Eur Respir J 2012; 39: 1230–1240
DOI: 10.1183/09031936.00126011

REVIEW

Early detection of COPD is important for lung cancer surveillance

Yasuo Sekine*, Hideki Katsura#, Eitetsu Koh*, Kenzo Hiroshima¶ and Takehiko Fujisawa+

ABSTRACT: It is well known that chronic obstructive pulmonary disease (COPD) is a significant risk factor for lung cancer. Approximately 1% of COPD patients develop lung cancer every year, which may be associated with genetic susceptibility to cigarette smoke. Chronic inflammation caused by toxic gases can induce COPD and lung cancer. Inflammatory mediators may promote the growth of bronchioalveolar stem cells, and activation of nuclear factor-κB and signal transducer and activator of transcription 3 play crucial roles in the development of lung cancer from COPD.

Low-dose computed tomography (LDCT) is an effective procedure for the early detection of lung cancer in high-risk patients. However, determining which patients should be screened for lung cancer in a primary care setting is difficult. In this article, we review the epidemiology and aetiology of lung cancer associated with COPD, verify the efficacy of lung cancer screening by LDCT, and discuss the importance of early detection of COPD for lung cancer surveillance.

We propose that, for the prevention of both diseases, COPD screening in smokers should be initiated as early as possible, so they can stop smoking and so that candidates for an efficient lung cancer screening programme can be identified.

KEYWORDS: Aetiology, low-dose computed tomography, pulmonary function test, risk factor, screening, smoking cessation

Chronic obstructive pulmonary disease (COPD) and lung cancer are rapidly growing, worldwide health problems. In 2008, the World Health Organization published the top 10 causes of death, with COPD as the fourth most common, with 3.28 million deaths (5.8% of all deaths), and lung cancer as the seventh, with 1.39 million deaths (2.4%) [1].

It is well known that exposure to toxic gases and particulates, especially those in cigarette smoke, induces both diseases. COPD has been reported to be a risk factor for lung cancer independent of cigarette smoking [2, 3]. The Multiple Risk Factor Intervention Trial reported that patients with airflow limitations had a significantly higher prevalence of lung cancer than patients without airflow limitations, after adjusting for smoking (3.02 *versus* 0.43 per 1,000 persons per yr, respectively), and that the lag time for beneficial effects on lung cancer development after smoking cessation may be as long as 20 yrs [4]. This suggests that COPD patients are more likely to develop lung cancer compared with current or former smokers with normal pulmonary function. Although the close association of these two major pulmonary diseases has long been of interest, details of the molecular pathways involved and their clinical correlates have only begun to be clarified within the past decade.

Lung cancer screening in the 1980s employed chest radiography (CXR) and sputum cytology, and whether or not they provided any decrease in mortality has been inconclusive [5]. During the 2000s, early detection of lung cancer by low-dose computed tomography (LDCT) achieved acceptable early stage detection and increased resectability rates [6, 7]. However, mortality benefits have not been proven [7].

Initial results from the National Lung Screening Trial (NLST) indicated that there were 20% fewer lung cancer deaths among trial participants who were screened by LDCT compared with subjects who were screened by CXR [8]. Participants were 55–74 yrs of age, and current and former smokers. This study comprised >53,000 subjects and focused

AFFILIATIONS
Depts of *Thoracic Surgery, #Pulmonary Medicine and ¶Pathology, Tokyo Women's Medical University Yachiyo Medical Center, and +Chiba Foundation for Health Promotion and Disease Prevention, Chiba, Japan.

CORRESPONDENCE
Y. Sekine
Dept of Thoracic Surgery
Tokyo Women's Medical University
Yachiyo Medical Center
477-96 Owada-Shinden
Yachiyo
Chiba
276-8524
Japan
E-mail: ysekine@tymc.twmu.ac.jp

Received:
July 23 2011
Accepted after revision:
Oct 11 2011
First published online:
Nov 16 2011

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

on heavy smokers, defined as those with a smoking history of ⩾30 pack-yrs. By comparison, patients with COPD are generally 50–80 yrs of age, and patients with COPD have a higher risk for lung cancer than heavy smokers with normal lung function [4]. Therefore, LDCT screening of COPD patients may be expected to achieve a higher lung cancer detection rate than detection by screening heavy smokers.

This article reviews the relationship between COPD and lung cancer, and discusses the importance of early detection of COPD for lung cancer surveillance.

EPIDEMIOLOGY AND RISK OF LUNG CANCER IN COPD PATIENTS

Several reports have shown that the prevalence of COPD in lung cancer patients varies from 8% to 50% [9, 10]. The annual incidence of lung cancer arising from COPD has been reported to be 0.8% to 1.2% [11–13]. SKILLRUD *et al*. [11] assessed the risk of lung cancer in patients with COPD in a matched case–control study and estimated that the cumulative probability of developing lung cancer within 10 yrs was 8.8% for those with COPD and 2.0% for patients with normal pulmonary function ($p=0.024$). This indicates that ~1% of patients with COPD develop lung cancer each year, while only 0.2% of patients with normal pulmonary function develop lung cancer (five-fold increased risk of lung cancer). Recently, DE TORRES *et al*. [14] reported that 215 out of 2,507 COPD patients developed lung cancer (incidence density of 16.7 cases per 1,000 person-yrs) with a median follow-up of 60 months. This result suggested that, in a well characterised population of smokers with established COPD who were attending pulmonary clinics, the incidence of lung cancer from COPD was higher than previously reported [11].

The Environment and Genetics in Lung Cancer Etiology population-based case–control study recruited 2,100 lung cancer cases and 2,120 controls. This study showed that lung cancer risk was increased among individuals with chronic bronchitis (OR 2.0, 95% CI 1.5–2.5), emphysema (OR 1.9, 95% CI 1.4–2.8) and COPD (OR 2.5, 95% CI 2.0–3.1) [2]. From a 20-yr follow-up study of 448,600 lifelong nonsmokers, TURNER *et al*. [3] also reported that lung cancer mortality was significantly associated with both emphysema (hazard ratio (HR) 1.66, 95% CI 1.06–2.59) and emphysema combined with chronic bronchitis (COPD) (HR 2.44, 95% CI 1.22–4.90), but not with chronic bronchitis alone (HR 0.96, 95% CI 0.72–1.28). In both studies, COPD was diagnosed by the presence of the clinical symptoms of emphysema or chronic bronchitis and patient questionnaires, but not by spirometry or computed tomography scans.

The severity of COPD also influences the incidence of lung cancer. The first National Health and Nutrition Examination Survey collected data from a 22-yr follow-up of 5,402 participants and demonstrated a positive correlation between the degree of airflow obstruction and lung cancer incidence [15]. Multivariate proportional hazards analysis of the data in this survey showed that mild COPD had a relatively higher risk (HR 1.4, 95% CI 0.8–2.6) and moderate or severe COPD had a significantly higher risk of lung cancer incidence compared with normal pulmonary function (HR 2.8, 95% CI 1.8–4.4). Conversely, DE TORRES *et al*. [14] reported that lung cancer incidence decreased in a stepwise manner from COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages I to IV, and the incidence at stage IV (9.2 per 1,000 person-yrs) was less than half the incidence at stage I (19.9 per 1,000 person-yrs). They speculated that an active and non-tolerant immune system would act as a barrier against cancer development and progression.

Because only 15–20% of smokers are thought to develop lung cancer and/or COPD in their lifetimes, individuals may have different susceptibilities to these diseases [16]. COHEN [17] was the first to report on the genetic epidemiology of COPD. Patients whose first-degree relatives had COPD or lung cancer had an increased risk for airflow limitation, with or without smoking history. Furthermore, smokers with a family history of early-onset lung cancer among first-degree relatives had higher risk for lung cancer development with increasing age compared with smokers without a family history [18]. These findings suggest that there are susceptibility genes associated with these diseases [19].

Emphysema and airflow obstruction (chronic bronchitis) are both end phenotypes of COPD, and the majority of patients with COPD are found somewhere in the middle. It remains controversial which condition, emphysema or airflow obstruction, leads to greater susceptibility to lung cancer [20]. WILSON *et al*. [21] reported that although both airflow obstruction and emphysema, independent from cigarette smoking, were predictors of lung cancer, emphysema was a higher risk for lung cancer compared to small-airway obstruction. DE TORRES *et al*. [22] showed that emphysema found on computed tomography, but not airflow obstruction, was associated with an increased frequency of lung cancer. Results of lung cancer screening by the Mayo Clinic (Rochester, MN, USA) from multiple logistic regression models showed that emphysema (⩾5% on computed tomography) was associated with a 3.8-fold increased risk of lung cancer in Caucasians and with higher risks in subgroups that included younger people (<65 yrs of age, OR 4.64), heavy smokers (⩾40 pack-yrs, OR 4.46), and small-cell lung cancer (OR 5.62) [23]. Emphysema was assessed in these studies by visual semiquantitative scoring of computed tomography images. By contrast, MALDONADO *et al*. [24] reported that the radiographic evidence for emphysema, evaluated by automated quantitative computed tomography analysis, was not a significant risk for lung cancer (OR 1.042, 95% CI 0.816–1.329) and emphysema severity was also not associated with lung cancer (OR 1.57, 95% CI 0.73–3.37). However, decreased forced expiratory volume in 1 s (FEV_1) (OR 1.15, 95% CI 1.00–1.32) and FEV_1/forced vital capacity (FVC) (OR 1.29, 95% CI 1.02–1.62) were significant risk factors. KISHI *et al*. [25] also reported similar results from quantitative computed tomography analysis. GIERADA *et al*. [26] reported that not only emphysema but also bronchial measurements at segmental–subsegmental levels, as assessed by automated computed tomography analysis, were not also associated with lung cancer. WILSON *et al*. [27] reported that their case–control study of 117 lung cancer cases did not reveal any evidence that either airway obstruction or emphysema, as assessed by quantitative analysis of computed tomography images, was associated with increased risk of lung cancer. Therefore, emphysema as a risk for lung cancer remains controversial and requires additional clarification. As DHOPESHWARKAR *et al*. [28] have postulated, the study populations in which lung cancers were detected by screening may differ from the general pool of patients with lung cancers, with regard to cancer site, morphology (density, border), size, histology, stage at diagnosis, treatment and survival. Therefore, these results should be interpreted with care.

Interestingly, the majority of lung cancers among nonsmokers has been reported to occur in females [29], and 10% of males and 20% of females with lung cancer are reported to be never-smokers [30]. Reduced FEV1 has been reported to increase the risk for lung cancer in the never-smoking population [3]. CALABRÒ *et al*. [31] reported that a reduction of as little as 10% in the predicted FEV1 was associated with a nearly three-fold greater lung cancer risk. They suggested that recognition of minimal lung function impairments might identify the best candidates for trials of early detection and lung cancer screening. The evidence presented here suggests that both emphysema and airway obstruction are independent risk factors for lung cancer and that patients with these conditions should be screened.

COPD COMORBIDITIES AND ASSOCIATION WITH LUNG CANCER

COPD and cigarette smoking induce systemic inflammatory changes that result from localised chronic inflammation in the lung. COPD patients have a higher prevalence of certain co-morbidities, including coronary artery disease, congestive heart disease, other cardiovascular diseases, regional malignancies (mainly lung cancer) and neurological diseases [32]. They have an average of 3.7 chronic comorbidities, compared with 1.8 comorbidities in controls [32]. The US National Hospital Discharge Survey analysed more than 47 million hospital discharges between 1979 and 2001, and found that COPD was associated with higher age-adjusted in-hospital mortalities for pneumonia, hypertension, heart failure, ventilatory failure and thoracic malignancies, compared with discharges without COPD (all $p<0.01$) [33]. SIN *et al*. [34] summarised several series with regard to the underlying causes of death in COPD patients. They reported that the main causes of death in those with mild or moderate COPD were lung cancer and cardiovascular diseases, while in those with more advanced COPD (<60% of predicted FEV1), respiratory failure was the predominant cause. This suggests that early COPD detection and prudent, regular follow-ups are needed for early detection of lung cancer and increased survival.

The characteristics of lung cancer in patients with COPD are different from those without COPD [35]. Smokers with COPD have a higher risk of developing a specific histological subtype of non-small cell lung cancer, squamous cell carcinoma [35–37], although adenocarcinoma has been rapidly increasing among patients passively exposed to cigarette smoke, light smokers and females [22]. DE TORRES *et al*. [14] also reported that, although adenocarcinoma was the most prevalent histological type only in GOLD stage I patients, the most frequent type of lung cancer was squamous cell carcinoma in GOLD stage II and III patients. Recent new molecularly targeted drugs, such as gefitinib, erlotinib, bevacizumab and crizotinib, predominantly target adenocarcinoma, and there have been few new agents effective against squamous cell carcinoma. Investigating the association between a single histological type of lung cancer and severity of airflow obstruction may provide insight into the pathobiology of lung cancer in patients with COPD and lead to the development of new molecularly targeted drugs, especially for squamous cell carcinoma.

PROGNOSIS OF LUNG CANCER PATIENTS WITH COPD

The prognosis of lung cancer patients with COPD is worse than the prognosis of patients without COPD, because of inadequate cancer treatments, and poorer pulmonary function and quality of life [10]. We investigated post-operative long-term survival in stage IA lung cancer patients with COPD [38]. The 5-yr survival rate of patients with COPD was significantly lower than the rate of patients with normal pulmonary function, because of a higher recurrence rate (77.0% *versus* 91.6%, respectively; $p<0.0001$). These results suggested that the lung cancers developing in COPD patients tended to be higher grade malignancies, with lower rates of bronchioalveolar carcinoma and well-differentiated adenocarcinoma. Results of other studies demonstrated that COPD was a significant risk factor for the development of respiratory-related complications and poorer long-term survival, because of respiratory failure after pulmonary resection for lung cancer [39, 40]. LÓPEZ-ENCUENTRA *et al*. [41] reported that although overall survival was similar between COPD and non-COPD patients after lung cancer surgery, conditional survival in stage I lung cancer patients at 2 and 3 yrs was significantly worse in COPD patients than in non-COPD patients. Conversely, POMPILI *et al*. [42] reported that although COPD patients had a much higher rate of post-operative cardiopulmonary morbidity compared with non-COPD matched pairs, post-operative physical and mental quality of life scales and peri-operative changes did not differ between COPD and matched non-COPD patients. Because they did not report long-term results, the effects of their findings on survival are not known.

POSSIBLE COMMON PATHOGENIC PATHWAYS FOR DEVELOPMENT OF LUNG CANCER IN COPD PATIENTS

Several possible mechanisms and associated candidate genes have been proposed for the progression from airflow obstruction to lung cancer. Candidate genes that may be involved in susceptibility are shown in table 1.

TABLE 1 Candidate susceptibility genes involved in both chronic obstructive pulmonary disease and lung cancer

Inflammation [43–49]	COX-2, NF-κB, IL-1β, IL-6, STAT3, neutrophil elastase, IL-8/neutrophil MIF/macrophage
Mutation and polymorphisms [48, 50–54]	Kras, p53, p16, GSTM1, CYP2A6, nAChR, HHIP, GYPA
Methylation [44–56]	IL-12Rβ2, Wif-1, p16, DNMT1
Overexpression [55]	HER2
MMPs [19, 57]	MMP-1, MMP-2, MMP-12
Hypoxia/angiogenesis [44]	HIF1-α, HIF2-α, VEGF
Cell cycle regulator [44]	p21
Adhesion molecules [44]	Galectin-3
Others [58–60]	α_1-ATD allele, FAM13A

COX: cyclo-oxygenase; NF: nuclear transcription factor; IL: interleukin; STAT3: signal transducer and activator of transcription 3; MIF: macrophage migration inhibitory factor; GSTM1: glutathione S-transferase μ1; nAChR: nicotinic acetylcholine receptor; HHIP: Hedgehog-interacting protein; GYPA: glycophorin A; IL-12R: interleukin-12 receptor; Wif-1: WNT inhibitory factor 1; DNMT1: DNA methyltransferase 1; HER2: human EGFR-related 2; MMP: matrix metalloproteinase; HIF: hypoxia inducible factor; VEGF: vascular endothelial growth factor; α_1-ATD: α_1-antitrypsin deficiency; FAM13A: family with sequence similarity 13 member A.

First, mucociliary dysfunction caused by smoking or exposure to environmental substances results in the accumulation of toxicants in the airway, and COPD exacerbates dysfunction [61]. Mucociliary dysfunction is thought to occur mainly in the central airways. Secondly, an imbalance between oxidants and antioxidants can lead to free radical damage of DNA [62]. Thirdly, genetic mutations and polymorphisms may influence the acceleration or suppression of lung cancer development. DIALYNA *et al*. [50] reported that the frequency of a genetic null mutation of glutathione S-transferase μ1 (*GSTM1*), which is an enzyme that acts against tissue-injurious substances in tobacco, was significantly higher in COPD patients with lung cancer than in healthy controls. In contrast, a genetic mutation and polymorphisms of *CYP2A6* suppress carcinogenesis and exacerbation of COPD [51].

Fourthly, chronic inflammation, which has recently received the most attention, can lead to chronic mitogenesis and increase the likelihood of the conversion of endogenous DNA damage into mutations [63]. Chronic inflammation resulting from airway obstruction plays an important role in lung cancer development and could be an important component of the field-effect phenomenon [44, 64, 65]. COPD involves chronic inflammation of the respiratory tract, particularly of the small airways, and is manifested by the accumulation of macrophages, CD4+ and CD8+ T-cells, dendritic cells, and neutrophils [66]. It has been suggested that chronic inflammation in the lower respiratory tract can induce carcinogenesis [67–69], and that inflammatory mediators in the microenvironment promote bronchioalveolar stem cells to induce proneoplastic mutations, proliferation, resistance to apoptosis, angiogenesis, invasion, metastasis and secretion of immunosuppressive factors (fig. 1) [70, 71].

It has been recently proposed that activation of nuclear transcription factor (NF)-κB may have a crucial role in the development of lung cancer from COPD [72, 73]. NF-κB activation increases the release of inflammatory mediators that can induce COPD, and also inhibits apoptosis, induces proliferation and, finally, accelerates cancer development. NF-κB activation and the subsequent actions of inflammation-related genes may play a central role in both COPD and lung cancer. Signal transducer and activator of transcription 3 (STAT3) is a potent transcription factor with diverse biological functions. Persistent activation of STAT3 signalling pathway also induces pulmonary inflammation and adenocarcinoma formation in the lung. STAT3 and its downstream genes can serve as biomarkers for lung adenocarcinoma and COPD diagnosis and prognosis [45]. The tumour suppressor protein p53 is a general inhibitor of inflammation [74]; its gene, *TP53*, is often mutated by cigarette smoke and may be suppressed by oxidant activation of NF-κB-mediated inflammation [73].

SUNDAR *et al*. [56] reviewed epigenetic modifications in the pathogenesis of COPD and lung cancer. They reported that oxidative stress and inflammatory response alter the redox potential of cells, which leads to destabilisation of the genome, culminating in epigenetic modifications. Epigentic modifiers, including DNA methyltransferases, histone acetyltransferases and histone deacetylases, are involved in the ''opening and closing'' of chromatin, and play a crucial role in modulating gene expression.

Recent genome-wide association (GWA) studies in lung cancer and COPD have reported significant associations at several chromosomal loci and single nucleotide polymorphisms in these regions [54, 75, 76]. Results of GWA studies showed that many candidate loci for COPD and lung cancer overlap [75]. Pulmonary inflammation induced by smoking is thought to underlie COPD and to be characterised by elevated levels of growth factors and matrix metalloproteinases. In this microenvironment, premalignant transformation of the airway epithelium is known to occur, potentially linking COPD with the development of lung cancer [54]. YOUNG *et al*. [76] suggested that future genetic epidemiological studies of lung cancer might benefit greatly from the exploration of this overlap by subphenotyping cases and controls for coexisting COPD.

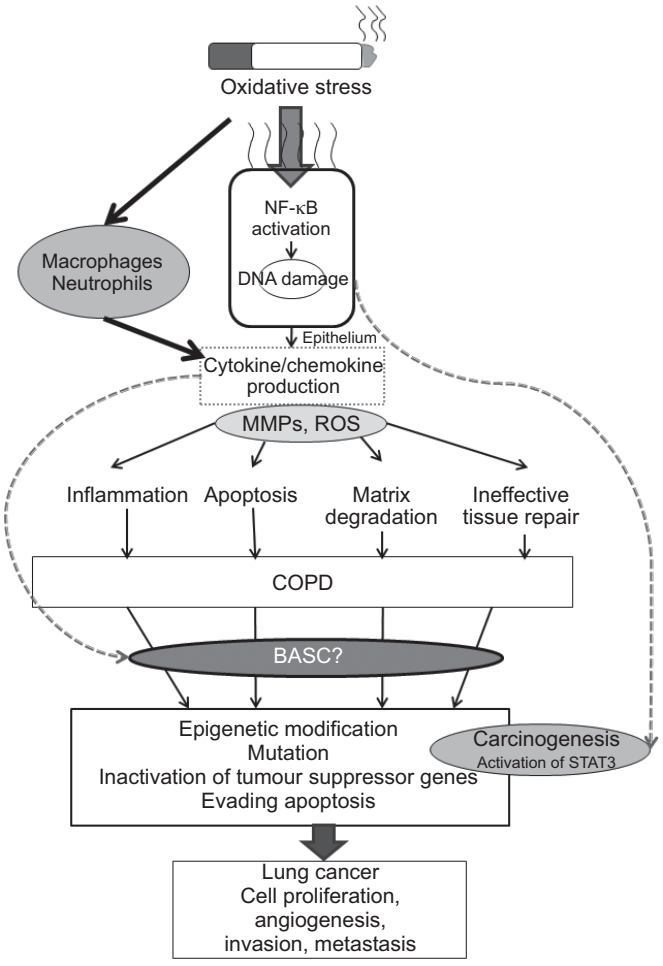

FIGURE 1. Putative mechanism of lung carcinogenesis from chronic obstructive pulmonary disease (COPD) in inflammatory microenvironment. Oxidative stress by cigarette smoke stimulates the nuclear factor (NF)-κB pathway in lung epithelium and recruits inflammatory cells, macrophages and neutrophils that release cytokines and chemokines. Released matrix metalloproteinases (MMPs) and reactive oxygen species (ROS) induce inflammation, apoptosis, matrix degradation, and ineffective tissue repair, leading to enlarged airspaces. Bronchioalveolar stem cells (BASC) may attempt to repair and replace damaged alveolar cells but enhance carcinogenesis in an inflammatory environment. Persistent activation of signal transducer and activator of transcription 3 (STAT3) signalling pathway also induces pulmonary inflammation and carcinogenesis in the lung.

Another specific genetic mechanism involved in the aetiology of progression from COPD to lung cancer is the α_1-antitrypsin deficiency (α_1-ATD) allele. Those who were α_1-ATD carriers had

a higher risk of lung cancer compared to the general population [58, 59]. YANG *et al*. [59] reported on a model of 1,585 case–control pairs with and without the α_1-ATD allele using multiple logistic regression analysis, and found that α_1-ATD carriers had a 70% higher risk of developing lung cancer than noncarriers (OR 1.7, 95% CI 1.2–2.4). This suggested that the α_1-ATD allele can almost double susceptibility to lung cancer.

LUNG CANCER PREVENTION IN COPD PATIENTS

Individuals at high risk for lung cancer should be appropriate candidates for screening surveillance and preventive intervention. DOLL and PETO [77] proposed a risk prediction model for smoking. They suggested that the duration of smoking had a stronger impact on the risk of lung cancer than the amount smoked per day. Most patients with COPD have a positive smoking history, and the progression of COPD is closely related to age of onset, and the duration and total amount of smoking. Thus, patients with mild to moderate COPD have a three-fold greater chance and those with severe COPD have a 10-fold greater chance of developing lung cancer within 10 yrs, compared to smokers with normal pulmonary function [15], although DE TORRES *et al*. [14] found an inverse relationship between lung function severity and lung cancer incidence. Even with mild COPD, patients with emphysema may have a high risk of lung cancer [14, 22], and thus patients with any stage of COPD need screening surveillance for lung cancer. BACH *et al*. [78] also constructed a prediction model for lung cancer risk that estimated the absolute risk that an individual current or ex-smoker ($\geqslant$20 pack-yrs) would be diagnosed with lung cancer within 10 yrs, by analysing data from a large randomised trial, the Carotene and Retinol Efficacy Trial. They reported that the risk of lung cancer varied widely, but accurate risk prediction might provide information that enables individuals to decide whether to be screened for lung cancer. SPITZ *et al*. [79] established a risk model for predicting lung cancer based on smoking status by additional development of Bach's model. They reported that a history of emphysema was the highest risk factor for lung cancer among current and former smokers.

The most effective lung cancer prevention measure is smoking cessation. A large longitudinal study by ANTHONISEN *et al*. [80] showed that 33% of asymptomatic smokers with mild-to-moderate COPD had died of lung cancer after a 14.5-yr follow-up. They reported that all-cause mortality was significantly lower in a special smoking cessation intervention group than in the usual-care group (8.83 per 1,000 person-yrs *versus* 10.38 per 1,000 person-yrs, respectively; $p=0.03$), although the difference was not statistically significant for lung cancer.

Regular use of an inhaled glucocorticoid may reduce the risk of lung cancer among former smokers with COPD [81, 82]. However, long-term inhalation of high-dose glucocorticoids did not induce any regression of bronchial dysplasia or secondary markers of carcinogenesis in smokers [83] and did not decrease the risk of lung cancer [84]. HARRIS [85] reported that a selective cyclo-oxygenase-2 inhibitor (celecoxib or rofecoxib) may reduce the risk of lung cancer. Other anti-inflammatory agents for lung cancer prevention include luteolin [86], tocopherols [87] and carboxyamido-triazole [88]. Statins have been recently noted to be important anti-inflammatory substances in the lung. Non-randomised studies have shown reductions in cardiovascular and respiratory morbidity and mortality in patients with COPD associated with statins. Moreover, statins may ameliorate declines in FEV1 and lessen the risk of lung cancer [89, 90].

IMPORTANCE OF LUNG CANCER SCREENING IN COPD PATIENTS

Lung cancer screening is one method for second-line cancer prevention. The most important primary end-point for lung cancer screening is the reduction of lung cancer mortality. The Lung Screening Study of the National Cancer Institute found that at baseline, 20.5% of subjects (325 out of 1,586) in the LDCT cohort and 9.8% of subjects (152 out of 1,550) in the CXR cohort were diagnosed with findings suspicious of lung cancer. The confirmed lung cancer detection rate was 1.9% (30 out of 1,586) in the LDCT cohort and 0.45% (seven out of 1,550) in the CXR cohort [91]. In their report of the final results of that study, out of a total of 1,660 patients enrolled in the LDCT cohort and 1,658 in the CXR cohort, 40 (2.4%) patients and 20 (1.2%) patients, respectively, were diagnosed with lung cancer [92].

Japanese studies and the US Early Lung Cancer Action Project (ELCAP) showed that in a high-risk population, more lung cancer could be detected by spiral computed tomography screening than by CXR [93, 94]. SOBUE *et al*. [95] reported that the 5-yr survival rates for computed tomography screen-detected lung cancer were 76.2% and 64.9% for initial and repeated screening, respectively. Of those patients who were screened by computed tomography in the International ELCAP (I-ELCAP) protocol, 85% had clinical stage I lung cancer, and the estimated 10-yr survival rate was 88% [6]. These studies all demonstrated remarkably high detection and survival rates, and suggest that computed tomography screening may be beneficial for the early detection and curative surgery of lung cancer (tables 2 and 3).

BECHTEL *et al*. [114] investigated the efficacy of early detection of lung cancer by chest computed tomography for patients with COPD, and reported that six lung cancer cases were detected among 88 high-risk patients with COPD (6.8%). There were three stage I patients, and three out of six survived for >5 yrs. This detection rate was higher than the initial cancer detection rates of 1.2% to 1.6% reported by others [6, 115].

In order to prove the efficacy of lung cancer screening, however, screening biases, such as lead time, length and over-diagnosis should be resolved [116]. Therefore, randomised controlled trials are preferable. Currently, there are several large randomised controlled trials ongoing in a number of countries. The NLST is the largest multicentre, randomised controlled trial [8]. The independent Data and Safety Monitoring Board of this trial announced that all-cause mortality was 7% lower in the LDCT group than in the CXR group, and ~25% of all deaths were due to lung cancer [111]. Interestingly, among the NLST participants, there were >17.4% with self-reported COPD and 7.7% with emphysema [112]. Ancillary analysis of the NLST results is expected to clarify the association of these high-risk medical conditions with lung cancer incidence.

Other recent advances in the early detection and screening of lung cancer have been reviewed by VAN'T WESTEINDE and VAN KLAVEREN [117]. They reported that light-induced fluorescence endoscopy or autofluorescence imaging endoscopy for bronchial carcinoma in the central airway, detection of circulating DNA in peripheral blood and methylated genes in plasma, measurement of circulating tumour-derived exosome levels, determination of

TABLE 2 Observational and randomised computed tomography screenings for lung cancer, study designs and results

No.	Reference	State of study progression	Years of enrolment	End of study	Published year	Study design	Age criteria	Eligibility of smoking status	Participants n	Tested	Classification
1	KANEKO *et al*. [93]	Completed	1993–1995	1995	1996	Observational	No restriction	No restriction	1369	3457	LDCT
2	ELCAP [94, 96]	Completed	1993	1998	1999, 2001	Observational	⩾60 yrs	⩾10 pack-yrs	1000	1000 (baseline) 1184 (repeated)	LDCT
3	SONE and co-workers [97, 98]	Completed	1996	1998	2001	Observational	40–74 yrs	No restriction	5483	5483 (1996) 4425 (1997) 3878 (1998)	LDCT
4	TIITOLA *et al*. [99]	Completed	NR	NR	2002	Observational	No restriction	No restriction	602	602	LDCT
5	ALCA [95]	Completed	1993	1998	2002	Observational	40–79 yrs	No restriction	1611	1611 (baseline) 7891 (repeated)	LDCT
6	DIEDERICH and co-workers [100, 101]	Completed	1995–1999	1999	2002	Observational	40–78 yrs	⩾20 pack-yrs	817	817 (baseline) 1735 (repeated)	LDCT
7	NAWA *et al*. [102]	Completed	1998–2000	2000	2002	Observational	50–69 yrs	No restriction	7956	7956 (baseline) 5568 (repeated)	LDCT
8	PASTORINO *et al*. [103]	Completed	2000–2002	2003	2003	Observational	⩾50 yrs	⩾20 pack-yrs	1035	1035	LDCT±PET
9	SWENSEN and co-workers [104–106]	Completed	1999	2003	2005	Observational	⩾50 yrs ⩾20 pack-yrs Quit <10 yrs		1520	1520 (baseline) 1464 (98% at year 1) (96% at year 2, 95% at year 3, 80% at year 4)	LDCT
10	LSS [91, 92]	Completed	2000	2001	2005	Pilot RCT	55–74 yrs	⩾30 pack-yrs Active or quit <10 yrs	3277	3277	LDCT 1660 CXR 1658
11	Dépiscan [107]	Completed	2002	2004	2007	Pilot RCT	50–75 yrs	⩾15 cigarettes per day for >20 yrs. Quit <15 yrs	756	621	LDCT 385 CXR 380
12	DANTE [7, 108]	3-yr follow-up	2001–2006	2006	2009	RCT	60–74 yrs	⩾20 pack-yrs Active or quit <10 yrs	2811	2472	LDCT 1276 Control 1196
13	NELSON [109, 110]	Ongoing	2003–2005	Ongoing	2008	RCT	50–75 yrs	>15 cigarettes per day for >25 yrs or >10 cigarettes per day for >30 yrs. Active or quit ⩽10 yrs	15428	15428	LDCT CXR
14	NLST [8, 111, 112]	Analysing	2002–2004	Ongoing	2010	RCT	55–74 yrs	⩾30 pack-yrs Active or quit <15 yrs	53476	NR	LDCT 26723 CXR 26733
15	I-ELCAP [6, 113]	Ongoing	1993–2005	Ongoing	2006, *etc*.	Multi-institutional research study	⩾40 yrs	No restriction	31567	31567 (baseline) 27456 (repeated)	CT

(I-)ELCAP: (International) Early Lung Cancer Action Project; ALCA: Anti-lung Cancer Association (Japan); LSS: Lung Screening Study; Dépiscan: a French randomised pilot trial of lung cancer screening; DANTE: Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays; NELSON: the Dutch-Belgian randomised lung cancer multi-slice CT screening trial; NLST: National Lung Screening Trial; NR: not reported; RCT: randomised controlled trial; (LD)CT: (low dose) computed tomography; PET: positron emission tomography; CXR: chest radiography.

TABLE 3 Observational and randomised computed tomography screenings for lung cancer, study designs and results, continued

No.	Median follow-up	Males %	Age yrs	Exposure (smoking status)	Ratio of COPD	Positive screening for nodules	Lung cancer	Stage I	Lung cancer operability	Mortality	Lung cancer mortality
1	NR	90	60.4 (38–83)	NR	NR	20.30%	15 (0.3%)	14 (93%)	14 (93%)	NR	NR
2	NR	54	67	Current 100%	NR	0.23	33 (3.3%)	28 (84.8%)	NR	NR	NR
3	NR	46	65	Current 54.3%	NR	5.1% (1996) 4.0% (1997) 3.5% (1998)	60 (0.4%)	55 (92%)	60 (100%)	5 (0.1%)	2 (0.04%)
4	NR	98	63 (38–81)	Current 97%	NR	18.4%	5 (0.8%)	2 (40%)	1 (20%)	NR	4 (0.7%)
5	NR	88	64	Current 61% Former 25%	NR	11.5% (initial) 9.1% (repeated)	14 (0.9% initial) 22 (0.3% repeated)	11 (78.6% initial) 18 (82% repeated)	12 (86% initial) 17 (77% repeated)	8 (0.5%)	3 (0.2%)
6	NR	72	53 (40–78)	Current 100%	NR	43%	11 (1.3%)	7/12 lesions (58%)	7/12 lesions (58%)	4 (0.5%)	2 (0.2%)
7	NR	79	NR	Current 62.1%	NR	26.4% (initial)	40 (0.5%)	35 (87.5%)	40 (100%)	NR	NR
8	NR	71	58 (50–84)	Current 86%	NR	29%	22 (2.1%)	17 (77%)	21 (95%)	8 (0.8%)	1 (0.1%)
9	5 yrs	52	59 (50–85)	Current 61%	NR	51% (initial), 74% (total)	66 (4.3%)	17/28 subsequent NSCLC cases (61%)	NR	48 (3.2%)	9 (0.6%)
10	NR	59	NR	Current 58%	NR	34.5%	40 (2.4%)	19 (48%)	NR	NR	NR
					NR	15.8%	20 (1.2%)	8 (40%)	NR	NR	NR
11	NR	71	56 (47–75)	Current 65.0%	NR	45.2%	8 (2.1%)	3 (37.5%)	NR	NR	NR
			56 (47–76)	Current 64.0%	NR	7.4%	1 (0.8%)	1 (100%)			
12	33.7 (1.8–79.2) months	100	64.3	Current 56.0%	446 (35%)#	27.5%	60 (4.7%)	33 (55%)	39 (65%)	46 (3.6%)	20 (1.6%)
			64.6	Current 56.9%	370 (30.1%)# p=0.04	8.9%	34 (2.8%) p=0.016	12 (35%) p=0.004	17 (50%) p=0.25	45 (3.8%) p=0.83	20 (1.7%) p=0.84
13	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
14	NR	59	61.4	Current 48%	4674 (17.5%) 4652 (17.4%)	NR	NR	NR	NR	NR	354 (1.3%) 442 (1.7%)
15	40 (1–123) months	NR	61 (40–85)	Current or former 82.8%	NR	NR	484	412 (85%)	411 (85%)	NR	75

Follow-up period data are provided with ranges where possible. Age data are presented as mean or median and range. COPD: chronic obstructive pulmonary disease; NR: not reported; NSCLC: nonsmall-cell lung cancer. #: chronic respiratory symptoms (DANTE trial).

micro-RNA patterns, comparative protein profiling, detection of autoantibodies against cancer-associated antigens, exhaled breath analysis, identification of genomic-based markers in bronchoalveolar lavage samples, and biomarkers in sputum are promising candidates.

EARLY DETECTION OF COPD FOR LUNG CANCER SURVEILLANCE

COPD is substantially under-diagnosed [118, 119] and frequently misdiagnosed [120]. SORIANO *et al*. [119] summarised reports of prevalence and under-diagnosis. They reported that 72% to 93% of COPD patients were not diagnosed. The Nippon (Japan) COPD Epidemiology study reported that the prevalence of airflow limitation (FEV1/FVC <70%) was 10.9%, and only 9.4% of patients with airflow limitation had a previously reported diagnosis of COPD [121]. Although the definitive diagnosis of COPD is made by spirometry, in general practice, it has been used for only 30% to 50% of new cases [122, 123].

The prevalence of COPD in the general population is thought to be about 1%, and the prevalence increases to 8% to 10% of the population over 40 yrs of age [124]. FUKUCHI *et al*. [121] reported that COPD prevalence steeply increased at age 60 yrs and older: 5.8% at 50–59 yrs *versus* 15.7% at 60–69 yrs, and 24.7% at 70 yrs and older.

Early diagnosis of COPD has been attempted for high-risk patients [125, 126], and spirometry has been proven to play an important role in COPD screening and early diagnosis. BUFFELS *et al*. [126] reported that spirometry confirmed airflow obstruction in 18% of individuals with respiratory symptoms and in 4% of those without these symptoms. VAN SCHAYCK *et al*. [125] investigated the effectiveness of cross-sectional case findings for patients with a history of cigarette smoking who were at risk for developing COPD, using a standardised questionnaire and spirometry. They reported that 18% of the participants had airway obstruction, and that when smokers were preselected based on respiratory symptoms, such as chronic cough, the percentage of patients with airway obstruction increased to 48% among those older than 60 yrs of age. The positive predictive value of cough for airflow obstruction was 27% and that of at least two respiratory symptoms, including cough, dyspnoea or wheezing, was 29%. In patients with all three symptoms, the prevalence was 35%. Therefore, they recommended that pulmonary function testing should be performed in all smokers with chronic cough.

These results suggest that at the minimum, current or former smokers aged 60 yrs or older and who have some respiratory symptoms, may be potential candidates for COPD and should be screened by pulmonary function testing. Furthermore, to prevent COPD and lung cancer, in accordance with suggestions by CALABRÒ *et al.* [31], COPD screening using pulmonary function tests should be initiated in patients as early as possible so that they stop smoking. Also, since the diagnosis of COPD may be very important for risk stratification in lung cancer screening, spirometric COPD criteria employing bronchodilators should be used.

The problem of limiting screening to individuals aged 60 yrs or older with a positive smoking history is that never-smokers and those younger than 60 yrs of age are not considered. Although the rates of lung cancer in younger age groups have been

declining over the past several decades [127], there has been an upward trend among nonsmoking females, although this is mostly confined to elderly females [128]. VAN SCHAYCK *et al*. [125] suggested that, although COPD screening for the general population is possible, implementing screening in primary care settings is rather difficult, and case findings are likely to be a more suitable approach. Therefore, cases that are younger than 60 yrs of age with a positive smoking history and chronic cough should undergo pulmonary function testing for COPD screening.

Another problem is that using a fixed cut-off of 70% of FEV1/FVC to identify airway obstruction may result in misclassification. To reduce over-diagnosis among elderly patients and under-diagnosis among younger adult patients, the use of age-related lower limits of normal for FEV1/FVC has been recommended for identifying airway obstruction [129, 130]. However, the use of varying cut-off points is difficult and is not appropriate for screening the general population.

In general, computed tomography is not necessary for COPD screening. However, because emphysema without airflow obstruction is still a risk for lung cancer, LDCT may be necessary for COPD candidates. Once patients are diagnosed with emphysema on computed tomography, they should be followed by computed tomography for the early detection of lung cancer.

CONCLUSIONS

Because both COPD and lung cancer have high mortality rates and incur severe economic burdens worldwide, early detection and intervention for both diseases is critical. Pulmonary function in former and active smokers could early identify COPD and help select the best candidates to be included in lung cancer screening programme with computed tomography. However, with regard to efficacy, disadvantages, potential harm, and cost-effectiveness, selection criteria for COPD and lung cancer screening are important and should be carefully determined.

SUPPORT STATEMENT

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan to Y. Sekine.

STATEMENT OF INTEREST

None declared.

REFERENCES

1 The Top 10 Causes of Death. Programmes and projects in World Health Organization (WHO). www.who.int/mediacentre/factsheets/fs310/en/index.html Date last updated: September 9, 2011. Date last accessed: September 9, 2011.
2 Koshiol J, Rotunno M, Consonni D, *et al.* Chronic obstructive pulmonary disease and altered risk of lung cancer in a population-based case-control study. *PLoS One* 2009; 4: e7380.
3 Turner MC, Chen Y, Krewski D, *et al.* 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: 285–290.
4 Kuller LH, Ockene J, Meilahn E, *et al.* Relation of forced expiratory volume in one second (FEV1) to lung cancer mortality in the Multiple Risk Factor Intervention Trial (MRFIT). *Am J Epidemiol* 1990; 132: 265–274.
5 Fontana RS, Sanderson DR, Taylor WF, *et al.* Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Mayo Clinic study. *Am Rev Respir Dis* 1984; 130: 561–565.
6 International Early Lung Cancer Action Program Investigators. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med* 2006; 355: 1763–1771.
7 Infante M, Cavuto S, Lutman FR, *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: 445–453.
8 National Lung Screening Trial (NLST). National Cancer Institute. U.S. National Institute of Health. Lung Cancer Screening Using Helical CT *vs.* Chest X-ray Reduces Deaths among Current and Former Heavy Smokers. http://benchmarks.cancer.gov/2010/11/lung-cancer-screening-using-helical-ct-vs-chest-x-ray-reduces-deaths-among-current-and-former-heavy-smokers/ Date last updated: July 23, 2011. Date last accessed: September 9, 2011.
9 Congleton J, Muers MF. The incidence of airflow obstruction in bronchial carcinoma, its relation to breathlessness, and response to bronchodilator therapy. *Respir Med* 1995; 89: 291–296.
10 Kurishima K, Satoh H, Ishikawa H, *et al.* Lung cancer patients with chronic obstructive pulmonary disease. *Oncol Rep* 2001; 8: 63–65.
11 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: 503–507.
12 Tockman MS, Anthonisen NR, Wright EC, *et al.* Airways obstruction and the risk for lung cancer. *Ann Intern Med* 1987; 106: 512–518.
13 Vineis P, Airoldi L, Veglia F, *et al.* Environmental tobacco smoke and risk of respiratory cancer and chronic obstructive pulmonary disease in former smokers and never smokers in the EPIC prospective study. *BMJ* 2005; 330: 277.
14 de Torres JP, Marín JM, Casanova C, *et al.* Lung cancer in patients with COPD: incidence and predicting factors. *Am J Respir Crit Care Med* 2011; 184: 913–919.
15 Mannino DM, Aguayo SM, Petty TL, *et al.* 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: 1475–1480.
16 Spitz MR, Wei Q, Dong Q, *et al.* Genetic susceptibility to lung cancer: the role of DNA damage and repair. *Cancer Epidemiol Biomarkers Prev* 2003; 12: 689–698.
17 Cohen BH. Chronic obstructive pulmonary disease: a challenge in genetic epidemiology. *Am J Epidemiol* 1980; 112: 274–288.
18 Coté ML, Kardia SL, Wenzlaff AS, *et al.* Risk of lung cancer among white and black relatives of individuals with early-onset lung cancer. *JAMA* 2005; 293: 3036–3042.
19 Schwartz AG, Ruckdeschel JC. Familial lung cancer: genetic susceptibility and relationship to chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006; 173: 16–22.
20 Mizuno S, Takiguchi Y, Fujikawa A, *et al.* Chronic obstructive pulmonary disease and interstitial lung disease in patients with lung cancer. *Respirology* 2009; 14: 377–383.
21 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: 738–744.
22 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: 1932–1938.
23 Li Y, Swensen SJ, Karabekmez LG, *et al.* Effect of emphysema on lung cancer risk in smokers: a computed tomography-based assessment. *Cancer Prev Res* 2011; 4: 43–50.
24 Maldonado F, Bartholmai BJ, Swensen SJ, *et al.* 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: 1295–1302.

25 Kishi K, Gurney JW, Schroeder DR, *et al.* The correlation of emphysema or airway obstruction with the risk of lung cancer: a matched case-controlled study. *Eur Respir J* 2002; 19: 1093–1098.
26 Gierada DS, Guniganti P, Newman BJ, *et al.* Quantitative CT assessment of emphysema and airways in relation to lung cancer risk. *Radiology* 2011; 261: 950–959.
27 Wilson DO, Leader JK, Fuhrman CR, *et al.* Quantitative computed tomography analysis, airflow obstruction, and lung cancer in the Pittsburgh lung screening study. *J Thorac Oncol* 2011; 6: 1200–1205.
28 Dhopeshwarkar MR, Roberts HC, Paul NS, *et al.* Screen-detected lung cancer: a retrospective analysis of CT appearance. *Acad Radiol* 2011; 18: 1270–1276.
29 Egleston BL, Meireles SI, Flieder DB, *et al.* Population-based trends in lung cancer incidence in women. *Semin Oncol* 2009; 36: 506–515.
30 Scagliotti GV, Longo M, Novello S. Nonsmall cell lung cancer in never smokers. *Curr Opin Oncol* 2009; 21: 99–104.
31 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: 146–151.
32 Mapel DW, Hurley JS, Frost FJ, *et al.* Health care utilization in chronic obstructive pulmonary disease. A case-control study in a health maintenance organization. *Arch Intern Med* 2000; 160: 2653–2658.
33 Holguin F, Folch E, Redd SC, *et al.* Comorbidity and mortality in COPD-related hospitalizations in the United States, 1979 to 2001. *Chest* 2005; 128: 2005–2011.
34 Sin DD, Anthonisen NR, Soriano JB, *et al.* Mortality in COPD: role of comorbidities. *Eur Respir J* 2006; 28: 1245–1257.
35 Caramori G, Casolari P, Cavallesco GN, *et al.* Mechanisms involved in lung cancer development in COPD. *Int J Biochem Cell Biol* 2011; 43: 1030–1044.
36 Purdue MP, Gold L, Järvholm B, *et al.* Impaired lung function and lung cancer incidence in a cohort of Swedish construction workers. *Thorax* 2007; 62: 51–56.
37 Papi A, Casoni G, Caramori G, *et al.* COPD increases the risk of squamous histological subtype in smokers who develop non-small cell lung carcinoma. *Thorax* 2004; 59: 679–681.
38 Sekine Y, Yamada Y, Chiyo M, *et al.* Association of chronic obstructive pulmonary disease and tumor recurrence in patients with stage IA lung cancer after complete resection. *Ann Thorac Surg* 2007; 84: 946–950.
39 Sekine Y, Behnia M, Fujisawa T. Impact of COPD on pulmonary complications and on long-term survival of patients undergoing surgery for NSCLC. *Lung Cancer* 2002; 37: 95–101.
40 Namajika T, Sekine Y, Yamada Y, *et al.* Long-term surgical outcome in patients with lung cancer and coexisting severe COPD. *Thorac Cardiovasc Surg* 2009; 57: 339–342.
41 López-Encuentra A, Astudillo J, Cerezal J, *et al.* Prognostic value of chronic obstructive pulmonary disease in 2994 cases of lung cancer. *Eur J Cardiothorac Surg* 2005; 27: 8–13.
42 Pompili C, Brunelli A, Refai M, *et al.* Does chronic obstructive pulmonary disease affect postoperative quality of life in patients undergoing lobectomy for lung cancer? A case-matched study. *Eur J Cardiothorac Surg* 2010; 37: 525–530.
43 Ballaz S, Mulshine JL. The potential contributions of chronic inflammation to lung carcinogenesis. *Clin Lung Cancer* 2003; 5: 46–62.
44 Yao H, Rahman I. Current concepts on the role of inflammation in COPD and lung cancer. *Curr Opin Pharmacol* 2009; 9: 375–383.
45 Qu P, Roberts J, Li Y, *et al.* Stat3 downstream genes serve as biomarkers in human lung carcinomas and chronic obstructive pulmonary disease. *Lung Cancer* 2009; 63: 341–347.
46 Ochoa CE, Mirabolfathinejad SG, Ruiz VA, *et al.* Interleukin 6, but not T helper 2 cytokines, promotes lung carcinogenesis. *Cancer Prev Res* 2011; 4: 51–64.
47 Houghton AM, Rzymkiewicz DM, Ji H, *et al.* Neutrophil elastase-mediated degradation of IRS-1 accelerates lung tumor growth. *Nat Med* 2010; 16: 219–223.
48 Moghaddam SJ, Li H, Cho SN, *et al.* Promotion of lung carcinogenesis by chronic obstructive pulmonary disease-like airway inflammation in a K-ras-induced mouse model. *Am J Respir Cell Mol Biol* 2009; 40: 443–453.
49 Arenberg D, Luckhardt TR, Carskadon S, *et al.* Macrophage migration inhibitory factor promotes tumor growth in the context of lung injury and repair. *Am J Respir Crit Care Med* 2010; 182: 1030–1037.
50 Dialyna IA, Miyakis S, Georgatou N, *et al.* Genetic polymorphisms of CYP1A1, GSTM1 and GSTT1 genes and lung cancer risk. *Oncol Rep* 2003; 10: 1829–1835.
51 London SJ, Idle JR, Daly AK, *et al.* Genetic variation of CYP2A6, smoking, and risk of cancer. *Lancet* 1999; 353: 898–899.
52 Hecht SS. Tobacco smoke carcinogens and lung cancer. *J Natl Cancer Inst* 1999; 91: 1194–1210.
53 Young RP, Hopkins RJ, Hay BA, *et al.* Lung cancer gene associated with COPD: triple whammy or possible confounding effect? *Eur Respir J* 2008; 32: 1158–1164.
54 Young RP, Whittington CF, Hopkins RJ, *et al.* Chromosome 4q31 locus in COPD is also associated with lung cancer. *Eur Respir J* 2010; 36: 1375–1382.
55 Suzuki M, Wada H, Yoshino M, *et al.* Molecular characterization of chronic obstructive pulmonary disease-related non-small cell lung cancer through aberrant methylation and alterations of EGFR signaling. *Ann Surg Oncol* 2010; 17: 878–888.
56 Sundar IK, Mullapudi N, Yao H, *et al.* Lung cancer and its association with chronic obstructive pulmonary disease: update on nexus of epigenetics. *Curr Opin Pulm Med* 2011; 17: 279–285.
57 Qu P, Du H, Wang X, *et al.* Matrix metalloproteinase 12 overexpression in lung epithelial cells plays a key role in emphysema to lung bronchioalveolar adenocarcinoma transition. *Cancer Res* 2009; 69: 7252–7261.
58 Yang P, Schwartz AG, McAllister AE, *et al.* Lung cancer risk in families of nonsmoking probands: heterogeneity by age at diagnosis. *Genet Epidemiol* 1999; 17: 253–723.
59 Yang P, Sun Z, Krowka MJ, *et al.* Alpha1-antitrypsin deficiency carriers, tobacco smoke, chronic obstructive pulmonary disease, and lung cancer risk. *Arch Intern Med* 2008; 168: 1097–1103.
60 Young RP, Hopkins RJ, Hay BA, *et al.* FAM13A locus in COPD is independently associated with lung cancer – evidence of a molecular genetic link between COPD and lung cancer. *Appl Clin Genet* 2011; 4: 1–10.
61 Lourenço RV, Klimek MF, Borowski CJ. Deposition and clearance of 2 micron particles in the tracheobronchial tree of normal subjects – smokers and nonsmokers. *J Clin Invest* 1971; 50: 1411–1420.
62 Cerda S, Weitzman SA. Influence of oxygen radical injury on DNA methylation. *Mutat Res* 1997; 386: 141–152.
63 Galaris D, Evangelou A. The role of oxidative stress in mechanisms of metal-induced carcinogenesis. *Crit Rev Oncol Hematol* 2002; 42: 93–103.
64 Adcock IM, Caramori G, Barnes PJ. Chronic obstructive pulmonary disease and lung cancer: new molecular insights. *Respiration* 2011; 81: 265–284.
65 Wistuba II. Genetics of preneoplasia: lessons from lung cancer. *Curr Mol Med* 2007; 7: 3–14.
66 Global initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Diagnosis, Management, and Prevention of COPD, Update 2010. www.goldcopd.org/Guidelineitem.asp?l1=2&l2=1&intId=989 Date last updated: July 23, 2011. Date last accessed: September 9, 2011.
67 Engels EA. Inflammation in the development of lung cancer: epidemiological evidence. *Expert Rev Anticancer Ther* 2008; 8: 605–615.

68 Lee JM, Yanagawa J, Peebles KA, *et al.* Inflammation in lung carcinogenesis: new targets for lung cancer chemoprevention and treatment. *Crit Rev Oncol Hematol* 2008; 66: 208–217.
69 Yang IA, Relan V, Wright CM, *et al.* Common pathogenic mechanisms and pathways in the development of COPD and lung cancer. *Expert Opin Ther Targets* 2011; 15: 439–456.
70 Houghton AM, Mouded M, Shapiro SD. Common origins of lung cancer and COPD. *Nat Med* 2008; 14: 1023–1024.
71 Kim CF, Jackson EL, Woolfenden AE, *et al.* Identification of bronchioalveolar stem cells in normal lung and lung cancer. *Cell* 2005; 121: 823–835.
72 Wright JG, Christman JW. The role of nuclear factor kappa B in the pathogenesis of pulmonary diseases: implications for therapy. *Am J Respir Med* 2003; 2: 211–219.
73 Brody JS, Spira A. State of the art. Chronic obstructive pulmonary disease, inflammation, and lung cancer. *Proc Am Thorac Soc* 2006; 3: 535–537.
74 Komarova EA, Krivokrysenko V, Wang K, *et al.* p53 is a suppressor of inflammatory response in mice. *FASEB J* 2005; 19: 1030–1032.
75 Office of Population Genomics. A Catalog of Published Genome-wide Association Studies, 2011. www.genome.gov/gwastudies Date last accessed: August 21, 2011.
76 Young RP, Hopkins RJ, Whittington CF, *et al.* Individual and cumulative effects of GWAS loci in lung cancer: associations after sub-phenotyping for COPD. *PLoS One* 2011; 6: e16476.
77 Doll R, Peto R. Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and lifelong non-smokers. *J Epidemiol Community Health* 1978; 32: 303–313.
78 Bach PB, Kattan MW, Thornquist MD, *et al.* Variations in lung cancer risk among smokers. *J Natl Cancer Inst* 2003; 95: 470–478.
79 Spitz MR, Hong WK, Amos CI, *et al.* A risk model for prediction of lung cancer. *J Natl Cancer Inst* 2007; 99: 715–726.
80 Anthonisen NR, Skeans MA, Wise RA, *et al.* The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med* 2005; 142: 233–239.
81 Khan A, Agarwal R. Lung cancer chemoprevention with inhaled corticosteroids? *Am J Respir Crit Care Med* 2007; 176: 1169.
82 Parimon T, Chien JW, Bryson CL, *et al.* Inhaled corticosteroids and risk of lung cancer among patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; 175: 712–719.
83 van den Berg RM, van Tinteren H, van Zandwijk N, *et al.* The influence of fluticasone inhalation on markers of carcinogenesis in bronchial epithelium. *Am J Respir Crit Care Med* 2007; 175: 1061–1065.
84 Calverley PM, Anderson JA, Celli B, *et al.* Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356: 775–789.
85 Harris RE. Cyclooxygenase-2 (cox-2) blockade in the chemoprevention of cancers of the colon, breast, prostate, and lung. *Inflammopharmacology* 2009; 17: 55–67.
86 Lin Y, Shi R, Wang X, *et al.* Luteolin, a flavonoid with potential for cancer prevention and therapy. *Curr Cancer Drug Targets* 2008; 8: 634–646.
87 Yang CS, Lu G, Ju J, *et al.* Inhibition of inflammation and carcinogenesis in the lung and colon by tocopherols. *Ann NY Acad Sci* 2010; 1203: 29–34.
88 Ju R, Wu D, Guo L, *et al.* Inhibition of pro-inflammatory cytokines in tumor associated macrophages is a potential anti-cancer mechanism of arboxyamidotriazole. *Eur J Cancer* 2011 [Epub ahead of print DOI: 10.1016/j.ejca.2011.06.050].
89 van Gestel YR, Hoeks SE, Sin DD, *et al.* COPD and cancer mortality: the influence of statins. *Thorax* 2009; 64: 963–967.
90 Young RP, Hopkins R, Eaton TE. Potential benefits of statins on morbidity and mortality in chronic obstructive pulmonary disease: a review of the evidence. *Postgrad Med J* 2009; 85: 414–421.
91 Gohagan J, Marcus P, Fagerstrom R, *et al.* Baseline findings of a randomized feasibility trial of lung cancer screening with spiral CT scan vs chest radiograph: the Lung Screening Study of the National Cancer Institute. *Chest* 2004; 126: 114–121.
92 Gohagan JK, Marcus PM, Fagerstrom RM, *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.
93 Kaneko M, Eguchi K, Ohmatsu H, *et al.* Peripheral lung cancer: screening and detection with low-dose spiral CT *versus* radiography. *Radiology* 1996; 201: 798–802.
94 Henschke CI, McCauley DI, Yankelevitz DF, *et al.* Early Lung Cancer Action Project: overall design and findings from baseline screening. *Lancet* 1999; 354: 99–105.
95 Sobue T, Moriyama N, Kaneko M, *et al.* Screening for lung cancer with low-dose helical computed tomography: anti-lung cancer association project. *J Clin Oncol* 2002; 20: 911–920.
96 Henschke CI, Yankelevitz DF, Libby DM, *et al.* Early lung cancer action project: annual screening using single-slice helical CT. *Ann NY Acad Sci* 2001; 952: 124–134.
97 Sone S, Takashima S, Li F, *et al.* Mass screening for lung cancer with mobile spiral computed tomography scanner. *Lancet* 1998; 351: 1242–1245.
98 Sone S, Li F, Yang ZG, *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.
99 Tiitola M, Kivisaari L, Huuskonen MS, *et al.* Computed tomography screening for lung cancer in asbestos-exposed workers. *Lung Cancer* 2002; 35: 17–22.
100 Diederich S, Wormanns D, Semik M, *et al.* Screening for early lung cancer with low-dose spiral CT: prevalence in 817 asymptomatic smokers. *Radiology* 2002; 222: 773–781.
101 Diederich S, Thomas M, Semik M, *et al.* Screening for early lung cancer with low-dose spiral computed tomography: results of annual follow-up examinations in asymptomatic smokers. *Eur Radiol* 2004; 14: 691–702.
102 Nawa T, Nakagawa T, Kusano S, *et al.* Lung cancer screening using low-dose spiral CT: results of baseline and 1-year follow-up studies. *Chest* 2002; 122: 15–20.
103 Pastorino U, Bellomi M, Landoni C, *et al.* Early lung-cancer detection with spiral CT and positron emission tomography in heavy smokers: 2-year results. *Lancet* 2003; 362: 593–597.
104 Swensen SJ, Jett JR, Sloan JA, *et al.* Screening for lung cancer with low-dose spiral computed tomography. *Am J Respir Crit Care Med* 2002; 165: 508–513.
105 Swensen SJ, Jett JR, Hartman TE, *et al.* Lung cancer screening with CT: Mayo Clinic experience. *Radiology* 2003; 226: 756–761.
106 Swensen SJ, Jett JR, Hartman TE, *et al.* CT screening for lung cancer: five-year prospective experience. *Radiology* 2005; 235: 259–265.
107 Blanchon T, Bréchot JM, Grenier PA, *et al.* Baseline results of the Dépiscan 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: 50–58.
108 Infante M, Lutman FR, Cavuto S, *et al.* Lung cancer screening with spiral CT: baseline results of the randomized DANTE trial. *Lung Cancer* 2008; 59: 355–363.
109 van den Bergh KA, Essink-Bot ML, Bunge EM, *et al.* Impact of computed tomography screening for lung cancer on participants in a randomized controlled trial (NELSON trial). *Cancer* 2008; 113: 396–404.
110 van Iersel CA, de Koning HJ, Draisma G, *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* 2006; 120: 868–874.

111 NIH (National Institute of Health) News. Lung Cancer Trial Results Show Mortality Benefit With Low-dose CT – Twenty Percent Fewer Lung Cancer Deaths Seen Among Those Who Were Screened With Low-dose Spiral CT Than With Chest X-ray. www.nih.gov/news/health/nov2010/nci-04.htm Date last updated: July 23, 2011. Date last accessed: September 9, 2011.

112 National Lung Screening Trial Research Team. Baseline characteristics of participants in the randomized national lung screening trial. *J Natl Cancer Inst* 2010; 102: 1771–1779.

113 International Early Lung Cancer Action Program Protocol. www.ielcap.org Date last updated: July 23, 2011. Date last accessed: September 9, 2011.

114 Bechtel JJ, Kelley WA, Coons TA, *et al.* Five-year outcome of lung cancer detection in patients with and without airflow obstruction in a primary care outpatient practice. *J Thorac Oncol* 2009; 4: 1347–1351.

115 Bach PB, Jett JR, Pastorino U, *et al.* Computed tomography screening and lung cancer outcomes. *JAMA* 2007; 297: 953–961.

116 Black WC, Welch HG. Screening for disease. *AJR Am J Roentgenol* 1997; 168: 3–11.

117 van't Westeinde SC, van Klaveren RJ. Screening and early detection of lung cancer. *Cancer J.* 2011; 17: 3–10.

118 Bednarek M, Maciejewski J, Wozniak M, *et al.* Prevalence, severity and underdiagnosis of COPD in the primary care setting. *Thorax* 2008; 63: 402–407.

119 Soriano JB, Zielinski J, Price D. Screening for and early detection of chronic obstructive pulmonary disease. *Lancet* 2009; 374: 721–732.

120 Rabe KF, Hurd S, 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* 2007; 176: 532–555.

121 Fukuchi Y, Nishimura M, Ichinose M, *et al.* COPD in Japan: the Nippon COPD Epidemiology study. *Respirology* 2004; 9: 458–465.

122 Joo MJ, Lee TA, Weiss KB. Geographic variation of spirometry use in newly diagnosed COPD. *Chest* 2008; 134: 38–45.

123 Bolton CE, Ionescu AA, Edwards PH, *et al.* Attaining a correct diagnosis of COPD in general practice. *Respir Med* 2005; 99: 493–500.

124 Halbert RJ, Natoli JL, Gano A, *et al.* Global burden of COPD: systematic review and meta-analysis. *Eur Respir J* 2006; 28: 523–532.

125 van Schayck CP, Loozen JM, Wagena E, *et al.* Detecting patients at a high risk of developing chronic obstructive pulmonary disease in general practice: cross sectional case finding study. *BMJ* 2002; 324: 1370.

126 Buffels J, Degryse J, Heyrman J, *et al.* Office spirometry significantly improves early detection of COPD in general practice: the DIDASCO Study. *Chest* 2004; 125: 1394–1399.

127 Jemal A, Travis WD, Tarone RE, *et al.* Lung cancer rates convergence in young men and women in the United States: analysis by birth cohort and histologic type. *Int J Cancer* 2003; 105: 101–107.

128 Thun MJ, Henley SJ, Burns D, *et al.* Lung cancer death rates in lifelong nonsmokers. *J Natl Cancer Inst* 2006; 98: 691–699.

129 Quanjer PH, Tammeling GJ, Cotes JE, *et al.* Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J* 1993; 6: Suppl. 16, 5–40.

130 Swanney MP, Ruppel G, Enright PL, *et al.* Using the lower limit of normal for the FEV_1/FVC ratio reduces the misclassification of airway obstruction. *Thorax* 2008; 63: 1046–1051.