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BRIEF REVIEW

# Association of Lung Cancer with Pneumonia and *Chlamydia pneumoniae* infection

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## Abstract

**Introduction:** The degree of association and type of causal versus non-causal relationship between pneumonia and lung cancer (LC) are evolving discussions. We reviewed English-language publications on the degree of association between pneumonia and subsequent LC.

**Methods:** We searched the PubMed database using keywords for pneumonia, LC, and Chlamydia infection. We selected peer-reviewed studies of patients with pneumonia and LC. Case reports and other literature reviews were excluded from this review.

**Results:** Five studies examined the incidence and/or risk of LC for a total of 415,750 patients, and four studies examined cases with *Chlamydia pneumoniae* chronic infection at the time of diagnosis of LC for a total of 1,467 patients. The overall risk and/or incidence of LC after pneumonia was from 2.3% to 10% for a median follow-up ranging from 109 days to 4.2 years. Three studies reported current tobacco smoking status, which ranged from 27.7% to 45% among those with LC. A history of prior malignancy was reported in 22.5% of patients with LC. Chlamydia immunoglobulin (Ig) A and LC were statistically non-significantly associated regardless of the age of the patients. In one study, Chlamydia heat shock protein (HSP)-60 IgG $\geq$1:50 was associated with significantly increased odds of LC in two respective models (odds ratios of 1.34 [95% confidence interval (CI) 1.06–1.69] and 1.30 [95% CI 1.02–1.67]). A fourth study reported *C. pneumoniae* IgA $\geq$ 64 titers to be 58%, 29%, and 5.5% among patients with LC, those without LC, and healthy blood donors, respectively.

**Conclusions:** The incidence of LC was reported to range from 2.3% to 10.3% following an episode of pneumonia. There is limited evidence of the association of chronic Chlamydia infection with LC, and Chlamydia could be a causal cofactor of LC.

## Introduction

According to the World Health Organization, lung cancer is the second most common cancer worldwide, with approximately 2.2 million new cases diagnosed in 2020, accounting for almost 25% of all cancers and 36% of all cancer deaths.[1, 2] In the US, there were 218,893 new cases of lung cancer and about 142,080 deaths from lung cancer.[3] Each year, more people die of lung cancer than colon, breast, and prostate cancers combined. Lung cancer mainly occurs in people older than 45 with an average age of 70 years.[4] Regardless of tobacco smoking status, the overall chance that a man will develop lung cancer in his lifetime is about 1 in 15 (and for a woman is 1 in 17), and for those who do smoke, the risk is much higher.[4]

The degree of association and type of causal *versus* non-causal relationship between pneumonia and lung cancer are evolving discussions. Pneumonia has been characterized as a surrogate of underlying lung cancers, while other reports have indicated some type of bidirectional causal relationship. According to the 2019 Infectious Diseases Society of America and American Thoracic Society guidelines for community-acquired pneumonia (CAP), the frequency of lung cancer in patients recovering from CAP ranges between 1.3% and 4%.[5] On the other hand, it was reported that abnormal chest images are found in up to 5% of cases of the unsuspected non-malignant condition. A chest X-ray after pneumonia has traditionally been performed to search for underlying lung cancer. Still, current recommendations advise against follow-up chest imaging in adult patients whose symptoms resolve within 5–7 days.[5]

Brenner *et al.* reviewed the association between lung diseases and the risk of lung cancer.[6] This review included 22 studies, but many were not about pneumonia or were concerned with self-reported pneumonia.[6] Ang *et al.* found a significant positive association between history of pneumonia and lung cancer risk with a pooled summary estimate of 1.49 (95% [CI] 1.23–1.66).[7] We reviewed current literature in the English language to examine the degree of association between pneumonia and subsequent lung cancer, focusing on the incidence and risk of lung cancer after a diagnosis of pneumonia.

## Methods

*Database search strategy*

We conducted a search of the PubMed database using terms such as "pneumonia AND lung cancer," "community-acquired pneumonia AND lung cancer," and "Chlamydia AND lung cancer." Due to the unique relationship between Chlamydia infection and cancer, it was analyzed separately from overall pneumonia.

*Inclusion criteria*

Peer-reviewed prospective or retrospective studies of patients with pneumonia and lung cancer were included.

*Exclusion criteria*

Case reports and other literature reviews were excluded from this review.

## Results

A total of 13 studies were selected for this review. Four studies were excluded due to patients' self-reported respiratory infection, antibiotic treatment as a predictor of lung cancer, or pneumonia in childhood. Finally, we selected (i) five studies that examined the incidence and/or risk of lung cancer (**Table 1**) for a total of 415,750 patients [8-12] and (ii) four studies of cases with and without *Chlamydia pneumoniae* chronic infection at the time of the diagnosis of lung cancer, with a total of 1,467 patients (**Figures 1** and **2**).[8, 10-17]

*Incidence and risk for lung cancer*

The overall risk or incidence of lung cancer after pneumonia ranged from 2.3% to 10% for a median follow-up ranging from 109 days to 4.2 years. Except for the study of Mortensen *et al.*, which included 98% males, males accounted for 53% to 77% of study participants. Three studies reported current tobacco smoking status, ranging from 28% to 45% among those with lung cancer, 10% to 23% greater frequency than those without cancer. In addition, a history of prior malignancy was reported in 23% of patients with lung cancer compared to 15% of those without lung cancer. Similarly, a history of tuberculosis was present in 12% of those with lung cancer and 9% of those without.

*Chlamydia pneumoniae chronic infection and lung cancer*

Among four studies of *C. pneumoniae*, three examined *Chlamydia* immunoglobulin (Ig) G and A titers, and one of these studies also examined Chlamydia heat shock protein-60 (CHSP-60) (**Figures 1** and **2a–b**). Laurila *et al.* and Chaturvedi *et al.* reported statistically insignificant associations of *Chlamydia* IgA with lung cancer for patients younger than 60 years, older than 70 years, and regardless of age (**Figures 1** and **2a**).[14, 15] Chaturvedi *et al.* reported that CHSP-60 IgG titers $\geq$1:50 were associated with significantly increased odds of lung cancer diagnosis in two respective models (odds ratios [OR] of 1.34 [95% CI 1.06–1.69] and 1.30 [95% CI 1.02–1.67]). The fourth study of Chlamydia examined a prospective cohort of patients with and without lung cancer compared with healthy blood donors.[16] All study participants were tobacco smokers or former smokers. The frequency of *C. pneumoniae* IgA $\geq$64 titers was 58%, 29%, and 5.5% among patients with lung cancer, those without lung cancer, and healthy blood donors. Among healthy blood donors, 20% of males and 9% of females had *C. pneumoniae* IgA titers $\geq$64.

## Discussion

This review includes eight retrospective studies and one prospective study from Scandinavia, Canada, and the US. These studies examined (i) the incidence and/or risk of lung cancer in adults after pneumonia and (ii) cases with positive tests for *C. pneumoniae*, including totals of 415,750 and 1,467 participants, respectively.

There are many potential confounders to take into consideration regarding the association between lung cancer and pneumonia. Male sex, aging, tobacco smoking, previous cancer, and history of tuberculosis are significantly more common among those with lung cancer after a diagnosis of pneumonia (**Table 1**). However, odds ratios remain statistically significant after adjustment for these confounders, indicating an independent association of pneumonia and lung cancer (**Figures 1** and **2**).

From a causality perspective, pneumonia could result from post-obstructive lung cancer or anatomic mucosal barrier compromises. Secondly, microbiome changes due to pneumonia could result in lung cancer or *vice versa*. Concerning the first possibility, a traditionally recommended practice was to repeat a chest X-ray (CXR) several weeks after the episode of pneumonia.

**Table 1.** Incidence of subsequent lung cancer in cohorts of patients with pneumonia.

| | Tang 2011, n (%) | | Søyseth 2007, n (%) | | Søgaard 2015, n (%) | | Mortensen 2010, n (%) | | Lin 2013, n (%) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Pneumonia | Cancer | Pneumonia | Cancer | Pneumonia | Cancer | Pneumonia | Cancer | Pneumonia | Cancer |
| *n* | 3,319 | 79 (2.3) | 7,044 | 177 (2.5) | 342,609 | 5,887 (2.52[a]) | 40,744 | 3,760 (9.2) | 22,034 | 2,274 (10.3) |
| Time to diagnosis[b] | | 109 days | | | | 4.2 years | | 297 days | | ≤1y: 67.7%<br>>1y: 32.3% |
| **Baseline characteristics** | | | | | | | | | | |
| Male | 1,762 (53.1) | 52 (65.8) | 3,905 (55.4) | 122 (68.9) | 177,918 (51.9) | 15,754 (55.3) | 39,983 (98.1) | 3,711 (98.7) | 14,623 (66.4) | 1,757 (77.3) |
| Age, mean±SD | | | | | | | 77.1±6.8 | 76.5±6.3 | | |
| Age ≥50 | 2,010 (60.6) | 76 (96.2) | | | | | | | | |
| Age ≥75 | | | 2,678 (38.0) | 49 (27.7) | 104,146 (30.4) | 10,641 (37.3) | | | 8,367 (38.0) | 822 (36.1) |
| Current smoker | 575 (17.3) | 22 (27.8) | 2,324 (33.0) | 105 (59.3) | | | 14,370 (35.3) | 1,700 (45.2) | | |
| Former smoker | | | 896 (12.7) | 26 (14.7) | | | | | | |
| Non-smoker | | | 932 (13.2) | 22 (12.4) | | | | | | |
| **Comorbidities** | | | | | | | | | | |
| Heart failure | | | | | | | 10,620 (26.1) | 842 (22.4) | | |
| COPD | 607 (18.3) | 24 (30.4) | | | 49,622 (14.5) | 5,812 (20.4) | 20,814 (51.1) | 2,129 (56.6) | 4,251 (19.3) | 445 (19.6) |
| Diabetes mellitus | 352 (10.6) | 14 (17.7) | | | | | 17,535 (43.0) | 1,430 (38.0) | 5,606 (25.4) | 463 (20.4) |
| Myocardial infarction | | | | | | | 2,891 (7.1) | 244 (6.5) | | |
| Peptic ulcer disease | | | | | | | 1,362 (3.3) | 135 (3.6) | | |
| Peripheral vascular disease | | | | | | | 6,079 (14.9) | 527 (14.0) | | |
| Prior metastatic solid tumor | | | | | | | 133 (0.3) | 33 (0.9) | | |
| Prior malignancy[c] | | | | | | | 6,116 (15.0) | 846 (22.5) | | |
| Renal disease | | | | | | | 5,148 (12.6) | 382 (10.2) | | |
| Rheumatologic disease | | | | | | | 1,103 (2.7) | 124 (3.3) | | |
| Stroke | | | | | | | 7,572 (18.6) | 561 (14.9) | | |
| Tuberculosis | | | | | | | | | 1,899 (8.6) | 274 (12.0) |

All studies were retrospective in design. **Abbreviations:** COPD, chronic obstructive pulmonary disease; SD, standard deviation.

[a] Standardized cancer incidence ratio for lung cancer. Other values in the column reflect any cancer;
[b] Median except where otherwise specified;
[c] Non-pulmonary.

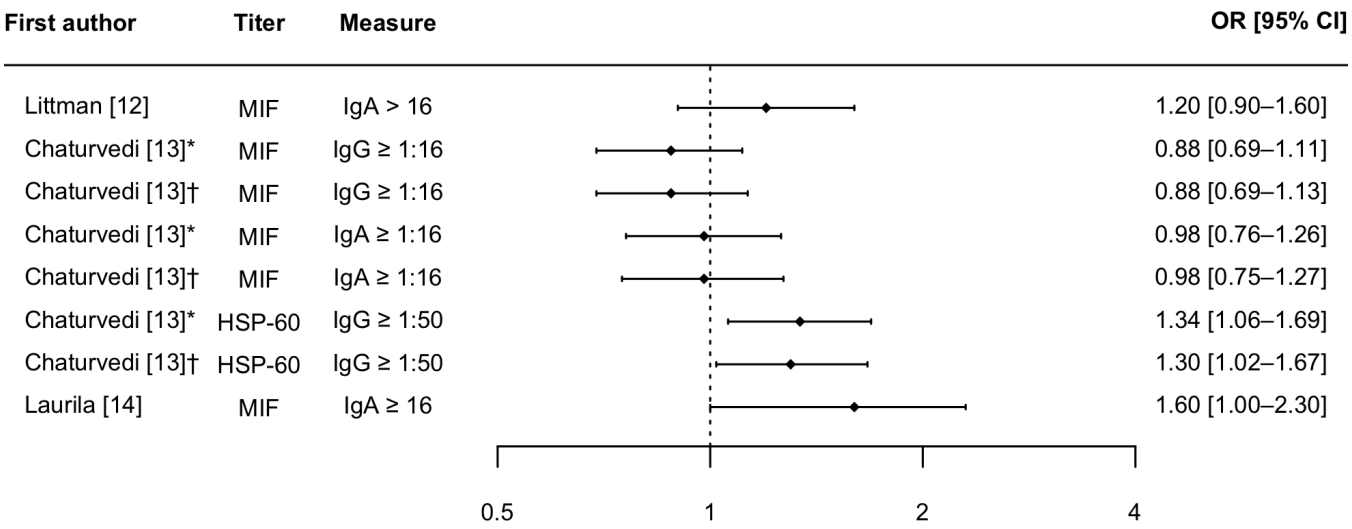



**Figure 1.** Association between serological evidence of *C. pneumoniae* and risk of lung cancer in three studies. Odds ratios and 95% confidence intervals displayed on a logarithmic scale.

Chaturvedi*: Case-control pairs matched by age, sex, year of randomization, follow-up time in study, smoking status, pack-years of smoking, and time since quitting smoking; adjusted for matching variables.

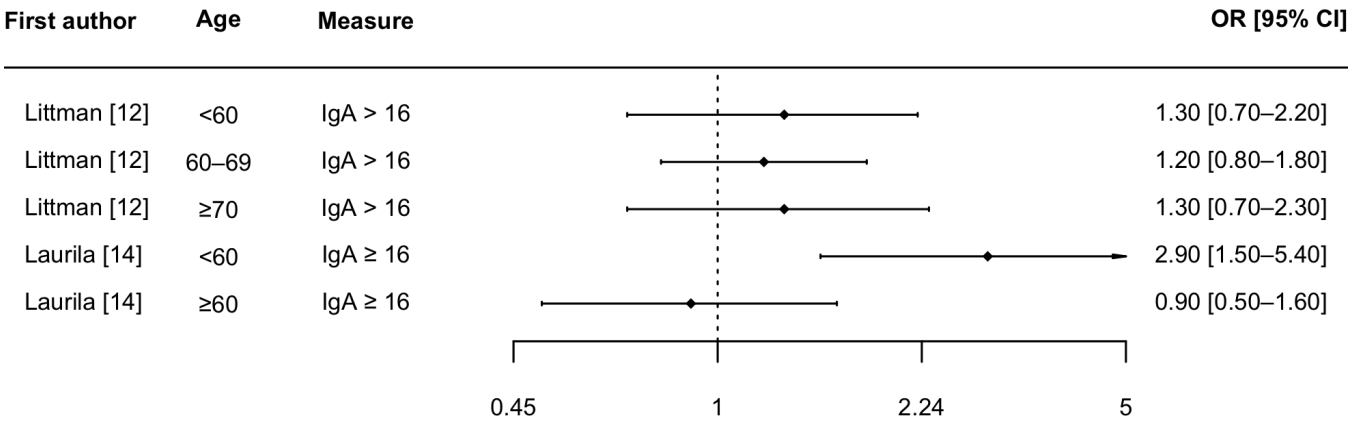
Chaturvedi†: Case-control pairs matched by age, sex, year of randomization, follow-up time in study, smoking status, pack-years of smoking, time since quitting smoking; adjusted for matching factors and for race, level of education, BMI at enrolment, regular use of aspirin/ibuprofen, family history of lung cancer, history of heart disease, and history of emphysema/bronchitis.

Laurila: Case control pairs matched by age, supplementation group, study center, and timing of serum sampling; adjusted for self-reported years of smoking and daily cigarette consumption.

Littman: Case-control pairs matched on year of randomization, age at randomization, sex, exposure cohort (sex, smoking, exposure to asbestos), pilot or efficacy study, smoking status at baseline; adjusted for years smoked, cigarettes smoked per day, education, and BMI.

**Abbreviations:** OR, odds ratio; CI, confidence interval; MIF, micro-immunofluorescence; Ig, immunoglobulin; HSP-60, heat shock protein 60.

**a)** Stratified by age.




**b)** Stratified by histological type.

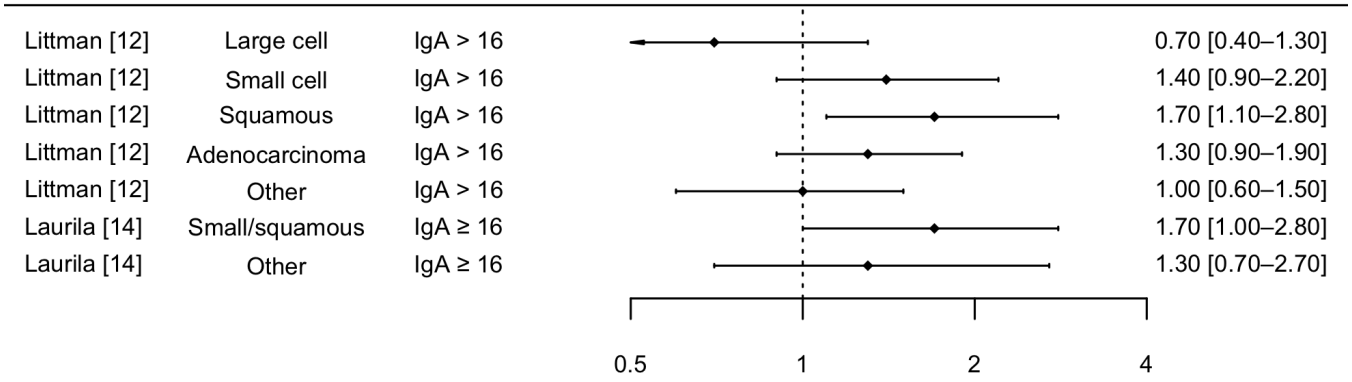



**Figure 2.** Association between serological evidence of *C. pneumoniae* and risk of lung cancer in two studies, stratified by (**a**) age and (**b**) histological type. Odds ratios and 95% confidence intervals displayed on a logarithmic scale.

Laurila: Case control pairs matched by age, supplementation group, study center, and timing of serum sampling; adjusted for self-reported years of smoking and daily cigarette consumption.

Littman: Case-control pairs matched on year of randomization, age at randomization, sex, exposure cohort (sex, smoking, exposure to asbestos), pilot or efficacy study, smoking status at baseline; adjusted for years smoked, cigarettes smoked per day, education, and BMI.

**Abbreviations:** OR, odds ratio; CI, confidence interval; Ig, immunoglobulin.

Current guidelines do not support this practice.[5] Tang *et al.* reported that the incidence of lung cancer after pneumonia is about 1% within 90 days and 2% over five years, suggesting that a CXR is not warranted after pneumonia.[8] The second possibility is that the interaction of the microbiome with lung cancer is bidirectional. Changes in the lung microbiome could lead to local lung changes, generating carcinogenic factors contributing to cancer development and *vice versa*. Granulicatella is one of the predominant bacteria in the sputum and bronchoalveolar lavage of patients with lung cancer.[18, 19] It has been proposed that the anaerobic environment secondary to lung cancer and the increasing volume of pyridoxal and polyamin compounds contribute to the selective growth of Granulicatella.[20] Furthermore, changes in airway microbiota have been associated with upregulation of the P13K pathway in patients with lung cancer.[21, 22] Similarly, chronic exposure to cytolethal distending toxins (CDT) produced by many bacteria, including *Salmonella typhi* [23], has been linked to impairment of the DNA damage response pathway and upregulation of mitogen-activated protein kinase pathway, favoring tumor survival and growth.[24] CDT-producing bacteria were more likely to be found near tumors rather than healthy colonic cells in human colorectal cancer patients.[25]

*C. pneumoniae IgA $\geq$ 1:16 and lung cancer*

There was a lack of association between *C. pneumoniae* IgA titers $\geq$1:16 and lung cancer for persons aged $<$60, $>$70, and regardless of age.[13] When stratified by type of lung cancer, *C. pneumoniae* IgA titers $\geq$ 1:16 were significantly associated with squamous lung cancer only.[13] This particular association of *C. pneumoniae* to squamous lung cancer could be because it was the most common type of cancer in this study.

*CHSP-60 IgG and lung cancer*

CHSP-60 is expressed by *C. pneumoniae* during its life cycle, including the chronic infection, triggering chronic inflammation.[26] Antibodies to CHSP-60 reflecting chronic infection and inflammation have been reported to be associated with tissue damage [26], and they could be a reliable marker of the mechanism of Chlamydia in the development of lung cancer. Chaturvedi *et al.* reported a statistically significant association between CHSP-60 IgG titers $\geq$1:50 and lung cancer.[14] Interestingly, this association was present from 2 to 5 years before lung cancer diagnosis, suggesting the potential causality of chronic Chlamydia infection. *Helicobacter pylori*, human papillomavirus, and Epstein–Barr virus, among other pathogens, are recognized etiologies of cancers in the setting of chronic infection. Although we observed some degree of association between chronic Chlamydia infection and lung cancer, current findings are not clear enough to draw strong conclusions, and likely, Chlamydia is merely a causal cofactor of lung cancer. This interpretation is bolstered by the fact that not all lung cancers are associated with Chlamydia infection, and not all Chlamydia infections result in cancer.

Our review has strengths and weaknesses. To our knowledge, our review is the first to evaluate studies in the English-language literature on the relation of pneumonia, chronic *Chlamydia* infection, and lung cancer. Furthermore, this review involved a critical analysis of the role of the microbiome in lung carcinogenesis. Concerning weaknesses, our review included a small number of studies, most of which were retrospective in design, in large part due to the limited number of studies in the field.

In conclusion, the incidence of lung cancer was reported to range from 2.3% to 10.3% following an episode of pneumonia. There is limited evidence of the association of chronic Chlamydia infection with lung cancer, and Chlamydia could be a causal cofactor of lung cancer. Metagenomic studies are needed to examine the changes in the lung microbiome triggering upregulation of the P13K signaling pathway.

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