

Early detection of COPD is important for lung cancer surveillance

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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 NF- κ B and signal transducer and activator of transcription 3 (STAT3) 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 etiology 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 candidates for an efficient lung cancer screening program identified.

Key Words: etiology, low-dose computed tomography, pulmonary function test, risk factor, screening, smoking cessation

Introduction

Chronic obstructive pulmonary disease (COPD) and lung cancer are rapidly growing, worldwide health problems. In 2008, the World Health Organization (WHO) published the top ten 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 of lung cancer independent from cigarette smoking [2,3]. The Multiple Risk Factor Intervention Trial (MRFIT) 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 vs. 0.43/1000 persons/year, respectively), and that the lag time for beneficial effects on lung cancer development after smoking cessation may be as long as 20 years [4]. This suggests that COPD patients are more likely to develop lung cancer compared to 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 last decade.

Lung cancer screening in the 1980's employed chest radiography and sputum cytology, and whether or not they provided any decrease in mortality has been inconclusive [5]. During the 2000's, 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 to subjects who were screened by chest x-rays (CXRs) [8]. Participants were 55 to 74 years of age, and current and former smokers. This study comprised more than 53,000 subjects and focused on heavy smokers, defined as those with a smoking history of 30 pack-years or more. By comparison, patients with COPD are generally 50 to 80 years 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. 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 years was 8.8% for those with COPD and 2.0% for patients with normal pulmonary function ($p = 0.024$) [11]. This indicates that approximately 1% of patients with COPD develop lung cancer each year, while only 0.2% of patients with normal pulmonary function develop lung cancer (5-fold increased risk of lung cancer). Recently, de Torres et al. reported that 215 of 2507 COPD patients developed lung cancer (incidence density of 16.7 cases/1000 person-years) with a median follow-up of 60 months [14]. This result suggested that in a well characterized 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 (EAGLE) population-based case-control study recruited 2100 lung cancer cases and 2120 controls. This study showed that lung cancer risk was increased among individuals with chronic bronchitis (odds ratio [OR] = 2.0; 95% confidence interval [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-year follow-up study of 448,600 lifelong nonsmokers, Turner et al. 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) [3]. 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 CT scans.

The severity of COPD also influences the incidence of lung cancer. The first National Health and Nutrition Examination Survey (NHANES I) collected data from a 22-year follow-up of 5402 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 to normal pulmonary function (HR = 2.8; 95% CI: 1.8-4.4). On the other hand, de Torres et al. reported that lung cancer incidence decreased in a stepwise manner from COPD GOLD stages I to IV, and the incidence at stage IV (9.2/1000 person-years) was less than half the incidence at stage I (19.9/1000 person-years) [14]. 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 first reported on the genetic epidemiology of COPD [17]. 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 to 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. 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 [21]. De Torres et al. showed that emphysema found on CT, but not airflow obstruction, was associated with an increased frequency of lung cancer [22]. Results of lung cancer screening by the Mayo Clinic from multiple logistic regression models showed that emphysema ($\geq 5\%$ on CT) 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 years of age; OR = 4.64), heavy smokers (≥ 40 -pack years; OR = 4.46), and small-cell lung cancer (OR = 5.62) [23]. Emphysema was assessed in these studies by visual semiquantitative scoring of CT images. By contrast, Maldonado et al. reported that the radiographic evidence for emphysema, evaluated by automated quantitative CT 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 one second (FEV1) (OR = 1.15; 95%CI: 1.00-1.32) and FEV1/forced vital capacity (FVC) (OR = 1.29, 95% CI: 1.02-1.62) were significant risk factors [24]. Kishi et al. also reported similar results from quantitative CT analysis [25]. Gierada et al. reported that not only emphysema but also bronchial measurements at segmental-subsegmental levels as assessed by automated CT analysis were not associated with lung cancer as well [26]. Wilson et al. 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 CT images, was associated with increased risk of lung cancer [27]. Therefore, emphysema as a risk for lung cancer remains controversial and requires additional clarification. As Dhopeswarkar et al. 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 [28]. Therefore, these results should be interpreted with care.

Interestingly, the majority of lung cancers among nonsmokers has been reported to occur in women [29], and 10% of men and 20% of women 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]. Calabro et al. reported that a reduction of as little as 10% in the predicted FEV1 was associated with a nearly 3-fold greater lung cancer risk [31]. 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 localized chronic inflammation in the lung. COPD patients have a higher prevalence of certain comorbidities, 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 analyzed 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 to discharges without COPD (all $p < 0.01$) [33]. Sin et al. summarized several series with regard to the underlying causes of death in COPD patients [34]. 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. 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 [14]. 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 histologic 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 (QOL) [10]. We investigated postoperative long-term survival in stage IA lung cancer patients with COPD [38]. The 5-year 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% vs. 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 (BAC) 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]. Lopez-Encuentra et al. 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 years was significantly worse in COPD patients than in non-COPD patients [41]. On the other hand, Pompili et al. reported that although COPD patients had a much higher rate of postoperative cardiopulmonary morbidity compared with non-COPD matched pairs, postoperative physical and mental QOL scales and perioperative changes did not differ between COPD and matched non-COPD patients [42]. 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.

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. Second, an imbalance between oxidants and antioxidants can lead to free radical damage of DNA [62]. Third, genetic mutations and polymorphisms may influence the acceleration or suppression of lung cancer development. Dialyna et al. reported that the frequency of a genetic null mutation of glutathione S-transferase M1 (*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 [50]. In contrast, a genetic mutation and polymorphisms of *CYP2A6* suppress carcinogenesis and exacerbation of COPD [51].

Fourth, 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 (BASC) to induce proneoplastic mutations, proliferation, resistance to apoptosis, angiogenesis, invasion, metastasis, and secretion of immunosuppressive factors [70,71]. (Fig.

1)

It has been recently proposed that activation of nuclear transcription factor (NF)- κ B may have a crucial role in the development of lung cancer from COPD [72,73]. NF- κ B activation increases the release of inflammatory mediators that can induce COPD, and also inhibits apoptosis, induces proliferation, and, finally, accelerates cancer development. NF- κ B 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 signaling 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 tumor 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- κ B-mediated inflammation [73].

Sundar et al. reviewed epigenetic modifications in the pathogenesis of COPD and lung cancer [56]. They reported that oxidative stress and inflammatory response alter the redox potential of cells, which leads to destabilization of the genome, culminating in epigenetic modifications. Epigenetic 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 (SNP) 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 characterized 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. suggested that future genetic epidemiological studies of lung cancer might benefit greatly from the exploration of this overlap by sub-phenotyping cases and controls for coexisting COPD [75].

Another specific genetic mechanism involved in the etiology of progression from COPD to lung cancer is the α 1-antitrypsin deficiency (α 1ATD) allele. Those who were α 1ATD carriers had a higher risk of lung cancer compared to the general population [58,59]. Yang et al. reported on a model of 1585 case-control pairs with and without the α 1ATD allele using multiple logistic regression analysis, and found that α 1ATD carriers had a 70% higher risk of developing lung cancer than noncarriers (OR = 1.7; 95% CI: 1.2-2.4) [59]. This suggested that the α 1ATD 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 proposed a risk prediction model for smoking [77]. 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 3-fold greater chance and those with severe COPD have a 10-fold greater chance of developing lung cancer within 10 years, compared to smokers with normal pulmonary function [15], although de Torres et al. found an inverse relationship between lung function severity and lung cancer incidence [14]. 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. also constructed a prediction model for lung cancer risk that estimated the absolute risk that an individual current or ex-smoker (at least 20 pack-years) would be diagnosed with lung cancer within 10 years, by analyzing data from a large randomized trial, the Carotene and Retinol Efficacy Trial (CARET) [78]. 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. established a risk model for predicting lung cancer based on smoking status by additional development of Bach's model [79]. 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. showed that 33% of asymptomatic smokers with mild-to-moderate COPD had died of lung cancer after a 14.5-year follow-up [80]. 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 1000 person-years vs. 10.38 per 1000 person-years, 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 et al. reported that a selective COX-2 inhibitor (celecoxib or rofecoxib) may reduce the risk of lung cancer [85]. 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. Nonrandomized 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 endpoint for lung cancer screening is the reduction of lung cancer mortality. The Lung Screening Study (LSS) of the National Cancer Institute found that at baseline, 20.5% of subjects (325/1586) in the low-dose computed tomography (LDCT) cohort and 9.8% of subjects (152/1550) in the chest radiography (CXR) cohort were diagnosed with findings suspicious of lung cancer. The confirmed lung cancer detection rate was 1.9% (30/1586) in the LDCT cohort and 0.45% (7/1550) in the CXR cohort [91]. In their report of the final results of that study, out of a total of 1660 patients enrolled in the LDCT cohort and 1658 in

the CXR cohort, 40 patients (2.4%) and 20 patients (1.2%) 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 CT screening than by chest radiography [93,94]. Sobue et al. reported that the 5-year survival rates for CT screen-detected lung cancer were 76.2% and 64.9% for initial and repeated screening, respectively [95]. Of those patients who were screened by CT in the International ELCAP (I-ELCAP) protocol, 85% had clinical stage I lung cancer, and the estimated 10-year survival rate was 88% [6]. These studies all demonstrated remarkably high detection and survival rates, and suggest that CT screening may be beneficial for the early detection and curative surgery of lung cancer (Table 2).

Bechtel et al. investigated the efficacy of early detection of lung cancer by chest CT for patients with COPD, and reported that 6 lung cancer cases were detected among 88 high risk patients with COPD (6.8%). There were 3 stage I patients, and 3 of 6 survived for more than 5 years [96]. This detection rate was higher than the initial cancer detection rates of 1.2% to 1.6% reported by others [6,97].

In order to prove the efficacy of lung cancer screening, however, screening biases, such as lead time, length, and over-diagnosis should be resolved [98]. Therefore, randomized control trials are preferable. Currently, there are several large randomized control trials ongoing in a

number of countries. The National Lung Screening Trial (NLST) is the largest multicenter, randomized control trial [8]. The independent Data and Safety Monitoring Board (DSMB) of this trial announced that all-cause mortality was 7% lower in the LDCT group than in the CXR group, and approximately 25% of all deaths were due to lung cancer [99]. Interestingly, among the NLST participants, there were more than 17.4% with self-reported COPD and 7.7% with emphysema [100]. 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 [101]. They reported that light-induced fluorescence endoscopy (LIFE) or autofluorescence imaging endoscopy (AFI) for bronchial carcinoma in the central airway, detection of circulating DNA in peripheral blood and methylated genes in plasma, measurement of circulating tumor-derived exosome levels, determination of micro-RNA patterns, comparative protein profiling, detection of autoantibodies against cancer-associated antigens, exhaled breath analysis, identification of genomic-based markers in bronchoalveolar lavage (BAL) samples, and biomarkers in sputum are promising candidates.

Early detection of COPD for lung cancer surveillance

COPD is substantially underdiagnosed [118,119] and frequently misdiagnosed [120]. Soriano et al. summarized reports of prevalence and under-diagnosis [119]. They reported that 72% to 93% of COPD patients were not diagnosed. The Nippon (Japan) COPD Epidemiology (NICE) study reported that the prevalence of airflow limitation ($FEV_1/FVC < 70\%$) 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 years of age [124]. Fukuchi et al. reported that COPD prevalence steeply increased at age 60 years and older: 5.8% at 50-59 years vs. 15.7% at 60-69 years, and 24.7% at 70 years and older [121].

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. reported that spirometry confirmed airflow obstruction in 18% of individuals with respiratory symptoms and in 4% of those without these symptoms [126]. Van Schayck et al. 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 standardized questionnaire and spirometry [125]. 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 years of age. The positive predictive value of cough for airflow obstruction was 27% and that of at least 2 respiratory symptoms, including cough, dyspnea or wheezing, was 29%. In patients with all 3 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 years 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 Calabro 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 years or older with a positive smoking history, is that never-smokers and those younger than 60 years 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 women [128]. Van Schayck et al. 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 [125]. Therefore, cases that are younger than 60 years 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, CT 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 CT, they should be followed by CT 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 are 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 program 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.

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Figure Legend

Fig. 1: Putative mechanism of lung carcinogenesis from COPD in inflammatory micro-environment

Oxidative stress by cigarette smoke stimulates the NF- κ B 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) signaling pathway also induces pulmonary inflammation and carcinogenesis in the lung.

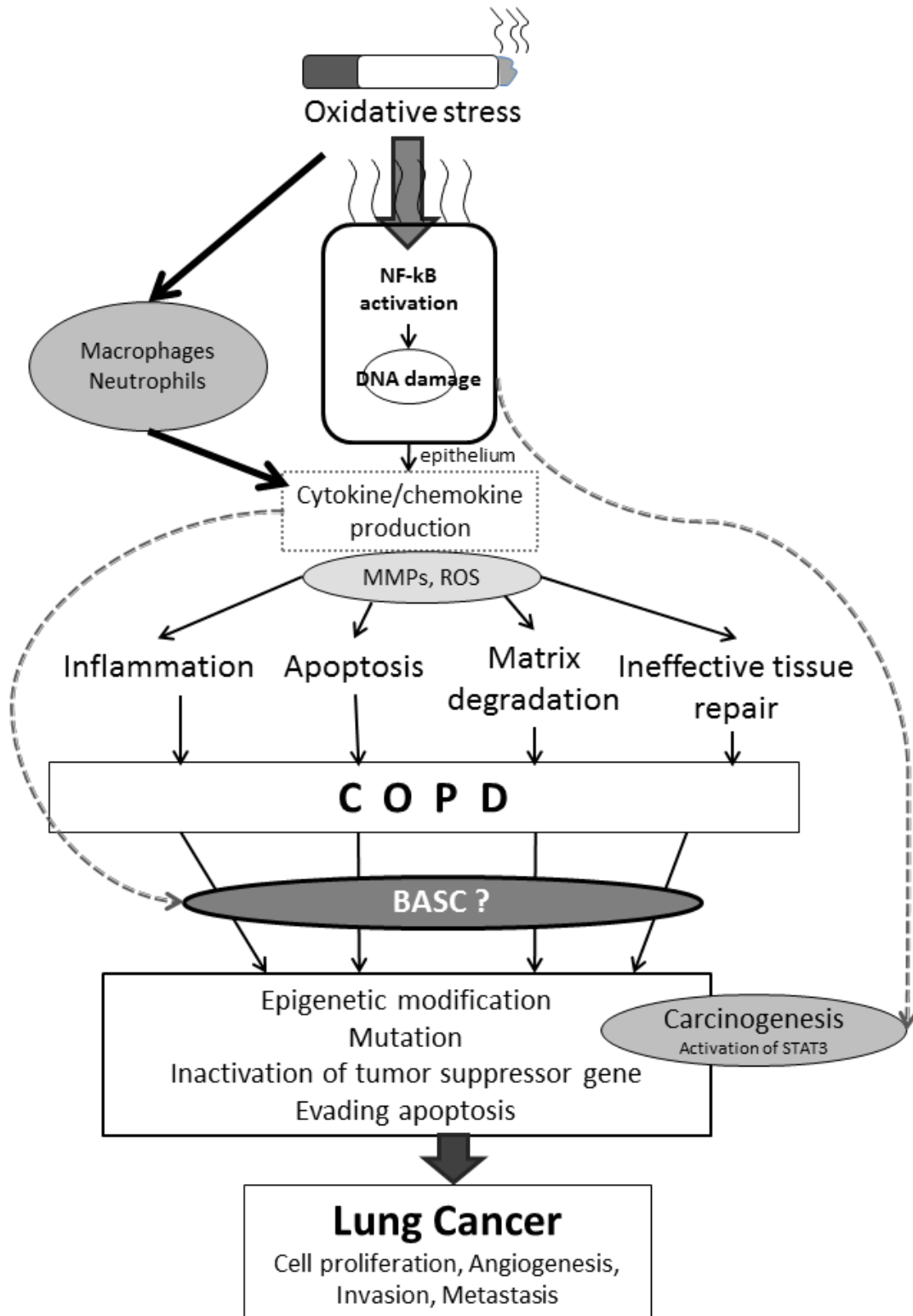


Table 1 Candidate susceptibility genes involved in both COPD and lung cancer

Inflammation [43-49]
COX-2, NF- κ B, IL-1 β , 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 [44,55,56]
IL-12R β 2, 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 1ATD allele, FAM13A
COX: cyclooxygenase, NF: nuclear transcription factor, STAT3: signal transducer and activator of transcription 3, GSTM1: glutathione S-transferase M1, nAChR: nicotinic acetylcholine receptor, HHIP: Hedgehog-interacting protein, GYPA: glycophorin A, 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 1ATD: α 1-antitrypsin deficiency, FAM13A: family with sequence similarity 13 member A

Table 2: Observational and randomized CT screenings for lung cancer, study designs and results

No.	Reference Project	Ref No.	State of study progression	Years of enrollment	End of study	Published Year	Study design	Age criteria	Eligibility of smoking status	No. of Participants	No. tested	Classification (n)
1	Kaneko	93	completed	1993–1995	1995	1996	Observational	no restriction	no restriction	1369	3457	LDCT
2	ELCAP	94,102	completed	1993	1998	1999, 2001	Observational	>=60	>=10 p-y	1000	1000 (baseline) 1184 (repeated)	LDCT
3	Sone	103,104	completed	1996	1998	2001	Observational	40–74	no restriction	5483	5483(1996) 4425(1997) 3878(1998)	LDCT
4	Tiitola	105	completed	NR	NR	2002	Observational	no restriction	no restriction	602	602	LDCT
5	ALCA	95	completed	1993	1998	2002	Observational	40–79	no restriction	1611	1611 (baseline) 7891(repeated)	LDCT
6	Diederich	106,107	completed	1995–1999	1999	2002	Observational	40–78	>=20 p-y	817	817 (baseline), 1735 (repeated)	LDCT
7	Nawa	108	completed	1998–2000	2000	2002	Observational	50–69	no restriction	7956	7956 (baseline), 5568 (repeated)	LDCT
8	Pastorino	109	completed	2000–2002	2003	2003	Observational	>=50	>=20 p-y	1035	1035	LDCT+/-PET
9	Swensen	110–112	completed	1999	2003	2005	Observational	>=50	>=20 p-y, quit <10 yr	1520	1520 (baseline) 1464 (98% at year 1) (96% at y2, 95% at y3, 80% at y4)	LDCT
10	LSS	91,92	completed	2000	2001	2005	pilot RCT	55–74	>=30 p-y, active or quit<10 yr	3277	3277	LDCT 1660 CXR 1658
11	Dépiscan	113	completed	2002	2004	2007	pilot RCT	50–75	>=15 cigarette/day for >20 yr, quit <15 yr	756	621	LDCT 385 CXR 380
12	DANTE	7,114	Three-yr follow-up	2001–2006	2006	2009	RCT	60–74	>=20 p-y, active or quit<10 yr	2811	2472	LDCT 1276 Control 1196
13	NELSON	115,116	ongoing	2003–2005	ongoing	2008	RCT	50–75	>15 cigarettes/day for >25 yr or >10 cigarettes/day for >30 yr, active or quit<10 yr	15428	15428	LDCT CXR
14	NLST	8,99,100	analyzing	2002–2004	ongoing	2010	RCT	55–74	>=30 p-y, active or quit<15 yr	53476	NR	LDCT 26723 CXR 26733
15	I-ELCAP	6,117	ongoing	1993–2005	ongoing	2006 etc.	Multi-institutional research study	>=40	no restriction	31567	31567 (baseline), 27456 (repeated)	CT

ELCAP: Early Lung Cancer Action Project, ALCA: Anti lung Cancer Association (Japan), LSS: Lung Screening Study, Dépiscan: a French randomized pilot trial of lung cancer screening, NELSON: the Dutch–Belgian randomised lung cancer multi-slice CT screening trial, DANTE, NLST: National Lung Screening Trial, I-ELCAP: International Early Lung Cancer Action Program

RCT: randomized control study, p-y: pack-years, LDCT: low dose computed tomography, CXR: chest X-ray, NR: not reported

No.	Median follow-up	Male (%)	Age (mean or median, range)	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)	60 (0.4%)	55 (92%)	60 (100%)	5 (0.1%)	2 (0.04%)
						4.0% (1997)					
						3.5% (1998)					
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%	NR	11.5% (initial)	14 (0.9% initial)	11 (78.6% initial)	12 (86% initial)	8 (0.5%)	3 (0.2%)
				former 25%		9.1% (repeated)	22 (0.3% repeated)	18 (82% repeated)	17 (77% repeated)		
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 years	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	33.7M (1.8–79.2)	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%)*	8.9%	34 (2.8%)	12 (35%)	17 (50%)	45 (3.8%)	20 (1.7%)
			p value		0.04		0.016	0.004	0.25	0.83	0.84
13	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
14	NR	59%	61.4	current 48%	4674 (17.5%)	NR	NR	NR	NR	NR	354(1.3%)
					4652 (17.4%)						442(1.7%)
15	40M (1–123M)	NR	61 (40–85)	current or former 82.8%	NR	NR	484	412 (85%)	411(85%)	NR	75
*: chronic respiratory symptoms (DANTE trial)											