www.brn.cat

PERMANYER

BRN Rev. 2015;1:39-47

BRN Reviews

REVIEW ARTICLE

Lung Cancer and Chronic Obstructive Pulmonary Disease: Role for Screening with Low-Dose Computed Tomography

Pablo Sánchez-Salcedo, Juan Berto and Javier J. Zulueta

Respiratory Medicine Service, Clínica Universidad de Navarra, Pamplona, Spain

ABSTRACT

Lung cancer and chronic obstructive pulmonary disease are two major public health problems that are projected to remain among the top leading causes of death worldwide over the next decade. Recently, lung cancer screening with low-dose computed tomography of the chest in a high-risk population of smokers has been shown to be effective in reducing mortality from lung cancer in the National Lung Screening Trial. There is increasing evidence that individuals with chronic obstructive pulmonary disease and/or emphysema are at increased risk of having lung cancer. When compared to smokers without chronic obstructive pulmonary disease, several studies have shown that patients with the disease (forced expiratory volume in one second to forced vital capacity ratio < 70%) have a 2-6-fold greater risk of having lung cancer. Radiographic emphysema is particularly interesting as its presence, even without airway obstruction, is an independent risk factor for lung cancer. The risk of lung cancer is greatest in individuals with concomitant airway obstruction and emphysema. There is evidence that screening patients with chronic obstructive pulmonary disease is effective and can potentially reduce mortality. A specific lung cancer screening score for patients with chronic obstructive pulmonary disease has been developed and can be useful to select those with the highest risk. Multidisciplinary evaluations of patients with chronic obstructive pulmonary disease should be useful in attenuating potential harms from diagnostic and therapeutic procedures, especially in those with severe disease.

Correspondence:
Javier J. Zulueta
Clínica Universidad de Navarra
Av. Pio XII, s/n
31008 Pamplona, España
E-mail: jzulueta@unav.es

Date of reception: 11-03-2015
Date of acceptance: 04-05-2015
DOI: 10.23866/BRNRev:2015-0005

This article reviews the evidence of the lung cancer-chronic obstructive pulmonary disease association, describes potential mechanisms that relate both diseases, evaluates lung cancer risk assessments in population-based studies and lung cancer screening cohorts, and discusses different clinical aspects to consider when performing screening in a chronic obstructive pulmonary disease population. (BRN Rev. 2015;1:39-47)

Corresponding author: Javier J. Zulueta, jzulueta@unav.es

Key words: COPD. Emphysema. LDCT. Lung cancer screening. Selection criteria.

INTRODUCTION

Lung cancer is the leading cause of death from malignant disease worldwide, with more deaths from lung cancer than from colon, breast, and prostate cancer together[1,2]. Lung cancer mortality hasn't changed significantly over the last decades, with an estimated 1.6 million deaths worldwide from this disease according to the International Agency for Research on Cancer[3]. It is estimated that by 2030, lung cancer will still be among the top leading causes of death, ranking third in high-income countries (Fig. 1)[4,5]. These estimations are mainly due to the fact that the great majority of lung cancers are diagnosed at an advanced stage, resulting in a poor overall survival[6]. Five-year lung cancer survival rates vary significantly depending on the stage of the disease in which it is diagnosed, ranging from 50% for stage IA, to 2% for stage IV[2]. Therefore, it is imperative to focus on early detection to improve survival.

Chronic obstructive pulmonary disease (COPD) is also a major public health problem, in part as a result of being an under-recognized and under-diagnosed disease. It is projected to rank fourth worldwide in terms of mortality by 2030[4], which could be explained by the expanding epidemic of smoking, a reduced mortality from other common causes of death, and aging of the world population (Fig. 1)[7]. The evidence associating COPD and lung cancer goes back almost 30 years, but the association has been systematically confirmed in more recent studies[8,9].

Lung cancer and COPD appear to share more than tobacco exposure as their common risk and causative factor and chronic inflammation and lung repair mechanisms present in COPD are thought to be very important contributors to lung cancer development[10].

In order to improve early lung cancer detection and thus improve survival, several studies involving the use of low-dose computed tomography (LDCT) of the chest have been planned and completed over the last two decades. The results from both the International Early Lung Cancer Action Program (I-ELCAP)[11] and the National Lung Screening Trial (NLST)[12] were decisive for the recent recommendation by the United States Preventive Services Task Force in favor of annual lung cancer screening[13].

This review summarizes the evidence linking COPD and lung cancer risk, and the potential

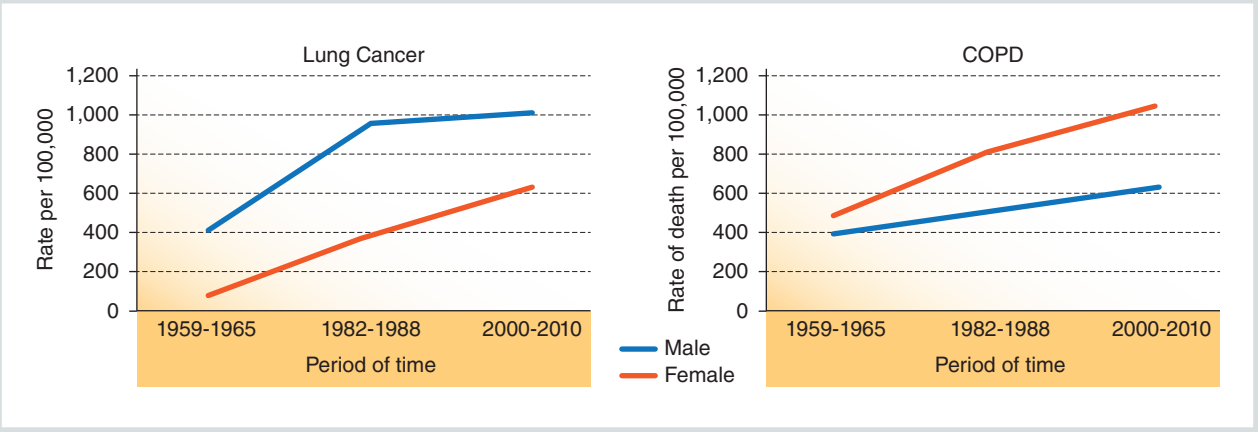

Figure 1. Lung cancer and COPD death rates per 100,000 over time among current and former smokers, stratified by sex. Data obtained from the first Cancer Prevention Study I (CPS I) for the period from 1959 to 1965, from the second Cancer Prevention Study (CPS II) for the period from 1982 to 1988, and from five contemporary cohort studies for the period from 2000-2010 *(adapted from Thun, et al.[5])*.

role of lung cancer screening in this high-risk population. The presence of COPD, defined by a forced expiratory volume in one second to forced vital capacity ratio (FEV_1/FVC) below 70%, and emphysema as determined by computed tomography (CT) scanning have been shown to be independent risk factors for lung cancer. Although COPD and emphysema frequently coexist, in this manuscript we will discuss them individually.

MECHANISMS INVOLVED IN LUNG CANCER DEVELOPMENT IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Several mechanisms have been postulated linking these two diseases, including but not limited to genetic susceptibility, deoxyribonucleic acid (DNA) damage and repair mechanisms, epigenetics involving DNA methylation and posttranslational modifications of histones, downregulation of certain microRNA (miRNA), expression of proinflammatory genes by hypoxia, and the role of the hypoxia-induced factor, tumor growth factor-β and integrins, and adaptive immune responses, among others[14-17] (Table 1). It is not the purpose of this review to thoroughly discuss these mechanisms and for a more comprehensive understanding, the reader should refer to the appropriate sources.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND RISK OF LUNG CANCER

Studies from the mid-1980s by Skillrud, et al.[8] and Tockman, et al.[9] found an association between lung cancer and COPD, an observation that has been confirmed over time. Several cohort studies, including some lung cancer screening trials, have indicated that patients with COPD are 2-6 times more likely to develop lung cancer than those without COPD, a risk that persists even after controlling for smoking exposure[18-21]. Furthermore, lung cancer risk has been shown to be strongly

Table 1. Potential mechanisms associating chronic obstructive pulmonary disease and lung cancer.

Genetic susceptibility			
MMP1	CHRNA3	RB1	MPO
CYP1A1	CHRNA5	TP53	EPHX1
Epigenetics			
– DNA promoter hypermethylation and DNA global hypomethylation.			
– Post-translational modifications of histones (acetylation, methylation, ubiquitination, sumoylation and phosphorylation).			
miRNA			
– miRNA silencing by DNA hypermethylation.			
DNA repair mechanisms			
– Induced by inhalation of cigarette smoke or toxic pollutants			
Inflammation			
Hypoxia-induced factor		STAT3	
TGF-β and integrins		TRAIL receptors 1, 2, 3	
Adaptive immune responses		COX-2	
Proteinases: neutrophil elastase, cathepsin S, various MMP			
NFκβ activation			

MMP: matrix metalloproteinase; miRNA: microRNA; CYP1A1: cytochrome P450 subfamily 1, polypeptide 1; MPO: myeloperoxidase; EPHX1: epoxide hydrolase 1; CHRNA: cholinergic receptor, neuronal nicotinic, α-polypeptide; RB1: retinoblastoma 1; DNA: deoxyribonucleic acid; TGF-β: tumor growth factor β; STAT3: signal transducer and activator of transcription; COX-2: cyclooxygenase 2.

dependent on the timing between COPD diagnosis and lung cancer detection, with a threefold greater risk in patients diagnosed with COPD in the previous six months as compared to those with a more than 10-year history of COPD[22].

The degree of airway obstruction appears to be associated with lung cancer. However, evidence in this matter is contradictive. In the Body mass index, Airflow obstruction, Dyspnea, Exercise performance (BODE) observational cohort of patients with COPD, de-Torres, et al. reported an increased risk of lung cancer in patients with mild and moderate degrees of airway obstruction (HR: 3.05; 95% CI: 1.41-6.59, and HR: 2.06; 95% CI: 1.01-4.18, respectively)[23]. This observation has been later confirmed in the Pamplona International Early Lung Cancer Detection Program (P-IELCAP), where 94% of the patients with COPD diagnosed with lung cancer had COPD in Global initiative for chronic Obstructive Lung Disease (GOLD) grades 1 and 2[24]. These results contrast with those of Wilson, et al. from the Pittsburgh Lung Screening Study (PLuSS), where the highest lung cancer risk was found among COPD patients with GOLD grades 3 and 4 (OR: 2.86; 95% CI: 1.48-5.53)[20]. Similarly, in a lung cancer screening trial from the Mayo Clinic, the risk of lung cancer increased as both the FEV_1 and the FEV_1/FVC ratio decreased[21]. Data from the First National Health and Nutrition Examination Survey also showed that moderate and severe obstructive lung disease were significant predictors of incident lung cancer (HR: 2.8; 95% CI: 1.8-4.4, and HR: 1.4; 95% CI; 0.8-2.6, respectively)[25].

A recent meta-analysis has confirmed the association between impaired lung function and the risk of lung cancer, where even a small reduction in FEV_1 (approximately 90% predicted) was associated with a 30% increase in the risk of lung cancer in men (RR: 1.30; 95% CI: 1.05-1.62), and a 2.64-fold increase in women (RR: 2.64; 95% CI: 1.30-5.31)[26]. Calabro, et al. have confirmed this observation in patients with COPD, where a cut-off value of $FEV_1 < 90\%$ predicted resulted in the highest sensitivity and specificity in predicting lung cancer[27].

Of note, in a population of never smokers, lung cancer risk was increased in individuals with a previous diagnosis of concomitant chronic bronchitis and emphysema (HR: 2.44; 95% CI: 1.22-4.90), whereas no significant association was found for chronic bronchitis alone[28].

EMPHYSEMA AND RISK OF LUNG CANCER

The presence of emphysema on a LDCT and its relationship with lung cancer has also been the subject of several studies. Most of the lung cancer screening studies that have assessed airway obstruction have also analyzed the impact of radiographic emphysema on lung cancer detection. Evidence suggests that most of the lung cancer risk attributed to spirometrically defined COPD ($FEV_1/FVC < 70\%$) could be in part a result of emphysema *per se*. In a study by de-Torres, et al., the lung cancer incidence density in participants with visually determined emphysema was threefold higher than in subjects without it. Even in individuals without airway obstruction, the presence of emphysema increased the risk of lung cancer fourfold (RR: 4.33; 95% CI: 1.04-18.16). In a multivariate regression analysis where COPD and emphysema were included in a single model, only emphysema remained as an independent significant risk factor for lung cancer[19]. These results were also observed in PLuSS: the risk of lung cancer in subjects with emphysema was 3.56 (95% CI: 2.21-5.73), remaining significant even after competing with COPD in a single regression model, a risk that was present even in subjects with no airway obstruction[20]. In a large population of never smokers, a previous diagnosis of emphysema was associated with a 66% increase in lung cancer mortality[28]. Moreover, data from the I-ELCAP trial showed that the presence of emphysema on the baseline LDCT significantly increased the risk of lung cancer in current, former, and never smokers who underwent screening (OR: 1.8; 95% CI: 1.4-2.2, OR: 1.7; 95% CI: 1.3-2.2, and OR: 6.3; 95% CI: 2.4-16.9, respectively)[29].

No clear trend between the severity of emphysema and risk of lung cancer development has been found, with the highest risk seen in those with mild emphysema (OR: 4.43; 95% CI: 2.53-7.79), followed by moderate-severe, and trace of emphysema, respectively[20]. However, in a lung cancer screening cohort from New York, a linear trend between the extent of visually assessed emphysema and the risk of death from lung cancer was observed, but the association was only significant for marked emphysema (areas of decreased attenuation in more than half of the lung parenchyma)[30].

In contrast, in other studies where emphysema was quantified automatically using software, a significant association between emphysema and the risk of lung cancer was not found[21,31]. In this regard, a meta-analysis by Smith, et al. found that only visually determined emphysema on CT was independently associated with an increased odds of lung cancer, an observation that did not hold for automated emphysema detection[32]. This highlights the value of simple visual determination of emphysema on LDCT over software-automated based quantification.

One important feature observed in some of the aforementioned studies is that the risk of lung cancer is significantly higher in individuals with concomitant airway obstruction and radiographic emphysema. For instance, in one study lung cancer incidence density in participants with both risk factors was almost 11-fold greater (37.5 lung cancers per 1000 person-years) than in healthy smokers (no emphysema and no airway obstruction)[19]. The incidence density in subjects with only emphysema or only airway obstruction was 18.8 lung cancers per 1000 person-years[19]. Similarly, Wilson, et al.

found that the combination of airway obstruction and emphysema increased the odds of lung cancer, independent of the degree of airway obstruction[20].

CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND EMPHYSEMA AS SELECTION CRITERIA FOR LUNG CANCER SCREENING

The results from the NLST provided enough evidence for different medical societies to recommend in favor of lung cancer screening. The American Cancer Society[33], the American Society of Clinical Oncology[34], the American College of Chest Physicians[35], and the American Lung Association[36] all have made positive recommendations for lung cancer screening based on the inclusion criteria used in the NLST (age between 55 and 74 years, current smoker or having quit within the previous 15 years, with a smoking history of at least 30 pack-years)[12]. However, there is evidence that these entry criteria might not be sensitive enough in detecting lung cancer cases, considering that in some representative lung cancer cohorts, about half of subjects participating in the trials do not meet NLST criteria[37-39]. Furthermore, a recent study has shown a decline over the last 25 years in the proportion of patients meeting the NLST high-risk profile, suggesting that more sensitive criteria may need to be identified[40]. Following this premise, other medical societies have included broader criteria than those from the NLST. For instance, both the American Association for Thoracic Surgery[41] and the National Comprehensive Cancer Network[42] guidelines have lowered the age and smoking history thresholds to 50 years and 20 pack-years, respectively, provided individuals had an additional risk factor such as COPD.

Kovalchik, et al.[43] applied a lung cancer death risk prediction model within the NLST population, with emphysema being the most important risk factor (HR: 1.56; 95% CI: 1.20-2.04). The greatest numbers of preventable deaths were observed in subjects at highest risk of death. However, considering the limitations of the NLST entry criteria, restricting the selection criteria even more could have important consequences.

Our group has recently published a different strategy, complementing NLST criteria with radiographic emphysema to select individuals for annual screening rounds[39]. This was based on the fact that, in a lung cancer screening cohort recruited at our center as part of the I-ELCAP study, as many as 80% of participants with lung cancer who did not meet NLST criteria (*a priori*, a lower risk population) had emphysema on their baseline LDCT[39]. By exclusively using NLST entry criteria in this lung cancer screening cohort from Pamplona (P-IELCAP), 39% of the original lung cancer cases would not have been detected. Complementing NLST criteria by including individuals with age younger than 55, but with emphysema on the LDCT (NLST/E), improved incident lung cancer detection by almost 70%. Furthermore, annual lung cancer detection rates and the number of individuals needed to be screened in one year to find one lung cancer were better in the NLST/E group than in the NLST-only group, highlighting the importance of emphysema in selecting individuals at high risk. Moreover, investigators from the Continuous Observation of Smoking Subjects (COSMOS)

Table 2. Chronic obstructive pulmonary disease lung cancer screening score

Variable	Points assigned
BMI < 25 kg/m^2	1
Pack-years > 60	2
Age > 60 years	3
Presence of emphysema on LDCT	4
Total	10

BMI: body mass index; LDCT: low-dose computed tomography.

lung cancer screening trial have also developed a model to stratify individual risk to develop lung cancer during annual screening rounds based on findings from the baseline LDCT. In this study, emphysema was found to be a significant lung cancer risk predictor[44].

Recently, de-Torres, et al. have developed and validated a lung cancer screening score specifically designed for patients with COPD (COPD-LUCSS) in two lung cancer screening cohorts from Spain (P-IELCAP) and the United States (PLuSS)[45]. Age, body mass index, pack-years of smoking history, and the presence of emphysema were included in the score (Table 2)[45]. According to their total score, patients with COPD could be categorized into low-risk (0-6 points) or high-risk categories (≥ 7 points). The latter group of patients had a significantly higher risk of developing lung cancer (HR: 3.5; 95% CI: 1.7-7.1) when compared to patients in the low-risk category[45]. These results do not mean that individuals in the low-risk group should not be included in screening programs as they still have a higher risk of lung cancer when compared to smokers without airway obstruction. The appropriate way to deal with this group of patients is yet to be determined, but it is possible that they may need less frequent screenings than those in the high-risk category.

Based on this data, the use of COPD and/or emphysema to select individuals at high risk of lung cancer outside the NLST selection criteria would presumably improve lung cancer detection. However, whether the significant reduction in lung cancer mortality observed in the NLST will also be seen in patients with COPD, remains to be confirmed.

CLINICAL CONSIDERATIONS

Concerns might exist on whether individuals with COPD and/or emphysema should be included in lung cancer screening programs, and if those diagnosed with lung cancer will eventually benefit from treatment, as this group of patients experience higher competing mortality risks, which could catalogue them as ineligible for surgical resections[18,46]. The impact of lung cancer screening has been assessed in patients with mild and moderate COPD by comparing a sample that underwent screening with a matched sample that did not. Mortality incidence density from lung cancer was 30-times lower in the screening group than in the control group (0.08 vs. 2.48 deaths per 100 person-years; $p < 0.001$)[47]. In individuals with severe disease and resectable lung cancer, there is evidence that newer surgical treatments (sublobar resection or lung volume reduction surgery [LVRS]) and ablative therapies (stereotactic radiosurgery or radiofrequency ablation) are valid alternatives to consider due to their acceptable risk and good long-term outcomes[48-53]. There are even reports of successful lung cancer surgical treatments in patients that previously underwent endobronchial LVRS for severe emphysema[54]. In any case, the potential harms of screening in this population should be

attenuated by the implementation of a multidisciplinary approach and registry monitoring as recommended by guidelines[35].

The implementation of a screening program could be useful in other scenarios. Firstly, it is an ideal setting to offer smoking cessation treatments. Data from the Danish Lung Cancer Screening Trial showed that being part of a lung cancer screening program significantly promotes smoking cessation[55]. Furthermore, a review of different studies concluded that positive LDCT results are associated with increased abstinence[56]. Smoking cessation will be especially useful in individuals with COPD as it is the most effective intervention in stopping the progression of COPD, as well as increasing survival and reducing morbidity, including lung cancer risk[57]. Furthermore, among patients with COPD, quitting smoking is also associated with transient improvement in spirometry, improvement in the transfer factor of lung for carbon monoxide, and a decrease in micronodules on high-resolution CT[58]. Secondly, the inclusion of smokers in a screening program could help diagnose COPD in previously considered healthy smokers, or adequately categorize patients already diagnosed with the disease, provided spirometric assessments are performed at least during the baseline screening round. This would be useful as it will allow early intervention for airway obstruction and adequate treatment according to guidelines.

CONCLUSIONS

Chronic obstructive pulmonary disease and emphysema are important risk factors for lung cancer, with impact in both lung cancer incidence and mortality. There is preliminary evidence that lung cancer screening with LDCT is effective in patients with COPD, and patients with the disease should be considered for inclusion in lung cancer screening programs. A specific lung cancer screening score for patients with COPD (LUCSS) has proven useful in identifying those with the highest risk of lung cancer[45]. A thorough evaluation by a multidisciplinary team should be implemented in order to attenuate potential harms from diagnostic and therapeutic procedures, especially in those with severe disease. Beyond improving early lung cancer detection, a lung cancer screening program could offer indirect benefits to patients with COPD, such as those resulting from smoking cessation and adequate COPD treatment.

REFERENCES

1. Spiro SG, Silvestri G. One hundred years of lung cancer. Am J Respir Crit Care Med. 2005;172:523-9.
2. 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.
3. GLOBOCAN 2012. Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. International Agency for Research on Cancer. World Health Organization. Available at: globocan.iarc.fr. [Accessed 16/12/2014].
4. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006;3:e442.
5. Thun MJ, Carter BD, Feskanich D, et al. 50-year trends in smoking-related mortality in the United States. N Engl J Med. 2013;368:351-64.
6. Tanoue LT, Tanner NT, Gould MK, Silvestri GA. Lung cancer screening. Am J Respir Crit Care Med. 2015;191:19-33.
7. Vestbo J, Hurd SS, Agustí AG, 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.
8. Skillrud DM, Offord KP, Miller RD. Higher risk of lung cancer in chronic obstructive pulmonary disease. A prospective, matched, controlled study. Ann Intern Med. 1986;105:503-7.
9. Tockman MS, Anthonisen NR, Wright EC, Donithan MG. Airways obstruction and the risk for lung cancer. Ann Intern Med. 1987;106:512-8.
10. Houghton AM, Mouded M, Shapiro SD. Common origins of lung cancer and COPD. Nat Med. 2008;14:1023-4.
11. 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.
12. Aberle D, Adams A, Berg C, et al. Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening. N Engl J Med. 2011;365:395-409.
13. Moyer VA. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;160:330-8.

14. Rooney C, Sethi T. The epithelial cell and lung cancer: the link between chronic obstructive pulmonary disease and lung cancer. Respiration. 2011;81:89-104.
15. Adcock IM, Caramori G, Barnes PJ. Chronic obstructive pulmonary disease and lung cancer: new molecular insights. Respiration. 2011;81:265-84.
16. Caramori G, Casolari P, Cavallesco GN, Giuffrè S, Adcock I, Papi A. Mechanisms involved in lung cancer development in COPD. Int J Biochem Cell Biol. 2011;43:1030-44.
17. Houghton a M. Mechanistic links between COPD and lung cancer. Nat Rev Cancer. 2013;13:233-45.
18. Lowry KP, Gazelle GS, Gilmore ME, et al. Personalizing annual lung cancer screening for patients with chronic obstructive pulmonary disease: A decision analysis. Cancer 2015. [Epub ahead of print].
19. De Torres JP, Bastarrika G, Wisnivesky JP, et al. Assessing the relationship between lung cancer risk and emphysema detected on low-dose CT of the chest. Chest 2007;132:1932-8.
20. Wilson DO, Weissfeld JL, Balkan A, et al. Association of radiographic emphysema and airflow obstruction with lung cancer. Am J Respir Crit Care Med. 2008;178:738-44.
21. Maldonado F, Bartholmai BJ, Swensen SJ, Midthun DE, Decker P, 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.
22. 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.
23. De Torres JP, Marín JM, Casanova C, 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.
24. Sanchez-Salcedo P, Berto J, De-Torres JP, et al. Lung Cancer Screening: Fourteen Year Experience of the Pamplona Early Detection Program (P-IELCAP). Arch Bronconeumol. 2015;51:169-76.
25. Mannino DM, Aguayo SM, Petty TL, Redd SC. Low lung function and incident lung cancer in the United States: data From the First National Health and Nutrition Examination Survey follow-up. Arch Intern Med. 2003;163:1475-80.
26. Wasswa-Kintu S, Gan WQ, Man SFP, Pare PD, Sin DD. Relationship between reduced forced expiratory volume in one second and the risk of lung cancer: a systematic review and meta-analysis. Thorax. 2005;60:570-5.
27. Calabrò E, Randi G, La Vecchia C, et al. Lung function predicts lung cancer risk in smokers: a tool for targeting screening programmes. Eur Respir J. 2010;35:146-51.
28. Turner MC, Chen Y, Krewski D, Calle EE, Thun MJ. Chronic obstructive pulmonary disease is associated with lung cancer mortality in a prospective study of never smokers. Am J Respir Crit Care Med. 2007;176:285-90.
29. Henschke CI, Yip R, Boffetta P, et al. CT screening for lung cancer: Importance of emphysema for never smokers and smokers. Lung Cancer. 2015;88:42-7.
30. Zulueta JJ, Wisnivesky JP, Henschke CI, et al. Emphysema scores predict death from COPD and lung cancer. Chest. 2012;141:1216-23.
31. Kishi K, Gurney JW, Schroeder DR, Scanlon PD, Swensen SJ, Jett JR. The correlation of emphysema or airway obstruction with the risk of lung cancer: a matched case-controlled study. Eur Respir J. 2002;19:1093-8.
32. Smith BM, Pinto L, Ezer N, Sverzellati N, Muro S, Schwartzman K. Emphysema detected on computed tomography and risk of lung cancer: a systematic review and meta-analysis. Lung Cancer. 2012;77:58-63.
33. Wender R, Fontham ETH, Barrera E, et al. American Cancer Society lung cancer screening guidelines. CA Cancer J Clin. 2013;63:107-17.
34. Bach PB, Mirkin JN, Oliver TK, et al. Benefits and harms of CT screening for lung cancer: a systematic review. JAMA. 2012;307:2418-29.
35. 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:e78-92S.
36. American Lung Association. Providing guidance on lung cancer screening to patients and physicians. April 23, 2012. Available at: http://www.lung.org/lung-disease/lung-cancer/lung-cancer-screening-guidelines/lung-cancer-screening.pdf [Accessed Oct 17, 2013].
37. Young RP, Hopkins RJ. Lung cancer risk prediction to select smokers for screening CT--letter. Cancer Prev Res (Phila). 2012;5:697-8; author reply 699.
38. Pinsky PF, Berg CD. Applying the National Lung Screening Trial eligibility criteria to the US population: what percent of the population and of incident lung cancers would be covered? J Med Screen. 2012;19:154-6.
39. Sanchez-Salcedo P, Wilson DO, De-Torres JP, et al. Improving selection criteria for lung cancer screening: the potential role of emphysema. Am J Respir Crit Care Med. 2015;191:924-31.
40. Wang Y, Midthun DE, Wampfler JA, et al. Trends in the proportion of patients with lung cancer meeting screening criteria. JAMA. 2015;313:853-5.
41. Jaklitsch MT, Jacobson FL, Austin JHM, et al. The American Association for Thoracic Surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups. J Thorac Cardiovasc Surg. 2012;144:33-8.
42. Wood DE, Eapen GA, Ettinger DS, et al. Lung cancer screening. J Natl Compr Canc Netw. 2012;10:240-65.
43. Kovalchik S, Tammemagi M, Berg CD, et al. Targeting of low-dose CT screening according to the risk of lung-cancer death. N Engl J Med. 2013;369:245-54.
44. Maisonneuve P, Bagnardi V, Bellomi M, et al. Lung cancer risk prediction to select smokers for screening CT--a model based on the Italian COSMOS trial. Cancer Prev Res (Phila). 2011;4:1778-89.
45. de-Torres JP, Wilson DO, Sanchez-Salcedo P, et al. Lung Cancer in COPD patients: development and validation of the COPD LUng Cancer Screening Score (COPD-LUCSS). Am J Respir Crit Care Med. 2015;191:285-91.
46. Gould MK. Lung-cancer screening with low-dose computed tomography. N Engl J Med. 2014;371:1813-20.
47. de-Torres JP, Casanova C, Marín JM, 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.
48. Choong CK, Meyers BF, Battafarano RJ, Guthrie TJ, Davis GE, Patterson GA, Cooper JD. Lung cancer resection combined with lung volume reduction in patients with severe emphysema. J Thorac Cardiovasc Surg. 2004;127:1323-31.
49. Wang W, Xu Z, Xiong X, et al. Video-assisted thoracoscopic lobectomy for non-small cell lung cancer in patients with severe chronic obstructive pulmonary disease. J Thorac Dis. 2013;5(Suppl 3):S253-9.
50. Vaughan P, Oey I, Nakas A, Martin-Ucar A, Edwards J, Waller D. Is there a role for therapeutic lobectomy for emphysema? Eur J Cardiothorac Surg. 2007;31:486-90; discussion 490.
51. Choong CK, Mahesh B, Patterson GA, Cooper JD. Concomitant lung cancer resection and lung volume reduction surgery. Thorac Surg Clin. 2009;19:209-16.
52. Zhang Y, Sun Y, Wang R, Ye T, Zhang Y, Chen H. Meta-analysis of lobectomy, segmentectomy, and wedge resection for stage I non-small cell lung cancer. J Surg Oncol. 2015;111:334-40.
53. Shirvani SM, Jiang J, Chang JY, et al. Lobectomy, sublobar resection, and stereotactic ablative radiotherapy for early-stage non-small cell lung cancers in the elderly. JAMA Surg. 2014;149:1244-53.
54. Fiorelli A, Costanzo S, di Costanzo E, Santini M. The early detection of lung cancer during follow-up of patients undergoing endobronchial one-way valve treatment for emphysema. Arch Bronconeumol. 2015;51:e13-15.
55. Ashraf H, Saghir Z, Dirksen A, et al. Smoking habits in the randomised Danish Lung Cancer Screening Trial with low-dose CT: final results after a 5-year screening programme. Thorax. 2014;69:574-9.
56. Slatore CG, Baumann C, Pappas M, Humphrey LL. Smoking behaviors among patients receiving computed tomography for lung cancer screening: Systematic review in support of the U.S. Preventive services task force. Ann Am Thorac Soc. 2014;11:619-27.
57. Tønnesen P. Smoking cessation and COPD. Eur Respir Rev. 2013;22:37-43.
58. Dhariwal J, Tennant RC, Hansell DM, et al. Smoking cessation in COPD causes a transient improvement in spirometry and decreases micronodules on high-resolution ct imaging. Chest. 2014;145:1006-15.