

# *Smoking and the Risk of Pneumonia: Research on the Impact of Tobacco on the Immune System of the Respiratory System*

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**Abstract:** This study retrospectively analyzes the impact of smoking on the composition ratio of respiratory pathogens and their drug sensitivity results in lung cancer patients with concurrent pneumonia. It aims to provide a theoretical basis for the selection of antibiotics in the clinical treatment of lung cancer patients with concurrent pneumonia. The study collected clinical data from hospitalized patients diagnosed with lung cancer and concurrent pneumonia from January 2018 to December 2022. Information on lung cancer patients with positive respiratory pathogen cultures was obtained, and a retrospective analysis of their clinical cases was conducted to assess their smoking status. The patients were then divided into smoking and non-smoking groups for comparison, and the composition ratio of respiratory pathogens and differences in drug sensitivity results were analyzed. Among the 287 lung cancer patients with concurrent pneumonia, the sputum culture results in the smoking group showed a significantly higher detection rate of *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* ( $P < 0.05$ ). However, the detection rate of *Staphylococcus epidermidis* was lower in the smoking group compared to the non-smoking group. There were no statistically significant differences between the smoking and non-smoking groups in the detection of *Acinetobacter baumannii*, *Enterobacter cloacae*, *Pseudomonas putida*, *Burkholderia cepacia*, *Burkholderia gladioli*, and *Burkholderia pseudomallei*. The detection rate of *Candida albicans* was higher in both groups, with a significantly higher detection rate in the smoking group ( $P < 0.05$ ). There were no significant differences between the smoking and non-smoking groups in the detection of *Cryptococcus neoformans* and *Candida tropicalis*. Additionally, there were no significant differences in the drug resistance rates of *Pseudomonas aeruginosa* to commonly used antibacterial drugs between the smoking and non-smoking groups. Smoking can lead to changes in the respiratory pathogen profile of lung cancer patients, promoting colonization of certain pathogenic bacteria and contributing to the occurrence of pneumonia. Smoking can also lead to an increased drug resistance rate of respiratory pathogens in lung cancer patients with concurrent pneumonia.

## 1. Introduction

Lung cancer, also known as bronchogenic carcinoma, mainly occurs in the bronchial mucosa or epithelium, and is one of the most common malignant tumors. Over the past half century, the incidence and mortality rates of lung cancer have shown a significant upward trend worldwide <sup>[1]</sup>. Additionally, patients are gradually presenting at a younger age <sup>[2]</sup>. In developed countries in Europe, America, and some major cities in China, lung cancer has become the most common malignant tumor in men, and its incidence in women is also rapidly increasing, ranking second or third among common malignant tumors in women. Lung cancer has become a major disease that threatens life and health. In 2012, there were 1.82 million new cases of lung cancer worldwide, with 1.6 million deaths due to lung cancer. Currently, the mortality rate of female lung cancer patients in China is 23.33 per 100,000, ranking first among cancer-related causes of death <sup>[3]</sup>, and the fatality rate of lung cancer ranks first among malignant tumors.

The respiratory tract has its own defense mechanisms. The first line of defense is composed of the physical barriers of the nose and vocal cords, as well as the anatomical branching angles of the respiratory tract, which can prevent the invasion of most harmful particulate matter into the distal airways. Cough reflex is also important, as effective coughing can expel most large harmful particles from the airways. The second line of defense is the mucociliary protection layer of the respiratory tract. The normal respiratory tract mucosa is covered by a very thin layer of mucus, which serves to capture bacteria and foreign substances.

Lung cancer is a global health issue. For a long time, it has been considered a disease determined by environmental factors. The addictive nature of nicotine leads people to continue smoking. In 1950, Doll first confirmed in the "British Medical Journal" that smoking is a significant cause of the development of lung cancer. The strength of the relationship between smoking and lung cancer reported domestically and internationally varies significantly. Reports from Western countries show a relationship of around 10 times, while in Asia, it's about 2-5 times. A meta-analysis in Japan regarding the relationship between smoking and lung cancer suggests a statistically significant difference in the relative risk (RR) of lung cancer occurrence between smokers and non-smokers <sup>[4]</sup>.

Cigarette smoke contains various toxic and carcinogenic substances. Some carcinogens can cause genetic damage, while others, such as polycyclic aromatic hydrocarbons, activate certain enzymes encoded by the P450 family, altering the body's susceptibility to cancer. Carcinogens in tobacco act on normal bronchial epithelial cells, leading to loss of HFIIT alleles and reduced protein expression. Bronchial epithelial cells lacking HFIIT gene expression gradually gain a proliferative advantage, leading to the formation of precancerous lesions and eventually developing into lung cancer. The impact of smoking on lung cancer EGFR is significant. Smoking is inversely related to EGFR mutations, and non-smokers have a higher mutation rate and positive expression of epidermal growth factor receptor (EGFR). EGFR-TKIs are more effective in lung cancer patients with no smoking history. The longer the smoking duration, the higher the likelihood of increased CEA levels in the blood. Elevated CEA levels are closely associated with the occurrence of lung cancer, thus increasing the likelihood of lung cancer in smokers compared to non-smokers. Additionally, the increasing death rate from lung cancer is closely related to cigarette consumption. Furthermore, bacteria present in tobacco enter the respiratory tract, leading to alterations in the long-term colonization of the bacterial community.

Epidemiological surveys show that smoking has become a global issue, with a worldwide population of smokers reaching 1.5 billion. Smoking is the leading cause of various lung diseases <sup>[5]</sup>. Smoking has a significant impact on the respiratory tract microbiota. Cigarettes produce over 4000 new chemicals during the combustion process, the vast majority of which are harmful toxic substances to the human body, including well-known nicotine, tar, and carbon monoxide. Tar is the

main culprit in causing lung cancer, containing various carcinogens, mainly nitrosamines and polycyclic aromatic hydrocarbons, as well as phenolic procarcinogens.

## **2. Research Material**

### **2.1 Clinical Data**

The sputum was collected from inpatients diagnosed with lung cancer and concurrent pneumonia at the Westmead Hospital of Australia from January 2018 to December 2022 for sputum culture and drug sensitivity testing, identifying patients with positive results.

### **2.2 Inclusion criteria**

(1) Patients hospitalized with complete clinical data for lung cancer combined with pneumonia from 2018 to 2022; (2) Patients meeting the 2018 Australia guidelines for the diagnosis and treatment of primary lung cancer <sup>[6]</sup>; (3) Patients meeting the 2017 guidelines for the diagnosis and treatment of community-acquired pneumonia or hospital-acquired pneumonia.

### **2.3 Exclusion criteria**

(1) Patients with a white blood cell count  $<3.0 \times 10^9/L$  or hemoglobin  $<90g/L$ . (2) Patients with concomitant chronic obstructive pulmonary disease or diabetes. (3) Patients with concomitant rheumatic immune system diseases or pneumoconiosis. (4) Patients who have used antibiotics within the past week.

## **3. Research methods**

### **3.1 Specimen collection**

The sputum was collected in the morning. Instruct the patient to repeatedly rinse their mouth with saline solution and then cough forcefully to expectorate deep sputum into a sterile sputum cup. For patients with artificial airways, use a sterile sputum collection device to collect sputum through the endotracheal tube. The collected sputum specimens should be immediately sent to the microbiology laboratory for sputum bacterial smear and sputum culture.

### **3.2 Instruments and reagents**

The identification and drug sensitivity tests of sputum culture strains are performed using the French bioMérieux VITEK2-compact fully automatic microbial analysis system and a 35°C constant temperature incubator, strictly following the operating procedures of the instruments for sputum culture strain identification and drug sensitivity tests. The presence of dominant bacteria in consecutive cultures two or more times, or pure cultures, is considered indicative of pathogenic bacteria. The 5% sheep blood agar and MacConkey agar (M-H) culture media are provided by Zhengzhou Antu Bioengineering Co. Ltd., and the drug sensitivity paper discs are provided by the British company Oxoid.

### **3.3 Bacterial identification and drug sensitivity testing**

The isolation, culture, and identification of strains strictly follow the "National Clinical Laboratory Operating Procedures". Qualified specimens (sputum smears are performed before

sputum culture, and if the microscopic examination shows more than 25 white blood cells/epithelial cells in a low-power field (10×10), the sputum is considered qualified) are inoculated on blood agar plates and chocolate agar plates, and then incubated at 35 °C for 18-24 hours to isolate the pathogenic bacteria. After pure bacterial culture, Gram staining, oxidase test, O/F test, and motility test are performed, followed by identification using the Vitek2-Compact bacterial identification instrument and ATB32GN identification strips, with an identification compliance rate of over 90.0%. The drug sensitivity test is performed using the paper disc diffusion (K-B) method, strictly following the guidelines and standards of the Clinical and Laboratory Standards Institute (CLSI) [7] for result interpretation.

### 3.4 Quality control strains

Standard strains such as *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 25923, and *Pseudomonas aeruginosa* ATCC 27853 are used as quality control strains. The determination of antimicrobial drug sensitivity is conducted according to the Clinical and Laboratory Standards Institute (CLSI) 2011 edition.

### 3.5 Research indicators

By culturing positive samples of respiratory flora from lung cancer patients, a retrospective analysis of clinical cases of lung cancer patients with concurrent pneumonia is conducted to collect data on their smoking status. The patients are then divided into smoking and non-smoking groups for comparison, analyzing the differences in the composition of lower respiratory tract flora and drug sensitivity results.

### 3.6 Statistical Analysis

The statistical analysis of the number of sputum culture strains and drug resistance rates is conducted using the IBM SPSS 19.0 statistical software, and the chi-square test is used to analyze the data. A significance level of  $P < 0.05$  is considered to indicate statistical significance.

## 4. Results

### 4.1 Comparison of Bacterial Cultures Detected in Sputum Cultures Between Two Groups

In 287 cases of lung cancer patients with pneumonia, the sputum culture results of the smoking group showed a significant increase in the detection rates of *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. The detection rate of *Staphylococcus epidermidis* was reduced in the smoking group compared to the non-smoking group. There were no statistically significant differences between the smoking and non-smoking groups in the detection of *Acinetobacter baumannii*, *Enterobacter cloacae*, *Pseudomonas putida*, *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, and *Burkholderia gladioli*.

### 4.2 Comparison of the detected fungi in both groups

Showed a higher detection rate of *Candida albicans* in both groups, with a higher detection rate in the smoking group. There were no significant differences in the detection of *Candida glabrata* and *Candida tropicalis* between the smoking and non-smoking groups.

### 4.3 Regarding the drug resistance of *Candida albicans*

Both groups showed a relatively high resistance to fluconazole, with the smoking group demonstrating a more significant resistance. However, they both exhibited high sensitivity to amphotericin B, itraconazole, and voriconazole, with no significant differences between the two groups.

### 4.4 The comparison of bacterial drug resistance rates

Between the smoking and non-smoking groups revealed statistically significant differences. The smoking group showed increased resistance of *Klebsiella pneumoniae* to cefotetan and ciprofloxacin, and increased resistance of *Escherichia coli* to cefotaxime and gentamicin, while still demonstrating high sensitivity to third-generation cephalosporins and carbapenems. The smoking group also exhibited increased resistance of *Staphylococcus aureus* to ampicillin-sulbactam, with higher sensitivity to quinolones. However, there were no significant differences in the resistance rates of *Pseudomonas aeruginosa* to commonly used antibiotics between the smoking and non-smoking groups.

## 5. Discussions

Smoking is an important risk factor for the occurrence of lung cancer. The age at which smoking starts, the daily amount of smoking, the depth of smoking, the duration of smoking, the total amount of smoking, and the time of smoking cessation are all related to the risk of developing lung cancer<sup>[8]</sup>. Studies have shown that the proportion of men among lung cancer smokers is higher, and the most common pathological type is squamous cell carcinoma, often accompanied by chronic airway inflammation. This may be related to the high expression levels of matrix metalloproteinase 9 mRNA and its protein in the respiratory epithelial cell matrix, as well as airway damage and remodeling, all of which are closely related to smoking<sup>[9]</sup>. Literature also reports a relatively strong relationship between smoking and the pathological types of lung cancer, squamous cell carcinoma, and small cell lung cancer. The respiratory tract of a normal person contains many colonizing bacteria, and due to natural and artificial factors, there is occurrence, development, and extinction of microorganisms in the human respiratory tract<sup>[10]</sup>. The dynamic balance between respiratory tract microorganisms and the body is disrupted by smoking, leading to a significant increase in pathogenic bacteria in the respiratory tract. Additionally, there are reports that compared to non-smokers, smokers have an increased variety and quantity of respiratory tract microorganisms, and the annual incidence of recurrent pneumonia can increase by 80%<sup>[11]</sup>. 2.4% to 5% of lung cancer patients experience varying degrees of pneumonia after surgery, mostly due to *Staphylococcus aureus*. 0.4% to 5% of lung cancer patients develop bronchopleural fistula or empyema after surgery, often as a mixed infection, mostly involving anaerobic bacteria, G-bacilli, and candida<sup>[12]</sup>. In recent years, although literature on the distribution of respiratory tract flora in lung cancer patients is not uncommon, the results are not completely consistent. According to statistics, as many as 50% to 70% of lung cancer patients often develop pneumonia for various reasons, especially elderly patients in the late stage, who are more susceptible. Moreover, among late-stage lung cancer patients, the incidence of fungal infections in the lungs of smokers also significantly increases.

Patients with lung cancer often experience complications such as infections, which not only reduce the effectiveness of cancer treatment but also shorten the patient's survival time to varying degrees<sup>[13]</sup>. The most common complication is respiratory tract infections, with 50% to 70% of lung cancer patients experiencing pneumonia. *Streptococcus pneumoniae* infections mainly occur

before or within 48 hours of hospital admission. As medical technology advances, the microbial flora in the lungs of lung cancer patients increases, leading to a higher probability of pneumonia occurrence, thus affecting the prognosis, especially for late-stage lung cancer patients with compromised immunity. Fungi are opportunistic pathogens that usually cause infections when the body's immune system is weakened. In advanced lung cancer patients, mixed infections are common, especially in those with central lung cancer, where bronchial obstruction leads to lung collapse, making it easier for pathogens to invade, persist, and proliferate, thus promoting pneumonia and exacerbating it repeatedly. Additionally, the increasing rate of lung cancer admissions and the correlation with rising incidence rates further contribute to the increased occurrence of lung fungal infections, especially when the body's immune system is compromised due to tumor growth, damage, airway obstruction, and prolonged use of cytotoxic drugs that further weaken immunity, as well as antibiotics that may disrupt the lung microbiome. During the diagnosis and treatment of lung cancer patients, vigilance for infectious diseases is crucial. Early clinical evidence should be sought to promptly diagnose and administer appropriate antibiotics for early treatment of concurrent infections. Cancer patients often develop candidiasis, especially with *Candida albicans*, which easily causes deep-seated fungal infections. Once a patient is diagnosed with deep respiratory fungal infections, cytotoxic drugs should be discontinued, and sputum samples should be repeatedly cultured early on to adjust the antimicrobial drugs based on culture and sensitivity test results. Targeted therapy plays a crucial role in lung cancer treatment as it reduces the suppression of the patient's overall immune system, thereby preventing life-threatening infectious complications.

Direct inhalation of harmful substances from cigarette smoke can lead to lung inflammation and tissue damage, impairing the normal defense and repair mechanisms of the lungs. Subsequent bacterial colonization can also cause persistent inflammatory reactions in the lungs. In COPD patients who smoke, the risk of developing emphysema is significantly increased, especially in male patients, and this risk increases with smoking index, indicating that smoking is not only a risk factor for COPD but also further leads to emphysema and gradual deterioration of lung function. Among lung cancer patients, a considerable proportion also have comorbid chronic obstructive pulmonary disease<sup>[14]</sup>. Research has also found that in patients who quit smoking two years ago, the positive rate of induced sputum bacterial culture decreased, and the decline in lung function slowed, reflecting that the damage to airway immunity caused by continuous smoking may be reversible to some extent. Smoking is detrimental to the treatment of small cell lung cancer during radiotherapy and chemotherapy, possibly because the body's cells are stimulated by the unique chemical components in tobacco, including nicotine, thereby reducing the body's immune defense. Surgery is an important treatment for lung cancer, but it can lead to many respiratory and circulatory complications, which can seriously threaten the patient's life. Pneumonia is a common complication after lung cancer surgery, with literature reporting a high incidence rate of 52.9%, of which respiratory complications account for 34.3%, and pneumonia is related to smoking and airway obstruction. Due to their weakened immune system, lung cancer patients, especially during the surgical process requiring the establishment of an artificial airway, and postoperatively requiring continued radiotherapy or chemotherapy, are prone to pneumonia. Most patients have poor drainage of airway secretions, leading to airway obstruction, thereby promoting the occurrence of pneumonia, further exacerbating the patient's condition and forming a vicious cycle, becoming an independent high-risk factor for death. Chemotherapy for lung cancer not only effectively kills cancer cells but also damages the immune system. After chemotherapy, when bone marrow hematopoietic function is severely suppressed and cell count is significantly reduced, the likelihood of patients developing infections is higher, especially for those who have undergone lung cancer surgery. Furthermore, long-term radiotherapy and chemotherapy further reduce the patient's resistance, making it easier

for opportunistic pathogens to cause hospital-acquired pneumonia, seriously affecting the patient's condition and prognosis. Existing research has also shown that pneumonia is a major factor affecting the quality of life and prognosis of advanced lung cancer patients.

This study shows that in patients with lung cancer combined with pneumonia, the main pathogens detected in sputum cultures are mainly G- bacteria, among which *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Enterobacter cloacae* are the most common, with *Staphylococcus aureus* being the most common among cocci. For the respiratory infection flora, the pathogenic bacteria in patients with lung cancer combined with pneumonia are mainly G- rods, most of which show some resistance to the tested antibiotics, some being multidrug-resistant or extensively drug-resistant. The leading pathogens are *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli* among Gram-negative rods, and *Staphylococcus aureus* among Gram-positive bacteria, consistent with the literature. The detection rate of pathogenic bacteria such as *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* in sputum cultures is significantly higher in smoking patients compared to non-smoking patients. The detection rate of *Staphylococcus epidermidis* in sputum cultures is lower in the smoking group than in the non-smoking group. Both groups of patients show high resistance of *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* to first- and second-generation cephalosporins. The smoking group shows a higher resistance rate of *Klebsiella pneumoniae* to cefoperazone compared to the non-smoking group, and *Escherichia coli* shows higher resistance to cefoperazone and colistin, while *Staphylococcus aureus* shows higher resistance to erythromycin and ampicillin-sulbactam. There is no significant difference in the resistance rate of *Pseudomonas aeruginosa* to commonly used antibiotics between the smoking and non-smoking groups. Bacteria detected in both groups show high sensitivity to third-generation cephalosporins and carbapenems. The detection rate of *Candida albicans* is higher in both groups of patients, with a higher detection rate in the smoking group. *Candida albicans* shows high resistance to fluconazole, with a more significant resistance in the smoking group, while it remains highly sensitive to amphotericin B, voriconazole, and itraconazole, with no significant difference between the two groups. When choosing antibiotics for patients with lung cancer complicated by pneumonia, it is important to primarily select anti-infective drugs targeting Gram-negative bacteria. Sputum routine pathogen culture, fungal smears, and fungal cultures should be performed before applying antibiotics. Sensitivity antibiotics should be selected based on the results of drug sensitivity tests.

## 6. Conclusion

Smoking is an important risk factor for the occurrence of lung cancer, and it can also lead to changes in the respiratory pathogeny of lung cancer patients, allowing certain pathogenic bacteria to colonize and promoting the occurrence of pneumonia. Among lung cancer patients, especially those in the terminal stage, the weakened immune system makes them more susceptible to developing pneumonia. Smoking is not only a risk factor for lung cancer but also for pneumonia. Therefore, long-term heavy smoking can lead to an increase in the respiratory pathogen resistance of lung cancer patients with pneumonia. When treating lung cancer patients with pneumonia, the patient's smoking status should be taken into account, and antibiotics should be selected reasonably based on the differences in sputum culture results, in order to improve the quality of life and prolong the survival period of lung cancer patients with pneumonia.

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