Original Article

Association between *Chlamydia pneumoniae* infection and lung cancer: a meta-analysis

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Background: The aim of this study is to explore the correlation between *Chlamydia pneumoniae* (*C. pneumoniae*) infection and lung carcinoma.

Methods: Databases of PubMed, Embase, Embase, Ovid, Wanfang and China National Knowledge Infrastructure (CNKI) database were investigated for eligible literatures from their establishments to February, 2019. Included studies were selected according to specific eligibility criteria. Statistical analysis was performed by RevMan 5.3 software.

Results: Thirteen studies with 2,553 lung carcinoma cases and 2,460 controls were eligible for meta-analysis. The pooled results indicated that the *C. pneumoniae* infection IgA significantly increased the risk of lung carcinoma (OR =3.19; 95% CI, 1.96–5.19; P<0.00001) by random effect model. And for serum IgG, the pooled OR was 2.02 (95% CI, 1.29–3.16; P<0.00001) by using the random effects model. The results indicated that the IgA positive rate was significantly higher in lung cancer patients than healthy controls.

Conclusions: This meta-analysis revealed that *C. pneumoniae* infection may be a potential risk factor for lung carcinoma. However, due to its significant heterogeneity in the included studies, the consequence should be understood with caution.

Keywords: *Chlamydia pneumoniae* infection; lung cancer; meta-analysis; risk factors

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Introduction

Lung cancer is the most common diagnosed cancer, accounting for 11.6% (2,093,876 new cases) of new carcinomatosis cases and 18.4% (1,761,007 deaths) of all cancer deaths in 2018 (1). The 1- and 5-year survival rates were 42% and 15%, respectively, and it is poor while compared with those in high incidence of other cancer (2). The mechanism of lung cancer has not been fully understood. Smoking status was identified as the most crucial independent risk element for lung cancer (3,4). Some literatures also proved that both genetic and environment factors were related to the risk of lung carcinoma, such as exposure to radon and asbestos, air pollution, second-hand smoking and chronic bacterial infection and parasitic infections [*Chlamydia pneumoniae* (*C. pneumoniae*)] (5,6).

C. pneumoniae, a gram-negative bacterium, has been present as an individual species since 1989, is a common respiratory pathogen that causes the chronic and persistent respiratory infections (7,8). *C. pneumoniae* infection not only lead to worldwide widespread respiratory infections such as pneumonia, pharyngitis, bronchitis, and sinusitis, but

also associated with asthma, chronic obstructive pulmonary disease, and atherosclerosis (9). Kuo *et al.* have reported that *C. pneumoniae* infection causes an average of 7–10% of community-acquired pneumonia (CAP) and 5% of bronchitis and sinusitis cases among adults (10). Laurila *et al.* (11) firstly discovered that *C. pneumoniae* infection might be an independent hazards for lung carcinoma in 1997 according to the relevant observation case-control research. Since then, the potential risk of *C. pneumoniae* and lung cancer has been vividly studied (12,13), but the results have been inconsistent. In order to comprehensively evaluate the association between *C. pneumonia* is infection and lung carcinoma, and to provide scientific basis for the etiology study, clinical treatment of lung cancer, we performed the meta-analysis from all eligible researches to explore the relationship between *C. pneumoniae* infection and lung carcinoma risk.

Methods

Search strategy

A systematic search was performed conducted on PubMed, Embase, Ovid, Wanfang and China National Knowledge Infrastructure (CNKI) databases. The search terms were as follows: "*Chlamydia pneumoniae*", "lung cancer" and their synonyms or similar words (from their inception to February, 2019). Searches were limited to English and Chinese literature and were first screened by two independent reviewers. Furthermore, reference lists of all included articles and related comments were searched manually to find other potentially eligible articles.

Inclusion and exclusion criteria

For inclusion, articles were selected on the basis of the following criteria: (I) evaluating the relationship between *C. pneumoniae* infection and lung carcinoma risk; (II) study design was limited to prospective cohort studies or retrospective case-control studies; (III) clinical pathology confirmed lung cancer patients; (IV) the control group was relative healthy people with no diagnosis of any cancer; (V) the *C. pneumoniae* infection rate can be extracted from the included individual studies.

Assessment of methodological quality of included articles

All articles that met the inclusion criteria were evaluated to assess the risk of bias in each outcome. The evaluation was conducted independently by two comments using the Cochrane Collaboration's risk of bias tool as depictive in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions, version 5.1.0. 2011, http://handbook.cochrane.org/). If there were any disagreements in the evaluation study, we have discussed it. The results of the assessment measured the following areas: random sequence generation, allocation concealment, blinding, incomplete outcome data addressed, free of selective outcome reporting, and other possible sources of bias. The consequences of the meta-analysis were comprehended as the results of the study on the risk of bias.

Data extraction

Data collection and analysis were carried out in accordance with the standard Cochrane protocol (14). Two authors independently reviewed and extracted the following data from every study: study design, study year, participants number, the positivity or negativity for *C. pneumoniae* (IgA, IgG) antibody.

We attempted to find and exclude duplicate data from different studies. For multiple studies of repeated or overlapping data (by population, time, location, and results), we followed the PRISMA reporting guidelines when submitting manuscripts.

Statistical analysis

Meta-analysis was performed with the Cochrane Collaboration's Review Manager Software (RevMan, version 5.1). Odds ratio (OR) with 95% CI (confidence interval) was performed to evaluate the potential relationship between chronic *C. pneumoniae* infection and lung carcinoma risk. Heterogeneity was evaluated by I square test. Random effects model was used if heterogeneity was significant (I^2>50%). When heterogeneity was not detected or the heterogeneity was relatively small, fixed effects model was performed.

Results

Literature selection and bias

Totally of 65 potentially related researches and abstracts were identified (*Figure 1*). After removal of repeats (n=21) and filtration of abstracts (n=23), 21 full-text researches were evaluated for eligibility. Eight studies were excluded for the following: abstract (n=2), letter (n=2), duplicated

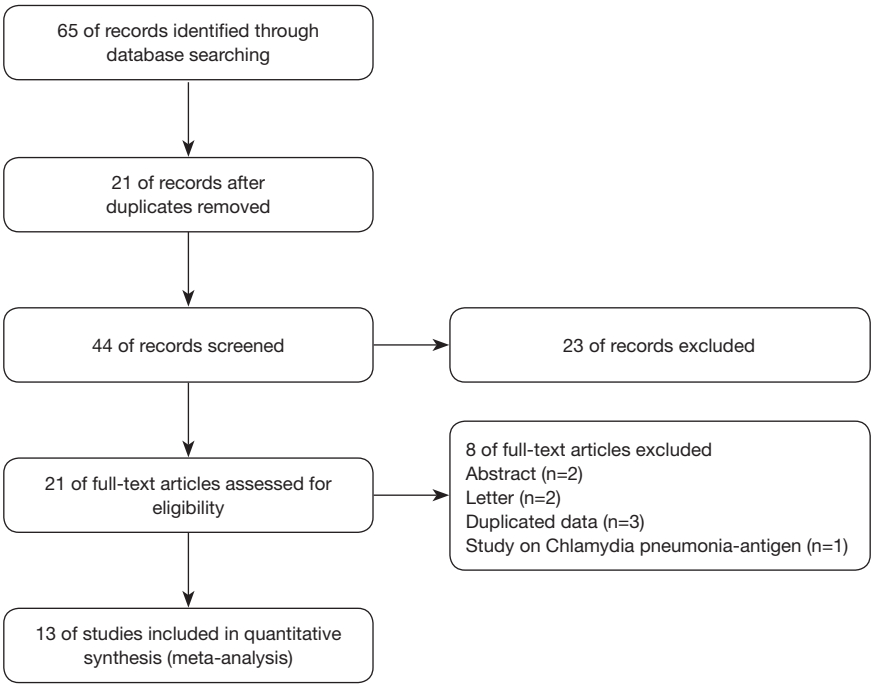

Figure 1 Flow chart showing results of the literature search and study inclusion.

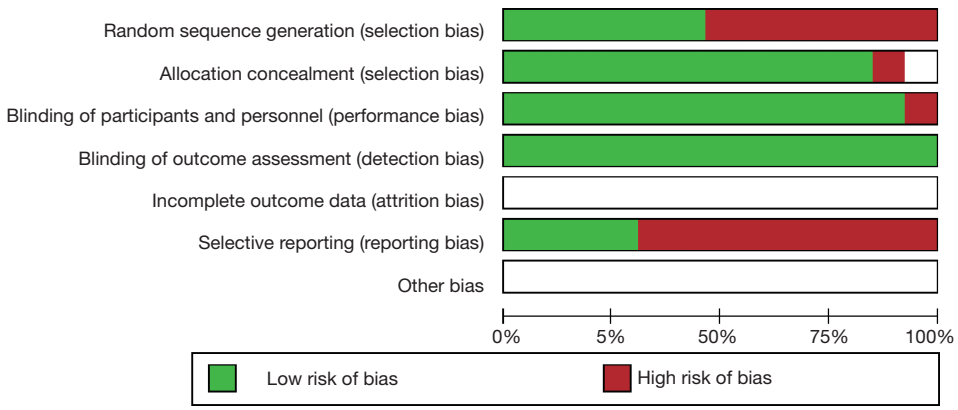

Figure 2 Risk of bias assessment in randomized trials and single-arm studies. Green indicates low risk of bias, yellow indicates medium risk of bias, and red indicates high risk of bias.

data (n=3), study on *Chlamydia pneumonia*-antigen (n=1). Thirteen publications (11,15-26) were ultimately eligible for final meta-analysis. No more citations were found from the reference review.

The detail of the risk-of-bias evaluation of included researches was summarized in *Figure 2*. All studies were evaluated as low risk according to the appropriate randomization sequence. However, many relative information in the studies wasn't available, such as allocation concealment and blinding of participants and personnel, blinding of outcome assessment. Nevertheless, the overall methodological quality was generally fair.

Intervention characteristics

The included articles were printed between 1997 and 2013, involving 2,553 lung cancer cases and 2,460 controls. Controls were predominantly healthy people and matched

Table 1 Main characteristics of the studies included in the meta-analysis

Included studies	Studies design	Sample size	Age, years	Sex (male/female)	Case (positive/all)		Control (positive/all)	
					IgA	IgG	IgA	IgG
Yuqing 2001	Case-control	80:80	58±17:57±19	64/16:64/16	69/80		57/80	
Yanbin 2004	Case-control	50:108	NA:40.8±8.5	NA:63/45	28/50		22/108	
Meichun 2004	Case-control	128:70	67.8:52.3	99/29:46/24		3/128		1/70
Yanbin 2005	Case-control	87:108	50.9±11:48.1±10.1	51/36:63/45	56/87	62/87	22/108	51/108
Xiumei 2010	Case-control	36:67	NA	NA:40/27	26/36		6/67	
Fei 2014	Case-control	185:190	58.57±9.49:57.96±9.28	133/52:135/55	49/185	110/185	13/190	65/190
Laurila 1997	Nest case-control	230:230	60.3:60.3	NA	129/230	225/230	106/230	219/230
Jackson 2000	Case-control	143:147	59.8:59.4	NA	67/143	114/143	56/147	118/147
Koyi 2001	Case-control	198:68		128/70: NA	116/198	88/198	11/68	13/68
Kocazeybek 2003	Case-control	123:123	55:55:00	101/22:101/22	62/123	98/123	25/123	62/123
Littman 2004	Nest case-control	508:508	59:59:00	254/254:254/254	281/508	324/508	261/508	326/508
Chaturvedi 2010	Nest case-control	593:671	NA	407/186:437/234	174/593	293/593	201/671	356/671
Liu 2010	Case-control	192:90	54.6±10.4:53.6±9.4	0/192:0/90		119/192		26/90

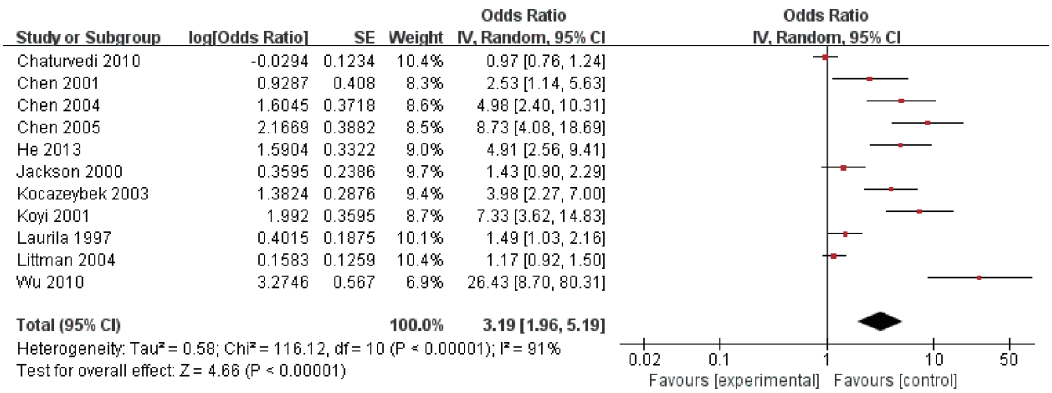

Figure 3 Forest plot for association between *C pneumonia* IgA infection and lung cancer risk.

for age, sex and/or smoking status. Of the 13 included articles (11,15-26), 6 were published in Chinese and 7 papers were published in English. For the study design, three articles were nest case-control and other 10 were case-control studies. Sample sizes ranged from 103 to 1,264. The characteristics of the studies is presented in *Table 1*.

Relationship between C. pneumoniae IgA antibody and lung carcinoma

Eleven studies reported the relationship between *C. pneumoniae* infection and lung carcinoma risk by using the serum IgA. Among them, significant heterogeneity was scanned (I^2=91%; heterogeneity P<0.00001; *Figure 3*). Random effect model was performed and the result showed that the *C. pneumoniae* infection significantly improved the risk of lung carcinoma (OR =3.19; 95% CI, 1.96–5.19; P<0.00001).

Relationship between C. pneumoniae IgG antibody and lung carcinoma

Ten studies reported the relationship between *C. pneumoniae* infection and lung carcinoma risk by using the serum

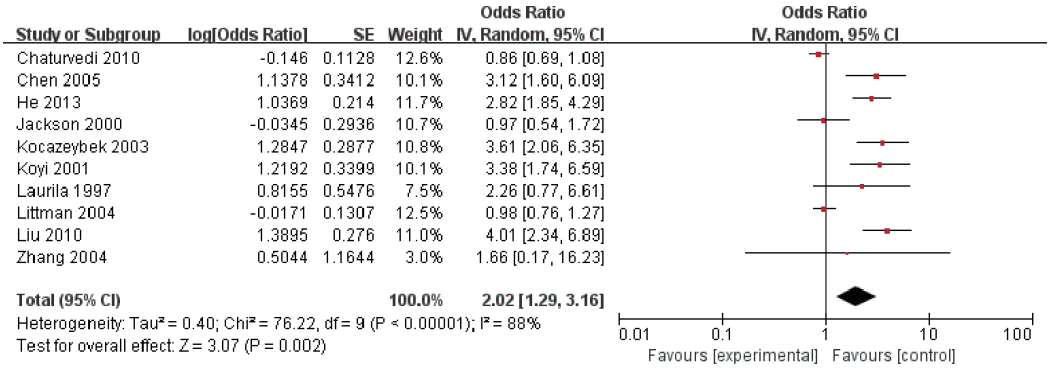

Figure 4 Forest plot for association between *C pneumonia* IgG infection and lung cancer risk.

IgG. Among them, significant heterogeneity was scanned (I^2=88%; heterogeneity P<0.00001; *Figure 4*). Random effect model was performed and the result showed that the *C. pneumoniae* infection significantly improved the risk of lung carcinoma (OR =2.02; 95% CI, 1.29–3.16; P=0.002).

Discussion

Lung carcinoma is reported to be the most common cancer among women and men, representing huge social and economic burdens in both developing and developed countries (27). However, the risk factors for its occurrence has not been fully understood. In recent years, studies have reported that the pulmonary inflammatory disease is significantly related to the risk of lung carcinoma. *C. pneumonia*, which is closely related to chronic lung inflammation and may act an significant part in progression of lung carcinoma (28). Therefore, we performed the meta-analysis of all published articles to determine the relationship between *C. pneumoniae* infection and lung carcinoma risk. Our meta-analysis included 13 studies, including 2,553 lung carcinoma cases and 2,460 controls. Results showed that *C. pneumoniae* infection was significantly related to the risk of lung carcinoma, with a 3.19-fold increased risk compared to a negative titre (95% CI, 1.96–5.19) for IgA and 2.02 times (95% CI, 1.29–3.16) for IgG.

The association between *C. pneumoniae* infection and lung carcinoma is reasonable in biology, but the mechanism is still not clear. There are three possible reasons for this mechanism.

Firstly, chronic inflammation played an important part in development of malignant transformation (11). Medicaments that induce inflammation, such as infectious substances, can induce stretched-out stimulation, leading to cell death and increased mitotic activity. Subsequent cell division that happens during the repair of the damaged tissue possibly enhance the risk of cancer in the affected area (29). For instance, several researches have linked chronic infection with Helicobacter pylori to an enhanced the risk of gastric adenocarcinoma (30,31). Chumduri *et al.* reported that *Chlamydia trachomatis* infection perturb host chromatin, DNA double-strand breaks (DSBs) repair, and cell-cycle regulation, thus promoting DNA double strand breaks in host cells, inducing genomic instability and leading to cancer (32). *C. pneumoniae* may act a similar part in the occurrence and progress of lung carcinoma. *C. pneumoniae* promotes the delivery of inflammatory mediators, such as tumor necrosis factor (TNF), interleukin-10, and interleukin-8 (33). Chronic infection mediators, especially interleukin-8, may lead to genetic damage. Interleukin-8 also promotes the growth of human non-small cell lung carcinoma (NSCLC) by its angiogenic characteristics. In addition, *C. pneumoniae* may damage or even block apoptosis in infected cells via inducting interleukin-10 (34), leading to chronic infection and increasing the risk of vicious transformation of infected cells.

On the other hand, molecular simulation theory. Persistent *C. pneumoniae* infection could cause the release of endotoxin-like substance chlamydial heat shock protein-60 (CHSP-60). CHSP-60 is expressed throughout the life cycle of *C. pneumoniae* infection and may act a major part in the pathogenesis of lung carcinoma (35). In addition, Mayer *et al.* also demonstrated that *C. pneumoniae* infection may cause the release of nitric oxide (36), the mutagenicity of nitric oxide and other metabolites has been confirmed elsewhere (37).

Last but not least, some studies have reported that *C. pneumoniae* infection promotes the liberation of

inflammatory mediators, such as nuclear factor-kappa B (NF-κB), TNF-α, and interleukin-8 (33), triggering the abnormal inflammatory response. Overexpression of inflammatory mediators and inadequate production of anti-inflammatory mediators can cause inflammatory reactions in the body, which in turn lead to overexpression of toll-like receptor (TLR) on the cell surface. However, the TLR signaling pathway may act a part in the carcinogenesis and progression of tumors. Bauer *et al.* revealed that TLR4-mediated gene expression pathways, which can be used as prognostic marks for predicting lung cancer susceptibility in mice (38).

The present study has several limitations that ought to be considered. Firstly, heterogeneity is an underlying conundrum when explanation all the studies of meta-analyses. Although we carefully searched the published articles, using explicit research inclusion criteria, strictly performed data collection and analysis, the significant heterogeneity between researches still existed. The existence of heterogeneity could arise from differences in the choice of controls, age distribution, prevalence rates and so on. Secondly, the inconsistency of the study population may lead to uncertainty in the research results.

In summary, the results of this meta-analysis demonstrate that the *C. pneumoniae* infection may increase the risk of lung carcinoma. Future prospective studies with extensive people are required to validate the connection of *C. pneumoniae* infection and lung carcinoma.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.10.35). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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