema in selecting high-risk patients.[32,33] This observation is further confirmed by measuring the lung cancer incidence density, where COPD and emphysema showed a three-fold increase (23 and 21 lung cancers per 1000 person/years, respectively, when compared to the entire cohort, 7 lung cancers per 1000 person/years). Interestingly, when both COPD and emphysema were present in a single individual, the incidence density was highest (39 lung cancers per 1000 person/years). Among patients with COPD, most of the lung cancer diagnoses were made in individuals with mild disease (33 cases within GOLD grades 1 and 2; whereas only 2 lung cancer cases were detected in severe grades). Our results are consistent with those from the BODE cohort, where increased risk was also observed in mild disease.[34,35] However, it contrasts with data from the PLuSS, where patients with

severe COPD had significantly higher risk for lung cancer.[32] Studies have been consistent in describing the relationship between COPD and lung cancer over the past two decades, and its importance in lung cancer screening was confirmed.[14,32,36,37] Other factors such as time between COPD diagnosis and lung cancer development have also shown a strong association.[38]

There are some potential limitations in our study. Firstly, P-IELCAP is a single-center, single-arm screening study, and comparisons with the aforementioned randomized trials should be interpreted cautiously. The reason for choosing these studies was to compare the Spanish experience with that of other European countries. Only the results from the NLST trial were included from outside Europe as it is a reference in the field.[6] Secondly, the screening compliance in our study was low, as only 56% of participants underwent at least a second screening round, compared to more than 90% compliance observed in most of the cited trials. This would be an important limitation if we were to compare global results. We believe this limitation is minimized by measuring prevalence and incidence rates independently in those participants who underwent 1, 2 or more screening rounds, respectively. This made our compliant group comparable to the other trials in terms of follow-up and number of screening rounds. We previously assessed the issue of low adherence in our screening program, finding that it varied according to sex, distance to the referral center, participant motivation, and risk perception, among others.[39] Thirdly, it is likely that a selection bias, particularly a healthy volunteer effect, could be present. The latter has been further described by Dominioni et al. in a chest X-ray lung cancer screening setting, where participants in the intervention group had higher lung cancer mortality than the control group.[40] In our study, although there was no significant differences in baseline lung function (percent predicted FEV1) between those who underwent 1 or more than 1 screening round, in the subgroup of patients with COPD those with milder disease were more compliant with the scheduled visits. We do not address the issue of over-diagnosis in this study because of the lack of a control group. However, the significant reduction in lung cancer mortality found in the NLST proves that over-diagnosis is not a limiting issue.[6] Finally, regarding possible unnecessary procedures or false positive results, we refer to the original I-ELCAP study, where 92% of biopsies (492 out of 535) performed after a positive LDCT resulted in a malignant diagnosis.[5]

We conclude that the experience in Spain's longest lung cancer screening program is comparable with findings from the rest of Europe, and confirms the feasibility and efficacy of lung cancer screening using low-dose computed tomography. COPD and emphysema are important risk factors for lung cancer and should be considered in the selection of high-risk individuals for lung cancer screening.

Contributions to the Study

The conception of the study and its design was carried out by P.S.S., J.B., J.P.d.T., A.C., A.B.A., A.V., J.C.P., M.D.L., M.J.G.V., L.M.S., J.G., G.B., and J.J.Z. P.S.S., J.P.d.T., L.M.S., and J.J.Z. also carried out the analysis and interpretation, and drafted the manuscript for important intellectual content.

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Conflict of Interests

The authors declare that they have no conflict of interests.

References

1. Henschke CI, McCauley DI, Yankelevitz DF, Naidich DP, McGuinness G, Miettinen OS, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet. 1999;354:99–105.
2. Diederich S, Wormanns D, Semik M, Thomas M, Lenzen H, Roos N, et al. Screening for early lung cancer with low-dose spiral CT: prevalence in 817 asymptomatic smokers. Radiology. 2002;222:773–81.
3. Sone S, Li F, Yang ZG, Honda T, Maruyama Y, Takashima S, et al. Results of three-year mass screening programme for lung cancer using mobile low-dose spiral computed tomography scanner. Br J Cancer. 2001;84:25–32.
4. Sobue T, Moriyama N, Kaneko M, Kusumoto M, Kobayashi T, Tsuchiya R, et al. Screening for lung cancer with low-dose helical computed tomography: anti-lung cancer association project. J Clin Oncol. 2002;20:911–20.
5. Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, Miettinen OS. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med. 2006;355:1763–71.
6. Aberle D, Adams A, Berg C, Black W, Clapp J, Fagerstrom R, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365:395–409.
7. Humphrey LL, Deffebach M, Pappas M, Baumann C, Artis K, Mitchell JP, et al. Screening for lung cancer with low-dose computed tomography: a systematic review to update the U.S. Preventive Services Task Force Recommendation. Ann Int Med. 2013;159:411–20.
8. Becker N, Motsch E, Gross M-L, Eigentopf A, Heussel CP, Dienemann H, et al. Randomized study on early detection of lung cancer with MSCT in Germany: study design and results of the first screening round. J Cancer Res Clin Oncol. 2012;138:1475–86.
9. Van Iersel CA, de Koning HJ, Draisma G, Mali WPTM, Scholten ET, Nackaerts K, et al. Risk-based selection from the general population in a screening trial: selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON). Int J Cancer. 2007;120:868–74.
10. Blanchon T, Bréchot J-M, Grenier PA, Ferretti GR, Lemarié E, Milleron B, et al. Baseline results of the Depiscan study: a French randomized pilot trial of lung cancer screening comparing low dose CT scan (LDCT) and chest X-ray (CXR). Lung Cancer. 2007;58:50–8.
11. Pedersen JH, Ashraf H, Dirksen A, Bach K, Hansen H, Toennesen P, et al. The Danish randomized lung cancer CT screening trial – overall design and results of the prevalence round. J Thorac Oncol. 2009;4:608–14.
12. Infante M, Lutman FR, Cavuto S, Brambilla G, Chiesa G, Passera E, et al. Lung cancer screening with spiral CT: baseline results of the randomized DANTE trial. Lung Cancer. 2008;59:355–63.
13. Lopes Pegna A, Picozzi G, Mascalchi M, Maria Carozzi F, Carrozzi L, Comin C, et al. Design, recruitment and baseline results of the ITALUNG trial for lung cancer screening with low-dose CT. Lung Cancer. 2009;64:34–40.
14. De Torres JP, Bastarrika G, Wisnivesky JP, Alcaide AB, Campo A, Seijo LM, et al. Assessing the relationship between lung cancer risk and emphysema detected on low-dose CT of the chest. Chest. 2007;132:1932–8.
15. Bastarrika G, García-Velloso MJ, Lozano MD, Montes U, Torre W, Spiteri N, et al. Early lung cancer detection using spiral computed tomography and positron emission tomography. Am J Respir Crit Care Med. 2005;171:1378–83.
16. International Early Lung Cancer Action Program protocol. Available from: http://www.IELCAP.org; [accessed 17.10.13].
17. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global Strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013;187:347–65.
18. Young RP, Hopkins RJ, Targeted CT. Image screening and its effect on lung cancer detection rate. Chest. 2013;144:1419–20.
19. Church TR, Black WC, Aberle DR, Berg CD, Clingan KL, Duan F, et al. Results of initial low-dose computed tomographic screening for lung cancer. N Engl J Med. 2013;368:1980–91.
20. Lopes Pegna A, Picozzi G, Falaschi F, Carrozzi L, Falchini M, Carozzi FM, et al. Four-year results of low-dose CT screening and nodule management in the ITALUNG trial. J Thorac Oncol. 2013;8:866–75.
21. Saghir Z, Dirksen A, Ashraf H, Bach KS, Brodersen J, Clementsen PF, et al. The randomised Danish Lung Cancer Screening Trial: Status after five annual screening rounds with low-dose CT. Thorax. 2012;67:296–301.
22. Infante M, Cavuto S, Lutman FR, Brambilla G, Chiesa G, Ceresoli G, et al. A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial. Am J Respir Crit Care Med. 2009;180:445–53.
23. Horeweg N, van der Aalst CM, Vliegenthart R, Zhao Y, Xie X, Scholten ET, et al. Volumetric computed tomography screening for lung cancer: three rounds of the NELSON trial. Eur Respir J. 2013;42:1659–67.
24. Ruano-Ravina A, Pérez Ríos M, Fernández-Villar A. Lung cancer screening with low-dose computed tomography after the National Lung Screening Trial. The debate is still open. Arch Bronconeumol. 2013;49:158–65.

25. Gohagan JK, Marcus PM, Fagerstrom RM, Pinsky PF, Kramer BS, Prorok PC, et al. Final results of the Lung Screening Study, a randomized feasibility study of spiral CT versus chest X-ray screening for lung cancer. Lung Cancer. 2005;47:9–15.

26. Wilson DO, Weissfeld JL, Fuhrman CR, Fisher SN, Balogh P, Landreneau RJ, et al. The Pittsburgh Lung Screening Study (PLuSS): outcomes within 3 years of a first computed tomography scan. Am J Respir Crit Care Med. 2008;178:956–61.

27. Swensen SJ, Jett JR, Sloan JA, Midthun DE, Hartman TE, Sykes A, et al. Screening for lung cancer with low-dose spiral computed tomography. Am J Respir Crit Care Med. 2002;165:508–13.

28. Aberle DR, DeMello S, Berg CD, Black WC, Brewer B, Church TR, et al. Results of the two incidence screenings in the National Lung Screening Trial. N Engl J Med. 2013;369:920–31.

29. Pyenson BS, Sander MS, Jiang Y, Kahn H, Mulshine JL. An actuarial analysis shows that offering lung cancer screening as an insurance benefit would save lives at relatively low cost. Health Aff (Millwood). 2012;31:770–9.

30. Detterbeck FC, Mazzone PJ, Naidich DP, Bach PB. Screening for lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143. pp. e78S–e92S.

31. Shlomi D, Ben-Avi R, Balmor GR, Onn A, Peled N. Screening for lung cancer: time for large-scale screening by chest computed tomography. Eur Respir J. 2014;44:217–38.

32. Wilson DO, Weissfeld JL, Balkan A, Schragin JG, Fuhrman CR, Fisher SN, et al. Association of radiographic emphysema and airflow obstruction with lung cancer. Am J Respir Crit Care Med. 2008;178:738–44.

33. Kovalchik SA, Tammemagi M, Berg CD, Caporaso NE, Riley TL, Korch M, et al. Targeting of low-dose CT screening according to the risk of lung-cancer death. N Engl J Med. 2013;369:245–54.

34. de Torres JP, Marín JM, Casanova C, Cote C, Carrizo S, Cordoba-Lanus E, et al. Lung cancer in patients with chronic obstructive pulmonary disease – incidence and predicting factors. Am J Respir Crit Care Med. 2011;184:913–9.

35. de-Torres JP, Casanova C, Marín JM, Zagaceta J, Alcaide AB, Seijo LM, et al. Exploring the impact of screening with low-dose CT on lung cancer mortality in mild to moderate COPD patients: a pilot study. Respir Med. 2013;107:702–7.

36. Maldonado F, Bartholmai BJ, Swensen SJ, Midthun DE, Decker PA, Jett JR. Are airflow obstruction and radiographic evidence of emphysema risk factors for lung cancer? A nested case-control study using quantitative emphysema analysis. Chest. 2010;138:1295–302.

37. Young RP, Hopkins RJ, Christmas T, Black PN, Metcalf P, Gamble GD. COPD prevalence is increased in lung cancer, independent of age, sex and smoking history. Eur Respir J. 2009;34:380–6.

38. Powell HA, Iyen-Omofoman B, Baldwin DR, Hubbard RB, Tata LJ. Chronic obstructive pulmonary disease and risk of lung cancer: the importance of smoking and timing of diagnosis. J Thorac Oncol. 2013;8:6–11.

39. Montes U, Seijo LM, Campo A, Alcaide AB, Bastarrika G, Zulueta JJ. Factors determining early adherence to a lung cancer screening protocol. Eur Respir J. 2007;30:532–7.

40. Dominioni L, Poli A, Mantovani W, Rotolo N, Imperatori A. Volunteer effect and compromised randomization in the Mayo Project of screening for lung cancer. Eur J Epidemiol. 2011;26:79–80.