

REVIEW ARTICLE

The relationship between chronic lung diseases and lung cancer – a narrative review

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Summary

Lung cancer and chronic lung diseases are currently two of the main causes of death in the world. Both conditions have common etiological factors and multiple research directions in the last decades demonstrated the presence of some common relevant biological mechanisms which can explain why patients with chronic respiratory diseases are at higher risk of developing lung cancer. In this review, we discuss the role of chronic pulmonary diseases, such as chronic obstructive pulmonary disease, tuberculosis, sarcoidosis, asthma, pneumoconioses, idiopathic pulmonary fibrosis and their impact

on lung cancer development. We also summarize the possible mechanisms involved in this relationship and how these chronic diseases influence the prognosis of patients with lung cancer. Our aim was to inform the clinicians in this respect for a careful follow-up of this category of patients and for the application of a personalized treatment approach.

Key words: lung cancer, chronic obstructive pulmonary disease, tuberculosis, asthma, sarcoidosis, idiopathic pulmonary fibrosis

Introduction

With a global incidence of 1.8 million cases in 2012, lung cancer (LC) is among the leading causes of death worldwide. LC represents approximately 13% of all newly diagnosed cases and 26% of all cancer-related fatalities [1]. The high mortality is caused by the absence of symptoms, substantially delaying diagnosis.

Recent evidence suggests that inflammatory processes play a central role in the carcinogenesis of LC. Chronic obstructive pulmonary disease (COPD), pneumonia or tuberculosis are major sources of inflammation in pulmonary tissues. Such pathologies may trigger lung cancer and be correlated with its development. They share the same etiology [2]. Although the association between chronic pulmonary diseases and LC has been researched for several decades, the evidence

remains unconvincing due to inconclusive results and insufficiently large cohorts (fewer than 500 cases in 65% of studies) [3].

1.1. Chronic obstructive pulmonary disease (COPD)

COPD is a progressive deterioration of pulmonary function which can lead to death. COPD lowers the patient's quality of life and affects approximately 50% of smokers. In 2018 COPD was the third most common cause of death with the number of new cases growing. Pulmonary damage in COPD is generated by oxidative stress (both exogenous- due to smoking, and endogenous), the release of inflammatory cytokines, the activation of proteases (protease-antiprotease imbalance) and

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the expression of antibodies. This lung disease may lead to the destruction and obstruction of airways, plus hyperinflation [4].

COPD and LC are caused by smoking, and evidence points to a common etiology. Also, COPD is an independent risk factor for LC, especially for squamous cell carcinoma. LC occurs 5 times more frequently in smokers who also suffer from obstructed airways than in those with normal pulmonary function [4].

LC and COPD may share the same physiopathological mechanisms: a genetic predisposition, telomere shortening, mitochondrial dysfunction or early aging. In most smokers, the carcinogenic effect of smoking may be counterbalanced by the body's antioxidant defense mechanisms: superoxide dismutase, antiproteases and DNA repair mechanisms. However, these may fail, leading to cancer if the mutations are not repaired, or to COPD if cellular or protein destruction is too great. Alternatively, COPD can drive LC by increased oxidative stress, DNA mutations, chronic exposure to proinflammatory cytokines, suppression of DNA repair mechanisms and increased cellular proliferation [3,5-7].

COPD has been reported as a risk factor for LC regardless of the patient's smoking status. Interventional studies aiming to identify risk factors have found that patients with obstructed airways are at significantly higher risk of developing COPD. This subsequently points to COPD patients also being predisposed to LC compared to smokers with normal pulmonary function or with former smokers. Despite substantial scientific interest in the association of these major lung diseases, the molecular details and their clinical implications have only begun to be understood during the last decade [8,9].

1.2. Chronic obstructive pulmonary disease as a fertile ground for lung cancer

COPD and LC share several pathways. All neoplastic tissues exhibit inflammation, which is why a large number of inflammatory diseases also predispose to cancer. Chronic inflammation in COPD may act as a potent driver for LC, as suggested by the efficacy of non-steroidal anti-inflammatory drugs. Inflammation is the main source of reactive oxygen species which are persistent in COPD [4,10].

1.3. The epidemiology and risk of lung cancer in chronic obstructive pulmonary disease patients

Several reports have shown that the prevalence of LC in COPD patients ranges from 8% to 50% [11].

Skillrud et al conducted a case-control study evaluating the risk of LC in COPD patients and estimated an 8.8% cumulative probability for COPD patients to develop LC in the first 10 years, compared to 2% in patients with normal pulmonary function [12]. This indicates that approximately 1% of COPD patients will develop LC (the risk being five times higher). In another study, De Torres et al found that 215 of 2,507 COPD patients developed LC (incidence of 16.7 cases per 1,000 person-years with a median follow-up of 60 months). Their result suggests that, in a population of smokers diagnosed with COPD and with a history of admissions to a pneumology clinic, the incidence of LC was higher than previously reported [11]. In yet another study of 2,100 LC patients, the risk of LC was superior in patients 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 2.0, 95% CI, 1.06-2.59). After a 20-year follow-up of 448,600 smokers, Turner et al. reported that mortality due to LC correlated significantly with emphysema (HR 1.66, 95% CI, 1.06-2.59) as well as with emphysema associated with chronic bronchitis (HR 2.44, 95% CI, 1.22-4.9), but not with chronic bronchitis alone (HR 0.96, 95% CI, 0.72-1.28) [12]. In both studies, COPD had been diagnosed based on the patients clinical symptoms of emphysema or chronic bronchitis and their answers to questionnaires, not by means of spirometry or CT scans [13].

Last but not least, LC incidence is also influenced by the severity of COPD. Data collected from 5,402 study participants over a period of 22 years revealed a significant correlation between the degree of airway obstruction and LC incidence [13]. Mild COPD was demonstrated to generate a relatively higher level of risk compared to the absence of comorbidities (HR 1.4, 95% CI, 0.8-2.6), while moderate and severe COPD was linked to higher rates of LC compared to normal pulmonary function (HR 2.8, 95% CI, 1.8-4.4) [12]. De Torres et al found that LC incidence in advanced stages of COPD (9.2 cases per 1,000 person-years) was less than half of that in stage I of COPD (19.9 cases in 1,000 person-years). The authors presumed that an active, intolerant immune system would act as a barrier against cancer development and progression [11].

1.4. Clinical and molecular features of lung cancer associated with COPD

Squamous cell carcinoma is most frequently associated with COPD or with emphysema and LC and its location is typically central in these patients. However, lower emphysema grades seem to

correlate with central lung tumors, while more severe grades tend to predict peripheral location [10]. There appears to be a strong relationship between the tumor location and the area with the higher grade of emphysema [14]. Schiavon et al. observed less invasive adenocarcinoma features such as increased lepidic components and reduced cellular proliferation compared to cases of adenocarcinoma not associated with COPD [15]. However, Murakami et al have asserted that neoplasms which develop in the vicinity of the emphysema exhibit more aggressive tumor biology [16].

Another research demonstrated that the doubling time of pulmonary nodules was shorter in smokers with reduced pulmonary function, thus suggesting that COPD is a useful clinical marker for appraising LC aggressiveness. Several studies have revealed that both EGFR mutations and ALK rearrangements were less frequent in COPD-associated LC, and that the presence of EGFR mutations correlated negatively with the severity of airway obstruction. KRAS mutations occurred regardless of COPD status [17,18].

I.5. The prognosis for patients with LC and COPD

The prognosis for COPD patients is poorer compared with patients without COPD as a result of added treatments, altered pulmonary function and reduced quality of life [19]. The long-term postsurgical survival of patients with COPD and stage IA LC has been subject to research, and the 5-year survival of COPD patients proved to be significantly lower than that of patients with normal pulmonary function due to a higher rate of recurrence (77% vs. 91.6%, $p < 0.0001$). Such results suggest that LC in patients with COPD tends to be more aggressive [18]. Other studies have found that COPD is a significant risk factor for respiratory complications and poorer long-term survival on account of the respiratory insufficiency following the resection of the cancerous tumors [19,20]. Lopez-Encuentra et al reported that despite the similar survival rates of patients with and without COPD soon after LC surgery after 2 and then 3 years, the survival rate of stage I LC patients with underlying COPD was significantly lower compared to that of patients without COPD [21]. Although COPD patients suffer from substantially more cardiopulmonary comorbidities, postsurgical physical and mental evaluations did not seem to differ between patients with and without COPD [22-25]. Because long-term results are yet to be reported, the effects of comorbidities upon survival remain controversial [26].

II. Lung cancer and tuberculosis

According to the World Health Organisation, tuberculosis (TB) occurs with an incidence of 9.4 cases yearly and causes approximately 1.7 million deaths. TB is the result of the reactivation of a latent infection with *Mycobacterium tuberculosis*, which currently colonizes a third of the global population. Pulmonary infections may contribute to cancer etiology. TB increases the risk of LC by prolonged and substantial pulmonary inflammation which damages the host tissue, causes fibrosis, scarring and genetic alterations [27]. In a recent meta-analysis, TB was reported to increase the risk of LC by 1.7 times. Most of the previous research consisted of case-control studies and there is little prospective data on TB and the risk of LC. TB infection triggers a widespread immune response in the host, and inflammatory cells generate cytokine signalling cascades, reactive nitrogen and oxygen species, prostaglandins and proteases which destroy the tissues [28,29]. Even TB patients undergoing treatment may suffer from prolonged pulmonary inflammation because the symptoms have already occurred months before diagnosis, and treating tuberculosis requires lengthy periods of medication. Such prolonged pulmonary inflammation may cause tissue damage and genomic alteration. The repair of the TB-damaged tissue may lead to pulmonary fibrosis and scarring, which also increase the risk of LC. It is worth mentioning that men diagnosed with TB sequelae are exposed to such elevated risk. This diagnosis is very likely in men suffering from severe lung damage due to TB, and this observation is meant to underscore the role of fibrosis in facilitating carcinogenesis [29].

Two cohort studies and other case-control studies investigated the relationship between TB and LC. Although one study found the risk of LC to be six times higher in patients with TB than in those without it, another cohort study did not establish any such correlation. Some case-control studies reported notable associations between TB and LC, rating the level of risk between 1.6 and 4.2, while others did not. When patients with LC were stratified based on histology, TB related significantly to squamous cell carcinoma [28]. A review of 41 studies aiming to establish if preexisting TB increases the risk of LC found TB to be associated with the adenocarcinoma group mostly in non-western countries. Inconclusive results justify the need for more research regarding the relationship between TB and LC [29].

III. Lung cancer and sarcoidosis

Sarcoidosis is a granulomatous inflammatory disease whose cause is yet unknown. Some charac-

teristics point to it having an infectious origin, others suggest genetic susceptibility. In Scandinavian and Caucasian patients, there is a strong correlation between genetic rearrangement for the specific T cell receptor, HLA-DR17, and favorable prognosis, thus indicating the presence of a single antigen and underlining the importance of host predisposition. Chronic inflammation is associated with a high risk of malignant lymphoma or cancer in the affected tissue. Theoretically, this could apply to sarcoidosis as well, which most often involves intrathoracic organs, the liver and the skin [30].

The literature is scarce on the risk of cancer after sarcoidosis. One retrospective cohort study tested the hypothesis of elevated risk for LC and included 8541 patients from the Swedish Patient Registry [31]. The relative risks were estimated using standardized incidence and proved to be similarly high in both groups. For LC, the relative risk was double in the first decade of follow-up. Also, sarcoidosis was noticed to increase the risk of cancer in the affected organs, with chronic inflammation being an important mediator of this risk [30,31].

IV. Lung cancer and asthma

Asthma is one of the most common diseases of childhood, with a global prevalence of 10% among children aged 6-7. It is characterized by chronic pulmonary inflammation, bronchial hyperreactivity, excessive mucus production, and airway obstruction. Some studies found a significant association between asthma and LC, but these results are inconclusive. A meta-analysis of 22 studies conducted in order to establish if LC is indeed associated with asthma, indicated a high level of risk (OR=1.44). In addition, non-smoking asthma patients were also found to be at high risk of LC (OR=1.28). The analysis of racial subgroups revealed elevated risks in both Caucasians and Asians (OR=1.53, 95% CI, 1.37-1.72, $p<0.00001$, $I^2=56\%$, and OR=1.52, 95% CI, 1.15-2.01, $p<0.00001$, $I^2=93\%$). Gender analysis revealed high levels of risk for LC in both men and women suffering from asthma (OR = 1.38, 95% CI, 1.31-1.46, $p<0.00001$, $I^2 = 24\%$, and OR=1.68, 95% CI, 1.45-1.95, $p<0.00001$). However, asthma was not found to increase the risk of lung adenocarcinoma (OR=1.01, 95% CI, 0.69-1.50, $p=0.95$, $I^2=45\%$). These results suggest that asthma may be an independent risk factor for LC. Further studies are needed to assess the relationship between asthma and other histopathological types of LC [32,33]. Meta-analyses concluded that asthma may be associated with LC [34,35].

V. Lung cancer and pneumoconioses

Pneumoconioses are a group of lung diseases caused by the inhalation of mineral dusts. There are three types of inorganic mineral dusts responsible for the typical form of pneumoconiosis: coal, asbestos and silica powders. Coal dusts may trigger pneumoconiosis and chronic inflammatory disease such as massive progressive pulmonary fibrosis, COPD, or emphysema. Inhaled silica crystals have been associated with silicosis, tuberculosis, fungal infections, COPD, malignant illnesses, autoimmune diseases, and kidney diseases. Exposure to asbestos dusts may cause pulmonary fibrosis. Epidemiological studies have revealed that the risk of developing LC is high after prolonged exposure to silica crystals. The International Agency for Cancer Research has classified them as part of the group I carcinogens [33].

Some studies reveal a connection between the exposure of workers in coal mines, and the incidence of digestive and respiratory cancers. Ping Hung et al. conducted a study on 8051 patients working with coal. Cancer incidence was higher in the coal mine workers than in the general population. Men aged 80 or older were most at risk. The risk of cancer was higher in patients who had worked in coal mines and who were monitored for more than 5 years than in the general population. When individual types of cancer were assessed, the risk of developing cancer of the esophagus, stomach, liver, bile ducts and lung was found to be significantly higher in patients with occupational risks. The study was thoroughly designed with bias-free inclusion criteria due to the accurate diagnostic algorithm established in methodology [34]. A study from the Czech Republic revealed that coal mine workers are exposed to a higher risk of LC [35]. The mechanism by which coal increases the risk of cancer is not clear, the nature of these cancers pointing out several possibilities. Silica and asbestos generate reactive oxygen species which may play a role in LC pathology: long-term inflammation and oxidative stress increase the risk of cancer [35].

The distribution of the prevalence of these cancers may be explained by the theory of field cancerization: the surface of the aerodigestive epithelium, by being continuously exposed to carcinogens, has a higher risk of developing malignant diseases. These mechanisms may explain wherefore the neoplasms were more frequent in esophagus, stomach and lung. Moreover, exposure to coal powders and cancer may share some of the following risk factors: exposure to silica dusts, heavy metals, organic solvents or smoking. In addition, the particles ex-

haled by the respiratory system can be swallowed and then play a carcinogenic role in the digestive system. Some of these particles act directly as carcinogens, while cement and quartz dusts may have an irritating, abrasive effect on the mucus [30].

This study demonstrated that patients working in coal mines have a higher risk of cancer. The risk was significantly higher after a follow-up of more than 5 years. The male gender, age older than 60 and liver cirrhosis were independent predictors of cancer development in coal miner patients [34,35].

VI. Lung cancer and idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is an interstitial lung disease with poor prognosis and undefined etiopathogenesis. Several genetic and environmental risk factors have been identified to be involved in its pathogenesis: smoking, inorganic dusts, genetic mutations and polymorphisms [36]. Survival in IPF is less than 5 years [37]. LC incidence is much higher among patients with IPF than in the general population. For IPF patients, Ozawa et al reported rates of LC incidence of 3.3% at the one-year mark, 15.4% at 5 years, and 54.7% after 10 years. Mechanisms shared by both diseases are yet to be discovered [36,37].

LC significantly reduces the survival of IPF patients. Generally, it occurs in the peripheral areas of the inferior lobes, where fibrotic modifications are common. Specifically, LC develops in honeycombs or at the border between the honeycombs and the non-fibrotic areas. Squamous cell carcinoma is the predominant histological type [38].

Clinicians are faced with a dilemma: whether or not to treat LC in patients with IPF. Lee et al found that radiotherapy and surgical treatments for LC can further reduce the survival of IPF patients [39]. Voltolini et al. showed that surgical treatments have a negative impact on these patients [40].

Conclusions

The relationship between LC and chronic lung diseases has generated a great degree of scientific interest over the past decade. Consequently, relevant knowledge has increased exponentially. The role of inflammation in the promotion and development of LC is now undisputed. Deeper understanding is likely to be gained in the foreseeable future with regard to inflammation, oxidative stress, the genetic and molecular mechanisms which increase susceptibility to the disease, and new insights will lead to discoveries enabling early diagnosis and more effective treatments. Thus, there is hope that the quality of life and survival of these patients will improve.

Authors' contributions

Conception and design: Oana Miron and Lucian Miron; collection and assembly of data: Vlad Afrasanei, Marius Paduraru, Laura Mihaela Trandafir; manuscript writing: all authors. All authors approved the final version.

Conflict of interests

The authors declare no conflict of interests.

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