

WJCO 5th Anniversary Special Issues (1): Lung cancer**Chronic obstructive pulmonary disease as a risk factor for lung cancer**

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Author contributions: Takiguchi Y and Tatsumi K designed the investigation; Sekine I, Iwasawa S and Kurimoto R performed the literature searches; Takiguchi Y wrote the paper; all the authors analyzed the data, read the manuscript and approved its submission to the Journal.

Supported by The Ministry of Education, Culture, Sports, Science and Technology of Japan

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Received: December 23, 2013 **Revised:** January 27, 2014

Accepted: May 16, 2014

Published online: October 10, 2014

involvement of putative distal airway stem cells; and genetic factors that are common to both COPD and lung cancer. The existence of COPD in patients with lung cancer may potentially affect the process of diagnosis, surgical resection, radiotherapy, chemotherapy, and end-of-life care. The comprehensive management of COPD is extremely important for the appropriate treatment of lung cancer. Surgical resections with the aid of early interventions for COPD are often possible, even for patients with mild-to-moderate COPD. New challenges, such as lung cancer CT screening for individuals at high risk, are now in the process of being implemented. Evaluating the risk of lung cancer in patients with COPD may be warranted in community-based lung cancer screening.

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Key words: Chronic obstructive pulmonary disease; Airflow limitation; Inflammation; Lung cancer; Carcinogenesis; Cancer screening; Computed tomography screening; Early intervention

Core tip: This article reviews current perspectives on the epidemiological, clinical, and etiological problems associated with the coexistence of lung cancer and chronic obstructive pulmonary disease.

Takiguchi Y, Sekine I, Iwasawa S, Kurimoto R, Tatsumi K. Chronic obstructive pulmonary disease as a risk factor for lung cancer. *World J Clin Oncol* 2014; 5(4): 660-666 Available from: URL: <http://www.wjgnet.com/2218-4333/full/v5/i4/660.htm>
DOI: <http://dx.doi.org/10.5306/wjco.v5.i4.660>

Abstract

The association between chronic obstructive pulmonary disease (COPD) and lung cancer has long been a subject of intense debate. The high prevalence of COPD in elderly smokers inevitably strengthens their coincidence. In addition to this contingent coincidence, recent studies have revealed a close association between the two diseases that is independent of the smoking history; that is, the existence of COPD is an independent risk factor for the development of lung cancer. Molecular-based evidence has been accumulating as a result of the efforts to explain the underlying mechanisms of this association. These mechanisms may include the following: the retention of airborne carcinogens followed by the activation of oncogenes and the suppression of tumor suppressor genes; the complex molecular mechanism associated with chronic inflammation in the distal airways of patients with COPD; the possible in-

INTRODUCTION

Smoking causes many diseases including lung cancer

Table 1 Major causes of death reported in patients with chronic obstructive pulmonary disease

Author	Publication year	Total No. of COPD	Total deaths	Cause of death (%) ¹				
				COPD ²	Lung cancer	Other cancer	Cardiovascular	Others
Vilkman <i>et al</i> ^[14]	1997	2237	1070	30	12	8	33	17
Garecka <i>et al</i> ^[11]	1997	135	70	61	4	4	6	24
Antonelli Incalzi <i>et al</i> ^[8]	1997	270	228	63	5	4	16	12
Zielinski <i>et al</i> ^[15]	1997	215	215	49	7	ND	37	7
Keistinen <i>et al</i> ^[12]	1998	2727	973	22	13	8	32	25
Pauwel <i>et al</i> ^[13]	1999	1277	18	6	33	6	39	17
Garcia-Aymerich <i>et al</i> ^[10]	2003	340	98	74	5	2	12	6
Celli <i>et al</i> ^[9]	2004	625	162	61	12	ND	14	13
Anthonisen <i>et al</i> ^[16]	2005	5887	731	8	33	21	22	16

¹Calculated from the data reported by each literature; ²Including respiratory causes, respiratory failure, respiratory infection. Pulmonary embolism was included in cardiovascular cause. ND: Not described; COPD: Chronic obstructive pulmonary disease.

and chronic obstructive pulmonary disease (COPD). These diseases usually affect relatively elderly individuals. Because of the rapidly aging populations of many developed countries, the number of patients with lung cancer and/or COPD is growing. Lung cancer is one of the leading causes of death in many countries and accounted for approximately 1.37 million deaths worldwide in 2008^[1]. As was extensively discussed in the Global Initiative of Chronic Obstructive Lung Disease (GOLD)^[2], accurate estimations of the prevalence and mortality of COPD are difficult. The prevalence of COPD in a specific region varies because of differences in the survey methods, diagnostic criteria and analytic approaches^[3,4], ranging from 7.8% to 19.7% of the total population^[2]. COPD is often a primary cause of death. However, COPD can also contribute to death from other diseases, such as pneumonia, ischemic heart diseases and heart failure, making it difficult to estimate the COPD-associated mortality rate. Meanwhile, the Global Burden of Disease Study has projected that COPD will become the third leading cause of death worldwide by 2020^[5].

Because of the high prevalence of both conditions and strong common risk factors associated with smoking, the coexistence of lung cancer and COPD is inevitably high. In addition, recent studies have uncovered a non-confounding association between COPD and lung cancer development, together with its molecular mechanisms^[6,7]. Investigating and resolving the problems of the coexistence of these two diseases is important in view of their clinical relevance; their interaction leads to worse outcomes. This article reviews the current perspectives on the epidemiological, clinical, and etiological problems associated with the coexistence of lung cancer and COPD.

COEXISTENCE OF LUNG CANCER AND COPD ASSESSED ACCORDING TO PULMONARY FUNCTION

Because of the high mortality associated with lung cancer, the proportion of deaths from lung cancer among patients with COPD can reasonably be considered to

represent the coexistence of lung cancer among patients with COPD. As shown in Table 1, the causes of death reported in patients with COPD vary significantly among studies, and the proportion of deaths from lung cancer ranges from 4% to 33%^[8-16], presumably because of different patient characteristics and analytical methods. Among their investigation, a prospective study identified 731 deaths that occurred over 14.5 years out of 5887 asymptomatic non-smoking individuals who had mild or moderate airflow limitations, with an average FEV₁/FVC of 65.0% ± 6.1% and an average age of 48.4 ± 6.8 years. The primary cause of death was lung cancer, representing 33% of the total deaths^[16]. Three other prospective studies disclosed a high incidence of lung cancer development or mortality among patients with COPD or individuals with airflow limitations^[17-19]. Skillrud *et al*^[17] prospectively observed 113 individuals who had a %FEV₁ of 70% or less by comparing them with 113 age-matched, sex-matched, occupation-matched, and smoking history-matched individuals with a %FEV₁ of 85% or more. The 10-year cumulative rates of lung cancer development were 8.8% and 2.0% in the former and latter groups, respectively, resulting in a statistically significant difference ($P = 0.024$)^[17]. Kuller *et al*^[18] reported an increase in lung cancer mortality according to a reduction in the FEV₁. The lung cancer mortality per 1000 person-years was 3.02 and 0.43 in the lowest and highest quintiles of the FEV₁, respectively, and this association was not weakened by adjustments for smoking factors^[18]. The relative risk of COPD or airflow limitations associated with lung cancer was therefore calculated to be 4.4 and 7.0 in the studies by Skillrud *et al*^[17] and Kuller *et al*^[18], respectively. In a large-scale prospective study involving 448600 lifelong nonsmokers who were cancer-free at baseline and who had a 20-year follow-up period, Turner *et al*^[19] again found a significant association between lung cancer mortality and pulmonary emphysema, with a hazard ratio of 1.66 (95%CI: 1.06-2.59)^[19]. Wasswa-Kintu *et al*^[20] conducted a population-based meta-analysis to reveal that even a relatively small decrease in the FEV₁ (approximately 90% of predicted) increased the risk of lung cancer by 1.3-fold in men (95%CI: 1.05-1.62) and 2.6-fold in women (95%CI:

Table 2 Odds ratios for coincidental lung cancer based on factors indicative of chronic obstructive pulmonary disease or interstitial lung diseases, according to smoking status¹

	Never smoker (n = 284)	Ex-smoker (n = 101)	Current smoker (n = 179)	Total (n = 564)
FEV1/FVC < 70%	10.42 (2.82-38.55) ³	5.89 (2.02-17.22)	7.456 (3.48-15.95)	7.17 (4.03-12.74)
%VC < 80%	2.02 (0.42-9.86)	No data ⁴	2.25 (0.62-8.11)	4.73 (2.00-11.17)
LAA score ≥ 1 ²	0.98 (0.21-4.43)	3.43 (1.50-7.85)	5.07 (2.51-10.28)	3.63 (2.24-5.89)
Fibrosis score ≥ 1	6.39 (2.13-19.18)	3.94 (1.20-12.88)	5.45 (2.39-12.44)	5.10 (2.82-9.24)
GGA score ≥ 1	2.32 (0.80-6.71)	3.59 (1.09-11.80)	2.48 (1.06-5.77)	2.71 (1.52-4.81)

¹See the reference by Mizuno *et al.*^[24] for details; ²Low attenuation area (LAA) was assessed using Goddard's scoring system; fibrosis and ground glass attenuation (GGA) were assessed using Kazzeroni's scoring system; ³Numbers in parentheses indicate 95%CI; ⁴No data calculated because of insufficient number.

1.30-5.31), concluding that even a modest reduction in the %FEV₁ is a significant predictor of lung cancer, especially among women^[20].

COEXISTENCE OF LUNG CANCER AND COPD ASSESSED BY CT IMAGES

The National Lung Cancer Screening Trial (NLST) for annual low-dose CT screening reported a 20% decrease in lung cancer mortality among heavy smokers between the ages of 55 and 74 years^[21]. This great achievement has resulted in several established guidelines recommending low-dose CT lung cancer screening for individuals with defined conditions, and the time when screening will be implemented as a part of community health care is drawing closer^[22]. The more common use of chest CT examinations in asymptomatic individuals would increase the chance of detecting pulmonary diseases, including lung cancer and pulmonary emphysema. Because a definitive diagnoses of COPD and pulmonary emphysema are based on functional and pathological criteria, respectively, they cannot, by definition, be diagnosed using CT^[2]. Nevertheless, the presence of a substantially distributed low attenuation area (LAA) in the pulmonary fields strongly suggests pulmonary emphysema and COPD. In fact, Goddard *et al.*^[23] proposed a scoring system, which is used worldwide, to evaluate pulmonary emphysema using CT.

Six studies, consisting of 2 cohort and 4 case-control studies, evaluating the relationship between CT-based emphysema and the risk of lung cancer have been published^[24-29], and Zurawska *et al.*^[30] concisely reviewed these studies. The relative risk (RR) for lung cancer, according to CT-based emphysema assessed using semi-quantitative visual methods, ranged from 1.9 to 4.7, with a pooled RR of 2.34 (95%CI: 1.46-3.76). Using multivariate analyses adjusted for covariates including age, sex, and smoking status, the adjusted odds ratio for lung cancer, according to the CT-based detections of emphysema, ranged from 1.73 to 3.14. Mizuno *et al.*^[26] analyzed CT images from 947 healthy individuals who underwent a low-dose CT screening and 256 patients with lung cancer. After adjusting for sex and age, 423 matched healthy individuals and 141 patients with lung cancer were extracted for inclusion in multivariate analyses, with stratification according

to their smoking status. The results disclosed that many functional and CT image factors indicative of COPD (relative risks for lung cancer; 7.17 with FEV₁/FVC < 70% and 3.63 with LAA score ≥ 1) or interstitial lung diseases (relative risks for lung cancer; 4.73 with %VC < 80%, 5.10 with a fibrosis score ≥ 1 and 2.71 with a GGA score ≥ 1) were also risk factors for coincident lung cancer in a manner that was independent of the smoking status (Table 2). These observations suggesting a close association between COPD and lung cancer seem to imply at least three possibilities: first, airflow limitation itself is a risk factor for the development of lung cancer; second, some putative inter-individual variations in the sensitivity to harmful substances, such as active smoking, passive smoking, air pollutants, and cooking oil fumes, may link COPD and lung cancer; and third, some specific genotypes may predispose individuals to both COPD and lung cancer.

POSSIBLE MECHANISMS UNDERLYING THE COEXISTENCE OF LUNG CANCER AND COPD

A growing volume of evidence suggests that some molecular mechanisms may link COPD and lung cancer. A genome-wide association study has uncovered some putative common loci responsible for both COPD and lung cancer^[31]. Taking advantage of such modern technologies, we are soon likely to benefit from abundant information regarding the molecular mechanisms involving the pathogenesis of COPD and lung cancer. The current major possible explanations are outlined below.

Retention of airborne carcinogens because of airflow limitations may enhance carcinogenesis in the airways

In this speculative scenario, the airflow limitations that result from COPD suppress the clearance of carcinogens from the airway, leading to cancer in the airway. This classical scenario is now decorated with modern technical terms including DNA repair errors, oncogene activations, impaired tumor suppressor genes, oncogenic microRNA, the involvement of epithelial-mesenchymal transition, and a wide variety of epigenetic alterations.

Chronic inflammatory processes arising from COPD may enhance carcinogenesis in the airways

An association between persistent chronic inflammation and cancer has long been recognized. Examples include the relationships between cirrhosis and hepatocellular carcinoma, inflammatory bowel disease and colorectal cancer, burns and squamous cell carcinoma of the skin, and dental prostheses and lingual cancer. Recently, the relationship between chronic inflammation and cancer has been explained by a series of processes in which unscheduled necrotic cell death as a result of inflammation causes subsequent epithelial proliferation resulting in the suppression of immunity^[32]. Meanwhile, a volume of evidence has proven that complex inflammatory processes involving many types of immune cells, cytokines, matrix metalloproteinases, reactive oxygen species, and growth factors cause tissue damage and remodeling. This phenomenon ultimately results in the development of COPD^[2]. These factors also contribute to the enhancement of carcinogenesis^[33,34]. Parimon *et al.*^[35] observed a reduced lung cancer risk in patients using inhaled corticosteroids in a dose-dependent manner. This observation strongly supports the idea that the pathophysiology of COPD may enhance the development of lung cancer.

Putative lung stem cells activated by chronic inflammation in patients with COPD may transform to lung cancer stem cells

There is no evidence supporting the existence of lung stem cells in humans or cancer stem cells in human lung cancer^[36]. However, Kim *et al.*^[37,38] has reportedly identified bronchioalveolar stem cells in mice. If distal lung stem cells exist in humans, chronic inflammatory stimuli as a result of COPD might activate and transform these lung stem cells into lung cancer stem cells^[7].

Genetic backgrounds common to both COPD and the development of lung cancer may exist

A deficiency or decrease in alpha-1 antitrypsin is known to increase the risk of lung emphysema development. This condition, acting directly or indirectly through tissue damage to the lung, also increases the risk of lung cancer development^[39-42], although some controversy regarding this point still exists^[43]. Smoking is the strongest definitive risk factor for lung cancer development. Tobacco-derived pro-carcinogens are activated to become carcinogenic by a cluster of phase I enzymes. These activated carcinogens are then degraded and excreted by a cluster of phase II enzymes. Although not fully understood, some polymorphisms of these enzymes are known to lead to increased or decreased enzymatic activities, most likely causing inter-individual variations in the sensitivity to smoking^[44-49]. A better understanding of these mechanisms may identify individuals who are susceptible to lung cancer development when exposed to active or passive smoking. More recently, a decreased serum level of Clara (Clara) cell secretory protein (CC-16) has been found to increase the risk of both COPD^[50] and lung cancer^[51].

PROGNOSIS

As discussed above and illustrated in Table 1, a substantial proportion of patients with COPD die from lung cancer. The coexistence of lung cancer clearly worsens the prognosis of patients with COPD, but a discussion of how COPD worsens the outcome of patients with lung cancer and how this might be overcome is important.

The deterioration of pulmonary function together with the risk of acute exacerbation of COPD would, in theory, make invasive diagnostic procedures, surgery, radiotherapy and chemotherapy difficult in patients with lung cancer. A retrospective study by Sekine *et al.* reported an increased rate of postoperative complications, including pneumonia and the need for a tracheostomy, increased cancer recurrence, and a decreased 5-year survival rate in patients with completely resected stage IA non-small cell lung cancer (NSCLC) and coexisting COPD; the 5-year survival rates of patients with COPD ($n = 80$) and of those without COPD ($n = 362$) were 77.0% and 91.6%, respectively ($P = 0.0001$)^[52]. A recent retrospective study involving 902 patients with stage IA to IIB NSCLC treated with surgical resection also disclosed that 63.4% (572/902) of the patient population had self-reported, physician-diagnosed COPD, and the patients with COPD had a poorer 5-year progression-free survival rate (50.1% *vs* 60.6%, $P = 0.007$) and a poorer 5-year overall survival rate (54.4% *vs* 69.0%, $P = 0.0002$) than the patients without COPD^[53].

TREATMENT

Treatment algorithms can be complex when different diseases coexist in the same patient. It seems reasonable to prioritize the treatment of diseases with a more serious impact on the prognosis: for example, the treatment for stage III small cell lung cancer would be given preference over the treatment for a coincidental low-grade prostatic cancer in the same patient. The situation, however, is totally different in patients with coexisting COPD and lung cancer. It is very important to diagnose, evaluate, and manage both the COPD and lung cancer in a comprehensive manner for the following reasons.

To avoid the deterioration of quality of life because of COPD

COPD symptoms significantly overlap with those of lung cancer. Cough, sputum, shortness of breath, body-weight loss, appetite loss, and even depression may arise from COPD rather than from lung cancer, in some cases. The appropriate treatment for COPD may relieve these symptoms, leading to an improved quality of life (QOL).

To avoid the acute exacerbation of COPD during treatment for lung cancer

The acute exacerbation of COPD can be precipitated by upper respiratory tract viral infections, bacterial infec-

tions of the tracheobronchial trees, and other factors. Once acute exacerbation has occurred, the mortality rate is high. In patients with COPD and lung cancer, stress or immunosuppression as a result of surgery, radiotherapy, chemotherapy, or a terminally ill status can act as predisposing factors for an acute exacerbation. It is particularly important to understand that COPD exacerbations can often be prevented with the appropriate management of the disease^[2].

To decrease the complications associated with lung cancer treatment

Acute lung injury is a serious complication associated with lung cancer treatment, especially when patients suffer from symptomatic or asymptomatic idiopathic pulmonary fibrosis (IPF). Acute lung injury can occur in patients undergoing surgery, thoracic radiotherapy, or cytotoxic or molecular-targeted therapy^[54,55]. Although this complication seems to be more frequent in Japanese patients than in patients from other countries, the precise epidemiology and underlying mechanisms are not well known. In contrast to IPF, the presence of COPD is not recognized as a significant risk factor for acute lung injury associated with lung cancer treatment.

To ameliorate the outcome of the surgical resection of lung cancer

As a result of improvements in anesthesiology, surgical technique, and postoperative managements including rehabilitation, the curative-intent surgical resection of lung cancer in patients with COPD has become safer than previously expected^[56]. When a lung cancer is located within a severely damaged emphysematous region, its resection does not necessary impair pulmonary functions to the extent that a lung volume reduction surgery for severe emphysema would restore the impaired pulmonary function. In a study with a limited number of patients, Kobayashi *et al.*^[57] demonstrated better postoperative pulmonary functions than expected, with improved preoperative symptoms and pulmonary function, in patients with treatment-naïve COPD and lung cancer who were treated with inhaled tiotropium, a long-acting anticholinergic bronchodilator, starting 2 wk prior to surgery. As limited resections of lung cancer often result in poor outcomes, a curative-intent standard resection is recommended even for patients with mild to moderate COPD, with the aid of early interventions including drug therapy and rehabilitation for COPD^[56].

FUTURE DIRECTIONS

Low-dose CT screening effectively detects 10-fold more lung cancers at earlier stages compared with screenings using conventional chest X-rays^[58]. As mentioned earlier, the NLST, a randomized trial involving subjects with a high risk of lung cancer, confirmed a 20% reduction in the lung cancer mortality among subjects allocated to a low-dose CT screening group compared with an X-ray

screening group^[21]. This screening strategy targeting individuals at high risk was based on their smoking history and age. Sekine *et al.*^[59] emphasized the importance of the early detection of COPD for the purpose of lung cancer screening and proposed CT screening for individuals with suspected COPD as a strategy to target individuals at high risk. Based on a quick questionnaire that collected information about age, smoking history, and chronic respiratory symptoms, they identified 878 individuals fulfilling the defined criteria out of 89100 participants (1.0%). A total of 567 of the 878 participants (64.6%) underwent further evaluation consisting of CT and spirometry, resulting in the detection of COPD in 161 participants, with 38.5% of them requiring COPD treatment^[60]. Although the data regarding lung cancer detection are not yet available because the trial is still ongoing, this strategy for identifying a high-risk population based on suspected COPD could be an alternative to identification strategies based on age and smoking history. We envision that this new approach could enable us to evaluate and manage COPD and lung cancer comprehensively at early stages and from screening through specialized treatment.

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