Lung cancer in chronic obstructive pulmonary disease patients: importance of cellular senescence

Barbara Kuźnar-Kamińska¹, Justyna Mikuła-Pietrasik², Krzysztof Książek², Andrzej Tykarski², Halina Batura-Gabryel¹

¹ Department of Pulmonology, Allergology and Respiratory Oncology, Poznań University of Medical Sciences, Poznań, Poland  
² Department of Hypertensiology, Angiology and Internal Medicine, Poznan University of Medical Sciences, Poznań, Poland

KEY WORDS  
aging, cellular senescence, chronic obstructive pulmonary disease, inflammation, lung cancer

ABSTRACT

Patients with chronic obstructive pulmonary disease (COPD) are at increased risk of lung cancer, independently of smoking, although the link between these diseases remains unknown. Possible pathophysiologic mechanisms include inflammation and cellular senescence. COPD is a chronic inflammatory disease associated with secretion of numerous inflammatory mediators, many of which play a documented role in the promotion of cancer cell progression. COPD is also an age-related disease involving increased cellular senescence, an important hallmark of aging. Previous studies have confirmed the significant role of cellular senescence in the development of various tumors, including lung cancer. It is highly probable that cellular senescence contributes to carcinogenesis in COPD patients.

Introduction  
There is accumulating evidence confirming that chronic obstructive pulmonary disease (COPD) is a risk factor for lung cancer.¹ However, the mechanism linking the 2 diseases has not been fully elucidated. This review aims to present a novel insight into the common pathogenesis of COPD and lung cancer. We particularly focused on the new aspects of tumorigenesis in COPD patients, namely, inflammation as well as cellular senescence and aging.

Epidemiology of chronic obstructive pulmonary disease and lung cancer  
The increased risk of lung cancer in COPD patients was first described by Skirland et al² in 1987, who showed that the 10-year cumulative risk of lung cancer was 8.8% for COPD patients, compared with 2.0% for controls. The prevalence of lung cancer in COPD patients varies between studies, depending on the study population, and hence on disease phenotype, severity of obstruction, age, other respiratory diseases, and smoking status (TABLE 1, FIGURE 1).²⁻¹¹ At the same time, numerous studies have shown that airway obstruction in COPD is associated with an increased risk of lung cancer, independently of smoking.⁴⁻⁹,¹⁰ Calabro et al¹¹ documented that even mild obstruction, without a reduction in forced expiratory volume in 1 second, was a risk factor for lung cancer. Another independent indicator is the presence of emphysema on a low-radiation-dose computed tomography (CT) scan of the chest. Emphysema is associated with increased risk of lung cancer in individuals without airflow obstruction on spirometry, as well as those with coexistent airway obstruction and emphysema.¹²,¹³

The results of multiple analyses investigating the link between COPD and lung cancer also differ depending on the type of study, from lung-cancer screening trials to population-based and case-control studies.¹⁴,¹⁵ The causative role of COPD in lung cancer is supported by the finding that 40% to 70% of patients with lung cancer had clinically confirmed COPD that developed prior to cancer.¹⁶⁻¹⁸ According to mortality studies, 20% to 30% of patients with COPD die from lung cancer.¹⁹

Prevention and early detection of lung cancer in patients with chronic obstructive pulmonary disease: screening programs and reducing exposure to risk factors  
Given that COPD favors carcinogenesis in the respiratory system, there is a need to...
Multiple studies have confirmed the benefits of screening for lung cancer with low-dose CT in high-risk current and former smokers. CT, when performed at intervals in COPD patients with a history of smoking, was associated with a higher detection rate of lung cancer and diagnosis at earlier stages. The results of screening programs show that it is especially useful to implement screening procedures in emphysematous patients with severe obstruction and associated comorbidities. The available evidence shows that CT screening can reduce lung cancer-specific mortality. However, despite the numerous advantages, they are associated with the risk of false-positive results for small nodules, which must then be further evaluated. Therefore, there is a need for developing newer methods that could identify patients with COPD and smoking history who are at risk of lung cancer.

Lung cancer screening scores based on body mass index, history of smoking, age, and emphysema or carbon monoxide diffusion capacity are easy-to-employ diagnostic tools for assessing the risk of lung cancer. On the other hand, real-time elastography performed during endoscopic ultrasound, fluoroscopic-guided radial endobronchial ultrasound, chest ultrasound, and linear endobronchial ultrasound are more advanced procedures that may prove promising in the future.

### TABLE 1 Prevalence of lung cancer in patients with chronic obstructive pulmonary disease in various studies

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of cases: COPD, controls (n); description of the study group</th>
<th>Odds of lung cancer in COPD patients, fully adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartz et al</td>
<td>175, 81; women with combined obstructive lung disease classification</td>
<td>1.67 (1.15–2.41)</td>
</tr>
<tr>
<td>Koshiol et al</td>
<td>509, 174</td>
<td>2.5 (2.0–3.1)</td>
</tr>
<tr>
<td>Powell et al</td>
<td>2757, 2286</td>
<td>6.81 (5.49–8.45)</td>
</tr>
<tr>
<td></td>
<td>404, 140; COPD diagnosis within 6 months</td>
<td>2.52 (2.00–3.19)</td>
</tr>
<tr>
<td></td>
<td>198, 172; COPD diagnosis in 6–12 months</td>
<td>2.48 (2.24–2.75)</td>
</tr>
<tr>
<td></td>
<td>690, 580; COPD diagnosis in 5–10 years</td>
<td>2.68 (2.36–3.05)</td>
</tr>
<tr>
<td></td>
<td>431, 447; COPD diagnosis ≥10 years</td>
<td>2.18 (1.87–2.54)</td>
</tr>
<tr>
<td>Denholm et al</td>
<td>920, 647</td>
<td>1.39 (1.21–1.59)</td>
</tr>
<tr>
<td></td>
<td>751, 577; only bronchitis</td>
<td>1.70 (1.09–2.66)</td>
</tr>
<tr>
<td></td>
<td>77, 37; bronchitis and emphysema</td>
<td>2.68 (1.71–4.21)</td>
</tr>
<tr>
<td>Kishi et al</td>
<td>19, 64</td>
<td>1.6 (0.5–5.6)</td>
</tr>
<tr>
<td></td>
<td>4, 17; FEV$_1$/FVC × 100% (51–60)</td>
<td>1.7 (0.4–7.4)</td>
</tr>
<tr>
<td></td>
<td>7, 12; FEV$_1$/FVC × 100% ≤50</td>
<td>4.1 (1.0–17.2)</td>
</tr>
<tr>
<td>Mannino et al</td>
<td>54, 899</td>
<td>1.4 (0.8–2.6)</td>
</tr>
<tr>
<td></td>
<td>16, 423; mild obstruction</td>
<td>2.8 (1.8–4.4)</td>
</tr>
<tr>
<td>Calabro et al</td>
<td>17, 839</td>
<td>1.23 (0.68–2.25)</td>
</tr>
</tbody>
</table>

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; OR, odds ratio.

### FIGURE 1 Risk factors of lung cancer in patients with chronic obstructive pulmonary disease (COPD)

- Patient’s sex
- Duration of COPD
- Severity of obstruction
- Risk factors of lung cancer in COPD patients
- Other respiratory diseases (pneumonia, tuberculosis)
- Smoking habit
- Disease phenotype (emphysema, chronic bronchitis)
- Age

Protect against lung cancer and to reduce the risk of its occurrence by decreasing exposure to harmful factors.

Multiple studies have confirmed the benefits of screening for lung cancer with low-dose CT in high-risk current and former smokers. CT, when performed at intervals in COPD patients with a history of smoking, was associated with a higher detection rate of lung cancer and diagnosis at earlier stages. The results of screening programs show that it is especially useful to implement screening procedures in emphysematous patients with severe obstruction and associated comorbidities. The available evidence shows that CT screening can reduce lung cancer-specific mortality. However, despite the numerous advantages, they are associated with the risk of false-positive results for small nodules, which must then be further evaluated. Therefore, there is a need for developing newer methods that could identify patients with COPD and smoking history who are at risk of lung cancer.

Lung cancer screening scores based on body mass index, history of smoking, age, and emphysema or carbon monoxide diffusion capacity are easy-to-employ diagnostic tools for assessing the risk of lung cancer. On the other hand, real-time elastography performed during endoscopic ultrasound, fluoroscopic-guided radial endobronchial ultrasound, chest ultrasound, and linear endobronchial ultrasound are more advanced procedures that may prove promising in the future.
Cigarette smoke and air pollution remain the most common risk factors of both COPD and lung cancer.\textsuperscript{32,33} While cigarette smoke is responsible for even more than 90\% of lung cancer cases, occupational exposure to particles, including carcinogens, such as polycyclic aromatic hydrocarbons, arsenic, nickel, and chromium, is associated with geographical region and is estimated to be responsible for 1\% to 2\% of lung cancer cases.\textsuperscript{34} A substantial body of evidence has confirmed the benefits of quitting smoking. In COPD patients who quit smoking, the risk of non–small cell lung cancer was reduced, although did not return to baseline.\textsuperscript{35,36} The available data suggest that participation in screening programs increases the motivation to quit smoking, thus enhancing its effectiveness, which, however, is still quite low.\textsuperscript{37} The positive results of low-dose CT also correlated with the maintenance of nicotine abstinence.\textsuperscript{38} Regarding occupational exposure, air pollution prevention programs should be undertaken to reduce risk of smoking-dependent diseases, especially in urban areas.\textsuperscript{39}

**Inflammation in chronic obstructive pulmonary disease and its significance for promoting lung cancer**

A broad spectrum of different factors has been identified to be involved in tumorigenesis in COPD patients, including the deleterious activity of tobacco smoke, mutations, insufficiency of DNA repair mechanisms, and oxidative stress.\textsuperscript{40} Interestingly, a common element linking all these agents is chronic tissue inflammation.\textsuperscript{41} It is well known that inflammation that occurs in COPD results from chronic exposure to cigarette smoke, other risk factors, as well as aging.\textsuperscript{42} Cigarette smoke induces the secretion of numerous inflammatory mediators, including lipids, free radicals, cytokines, chemokines, and growth factors, such as interleukin (IL)-1, IL-8, transforming growth factor (TGF)-\(\beta\), and chemokine CCL21.\textsuperscript{43,44} Many of these mediators have been shown to promote various mechanisms involved in multiple cancer cell progression.\textsuperscript{45-47} They are also responsible for the major steps in lung cancer progression, including adhesion, migration, and proliferation. For example, IL-1B and tumor necrosis factor (TNF)-\(\alpha\), whose production is increased in COPD patients, have been found to induce the expression of adhesion molecules (eg, intercellular adhesion molecule 1 [ICAM-1]) in lung cancer cells and their more pronounced attachment to the vascular endothelium.\textsuperscript{48} In addition, the adhesion of lung cancer cells has been linked to the expression and activity of multivalent extracellular matrix (ECM) constituents (fibronectin, type IV collagen) and their interactions with \(\beta\)1 integrins.\textsuperscript{49,50} These interactions lead to phosphorylation of focal adhesion molecule, which, in turn, results in augmented cancer cell migration and proliferation. Lung cancer cell motility has also been stimulated by prostaglandin E2,\textsuperscript{51} urokinase-type plasminogen activator receptor (uPAR/CBD87),\textsuperscript{52} Cdc42,\textsuperscript{53} CYR 61,\textsuperscript{54} claudin-1,\textsuperscript{54} stromelysin-3,\textsuperscript{55} matrix metalloproteinase (MMP)-2, MMP-7, and MMP-9,\textsuperscript{56} CXCL12/SDF1,\textsuperscript{57} and CCL21.\textsuperscript{58,59}

Different cells are involved in the secretion of inflammatory molecules. Tertiary lymphoid aggregates created during inflammatory response to proteases and free radicals secreted by activated leukocytes may reflect lymphoid neogenesis, the first step of tumorigenesis, and could affect regulatory mechanisms, such as autophagy, apoptosis, angiogenesis, and cell repair.\textsuperscript{60} Moreover, molecules secreted by T cells may also participate in tumorigenesis. An increase in the blood levels of Th2 cytokines (IL-4 and IL-10) was observed in patients with lung cancer, while those released by Th1 (IL-2 and interferon \(\gamma\)) were shown to decrease.\textsuperscript{61} Additionally, myeloid-derived suppressor cells may affect T cells and regulate inflammation and carcinogenesis.\textsuperscript{62}

Other cells that participate in tumorigenesis include macrophages. During tumor progression, macrophages are recruited to the site of cancer by a wide spectrum of chemoattractants, derived from the tumor and surrounding stroma. Once present in the tumor microenvironment, the macrophages can change their functional phenotype. At the early stage of cancer, tumor-suppressive M1 phenotype of macrophages occurs, which limits the progression of the malignancy. As tumorigenesis progresses, the macrophages acquire the tumor-promoting M2 phenotype, turning into the so-called tumor-associated macrophages, and alter the microenvironment to support tumor development.\textsuperscript{63-65}

**Chronic obstructive pulmonary disease and cellular senescence of normal lung cells**

One of the functions of cellular senescence is to control the unlimited cell proliferation. In the 1960s, Hayflick and Moorhead\textsuperscript{66} observed for the first time that cultured normal human cells undergo a limited number of divisions, after which they become senescent (\textit{figure 2}). This phenomenon was described as replicative senescence. In contrast, premature senescence occurs as the result of various endogenous and exogenous stressors, including oxidative stress, oncogene activation, and DNA damage.\textsuperscript{67,68} Senescent cells change their morphology: they become bigger and flatter, contain more proteins, and their chromatin is reorganized. On becoming senescent, cells acquire an important ability to secrete a wide range of cytokines, chemokines, matrix remodeling proteases, and growth factors, which is referred to as senescence-associated secretory phenotype.\textsuperscript{69} Moreover, senescence occurs not only in cells directly localized in the airways, but also in the microenvironment. The intercellular communication of senescent cells with normal neighboring cells has been described in previous studies.\textsuperscript{70-72} Mikula-Pietraski et al\textsuperscript{73,74} reported that senescent human peritoneal mesothelial cells can alter the secretory profile of ovarian cancer cells in a paracrine manner, supporting their invasiveness in the peritoneal cavity.
Promote the growth of breast cancer cells in vitro and the development of solid tumors in vivo much more effectively than their younger counterparts. The same was observed for peritoneal mesothelial cells in which senescence appeared to stimulate ovarian, colorectal, and pancreatic cancer cell adhesion to a larger extent than in the case of young proliferating cells.

It is well known that senescent cells, which accumulate in tissues in vivo, have several pro-oncogenic features. The most relevant feature is the ability to increase secretion of numerous soluble mediators involved in important processes in cancer spread, such as inflammation, angiogenesis, ECM remodeling, and the epithelial–mesenchymal transition. This hallmark of senescence is called senescence-associated secretory phenotype, and the mediators include cytokines (IL-1, IL-6, and IL-7), chemokines (CXCL8/IL-8, CXCL12/SDF-1, CCL21/CCR7, and CXCL5/ENA-78), growth factors (chemokine growth-regulated oncogene 1, heregulin β, vascular endothelial growth factor, TGF-β1, connective tissue growth factor, hepatocyte growth factor, and fibroblast growth factor), shed surface molecules (ICAM-1, uPAR, and TNF receptors), and stromal ECM modulators (PAI-1, u-PA, MMP-2, and MMP-9).

Some of these agents are known to mediate various processes involved in lung tumorigenesis, such as proliferation (CXCL12 and CCL21), migration (CCL21), and invasion (CXCL5) (FIGURE 3).

COPD and lung cancer are age-related diseases (FIGURE 4). Increased cellular senescence is one of the major indicators of aging. There is growing evidence to support the presence of cellular senescence in COPD patients. Its role in promoting invasiveness of many tumors, including lung cancer, has been widely confirmed. A role of cellular senescence in the overlap of COPD and lung cancer in patients with COPD...
lungs. More studies are needed to confirm the involvement of COPD-related cellular senescence in the tumorigenesis of lung cancer.

**Conclusions** Multiple studies confirm the crucial role of inflammation in the development of lung cancer in COPD patients. An increasing body of research has focused on cellular senescence in COPD patients. In the light of the current knowledge that cellular senescence may promote oncogenic activation, it seems that there is only one step to confirm its significance for lung cancer progression in COPD patients.

**OPEN ACCESS** This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0), allowing third parties to copy and redistribute the material in any medium or format and to remix, transform, and build upon the material, provided the original work is properly cited, distributed under the same license, and used for noncommercial purposes only. For commercial use, please contact the journal office at pamw@mp.pl.

**REFERENCES**


468

POLISH ARCHIVES OF INTERNAL MEDICINE 2018; 128 (7-8)