Review

**Chlamydia pneumoniae** and Lung Cancer: Epidemiologic Evidence

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Abstract

**Chlamydia pneumoniae** is a common cause of acute respiratory infection and has been hypothesized to cause several chronic diseases, including lung cancer. The purpose of this article is to identify, describe, and critically examine the published studies on the association between **C. pneumoniae** infection and risk of lung cancer. In the six studies identified, previous **C. pneumoniae** infection was defined on the basis of serologic criteria, which varied between studies. All studies reported elevated relative risk estimates for the association of serologic evidence of infection and risk of lung cancer. The three studies in which past infection was defined based on testing of prediagnostic blood specimens tended to have weaker results (odds ratio range, 1.2-2.1) than those based on postdiagnostic blood specimens (odds ratio range, 1.4-9.9).

**Chlamydia pneumoniae**

**Chlamydia (Chlamydophila) pneumoniae** are obligate intracellular bacteria that have a unique biphasic developmental cycle. The small, dense elementary body is the metabolically inactive infectious form of the organism. Elementary bodies have a rigid cell wall resulting from the disulfide cross-linking of envelope proteins, allowing survival outside the host cell. After infection of a susceptible host eukaryotic cell by receptor-mediated endocytosis, the elementary bodies differentiate into reticulate bodies, which constitute the larger, metabolically active form of the organism.

**Review of C. pneumoniae Serology and Detection Methods**

Much of our knowledge of the epidemiology of **C. pneumoniae** infections has come from serologic studies. From these studies, we know that the prevalence of immunoglobulin (Ig) G antibodies directed against **C. pneumoniae** increases with age, from 10% at 5 to 10 years of age to 30% to 45% by adolescence, and often exceeding 80% in the elderly (1). In response to acute primary infection, IgM antibodies typically appear first, about 3 weeks after the onset of illness, followed by IgG antibodies, about 3 to 5 weeks later. In reinfection, IgM antibodies may not appear, or may appear only at low titers, whereas IgG antibodies appear relatively quickly, often in 1 to 2 weeks (2, 3). An expert panel published serologic criteria for diagnosis of **C. pneumoniae** infection in 2001 (4). Acute infection was defined as a 4-fold increase in the IgG titer or a single IgM titer of $\geq$1:16, whereas past infection was defined as an IgG titer $\geq$1:16 (4). However, neither elevated IgA titers nor any other serologic markers were felt to be validated markers of persistent or chronic infection (4). Moreover, whereas serology can indicate whether someone is experiencing an acute infection or has had a past infection, it gives us no information about the location, duration, and severity of infection.

Isolation of the organism in cell culture from clinical specimens is used to show current infection by **C. pneumoniae** and to establish the viability and thus the infectivity of the organism (5). However, **C. pneumoniae** is difficult to grow, especially from tissue samples. Consequently, sensitivity of isolation in cell culture is low, resulting in a high false-negative rate.

PCR can be used to rapidly amplify small amounts of DNA and RNA of microorganisms including **C. pneumoniae** and so provides a means to detect organisms that are present in small numbers, present in material that are not suitable for culture, or that are nonviable or growing slowly. However, **C. pneumoniae** PCR is not standardized. The assays reported in the literature are in-house tests, and most have not been validated compared with culture or even other PCR methods (4). There is evidence of major problems with both inter- and intralaboratory reproducibility (6-9). Much of the variation in the prevalence of **C. pneumoniae** DNA detected in human atheroma specimens reported in the literature (0-100%) is thought to be due to variation in methods, although true variation by type of specimen or population studied cannot be excluded. The advantages and disadvantages of different PCR methods can be found in a recent review (4).
In contrast to serology and PCR, detection methods such as immunohistochemistry and in situ hybridization offer the advantage of preserving tissue morphology and permitting localization of the infectious agent to the specific areas and cells. Of the tissue diagnostic methods, immunohistochemistry has been used most frequently in studies of C. pneumoniae. Careful interpretation is a major challenge because true-positive results of staining and false-positive results of staining can be difficult to distinguish (4).

Review of C. pneumoniae as a Cause of Acute and Chronic Disease

C. pneumoniae is transmitted via respiratory secretions and is believed to cause 7% to 10% of community-acquired pneumonia among adults (10). Most cases of pneumonia due to C. pneumoniae seem to be relatively mild and self-limited and are difficult to differentiate clinically from cases of pneumonia due to other organisms such as Mycoplasma pneumoniae. C. pneumoniae also accounts for ~5% of cases of bronchitis and sinusitis, but is a less frequent cause of pharyngitis, generally accounting for only ~1% of cases.

In addition to having a gradual onset, symptoms due to C. pneumoniae respiratory infections may be of prolonged duration, despite appropriate antibiotic therapy. The immunologic response to primary infection with C. pneumoniae is at best partially protective, and reinfection with the organism is common. Furthermore, like all chlamydial organisms, C. pneumoniae has a tendency to persist in tissues (10, 11). Chronic diseases that have been serologically associated with C. pneumoniae include atherosclerotic cardiovascular disease, asthma, and lung cancer.

The association of atherosclerosis and C. pneumoniae has been intensively studied since the time when serologic data were first presented suggesting a relationship (12). Multiple lines of evidence have linked C. pneumoniae with atherosclerosis. Many observational epidemiologic studies have found that individuals with atherosclerosis are more likely to have evidence of C. pneumoniae infection, detected either through serology, PCR, culture, or immunohistochemistry, than individuals who did not experience cardiovascular disease events. Furthermore, using PCR, culture, and immunohistochemistry, C. pneumoniae organisms have been located in atherosclerotic tissue more often than in normal tissue (13, 14). Experimental in vitro cell culture studies and animal model studies have also provided support for the positive studies observed in humans (13, 14). These studies have been reviewed extensively (15-17). Randomized controlled treatment trials among men and women with a history of atherosclerosis have generally not been positive, however. Overall, these studies indicate that 1 to 24 months of antibiotic treatment is not effective at lowering the risk of secondary events (18, 19). Nevertheless, these studies do not disprove that C. pneumoniae infection causes atherosclerosis. It is possible that C. pneumoniae plays a role in initiation of atherosclerosis, but not secondary events like myocardial infarctions. Other reasons for null findings despite a true association have been discussed elsewhere (14, 18, 20).

By comparison, research into the association between C. pneumoniae and lung cancer risk is still in its infancy. Laurila and colleagues first hypothesized that C. pneumoniae might be involved in lung cancer carcinogenesis in 1997 based on two related observations: first, infection with C. pneumoniae has been linked to an increased risk of chronic pulmonary diseases such as chronic bronchitis and adult onset asthma (2, 21); second, such conditions seem to increase the risk of lung cancer (22). Identification of C. pneumoniae as etiologically related to lung cancer, whether independent of tobacco smoking or as a cofactor, could have profound implications, particularly in the areas of primary and secondary prevention.

The purpose of this article is to identify, describe, and critically examine the published studies on the association between C. pneumoniae infection and risk of lung cancer. To this end, we compare study results, evaluate the strengths and limitations of study designs, and summarize proposed mechanisms. Based on these findings, we suggest directions for future research.

Review of Methods

To identify studies published before December 2004 that investigated an association between C. pneumoniae antibody titers and risk of lung cancer, we conducted computer-assisted searches using the terms “Chlamydia pneumoniae” or “Chlamyphilia pneumoniae” (both genus names are used and refer to the same organism) and “lung cancer”. We also scanned relevant reference lists.

Seven relevant studies were identified (23-29). One publication (24) had apparently overlapping cases with a second study (25); thus, only the final report (25) is included here. In Tables 1 and 2, we characterize the studies in terms of criteria for inclusion, duration of disease, population source and subject selection, criteria for defining C. pneumoniae infection, and analytic approach, including control for possible confounding effects of known risk factors. Table 1 summarizes information on the characteristics of nested case-control studies in which blood was collected before diagnosis in cases and a comparable time in controls. Of the three studies in which blood was collected before diagnosis, two were nested within randomized chemopreventive trials of β-carotene among heavy smokers (23, 29). The third study, by Anttila et al. (28), included Finnish women recruited in their first trimester of pregnancy.

Table 2 summarizes information on the three studies in which blood was sampled after diagnosis in cases. Of these studies, only one was population based (26). In that study, cases were identified from the Surveillance, Epidemiology and End Results cancer registry of western Washington; controls were selected by random digit dialing (26). The two other studies (25, 27) included hospital-based cases. Comparison groups included blood donors, healthy hospital staff, and relatives of patients. In one of these studies, cases were compared with two groups; results for each comparison group are presented separately (25).

C. pneumoniae infection status was defined by serologic criteria based on levels of either antibodies or immune complexes (antigen combined with antibody). The criteria used to define chronic C. pneumoniae infection (“exposed”) varied widely. Some studies used a combination of measures (IgA antibodies and immune complexes, or IgA and high IgG antibody titers; refs. 23, 27), whereas others used one or more cutoffs of IgG or IgA antibody titers alone (25, 26, 28, 29). In all studies, the microimmunofluorescence test was used to detect C. pneumoniae-specific IgA and IgG antibodies in serum, either using an in-house assay (23, 26, 28, 29) or a microimmunofluorescence kit from Organum (Helsinki, Finland) (27) or Ani Labsystems (Vantaa, Finland) (25).

Summary of Results

Most studies used logistic regression to estimate relative risks and 95% confidence intervals (CI) and to adjust for potential confounding factors (23, 26, 28, 29). In studies where only the proportion of subjects meeting the serologic criteria for
Infection was presented (25, 27), we calculated odds ratios (OR) and 95% CI from information presented in the published articles.

Table 3 gives overall and subgroup findings for each study. All studies reported elevated OR estimates. Studies in which blood was collected before diagnosis tended to have weaker results (OR range, 1.2-2.1) than studies in which blood was sampled after diagnosis (OR range, 1.4-9.9). ORs for IgA ≥ 16 (with or without immune complexes) ranged from 1.2 to 1.7 (23, 26, 28, 29). When a higher IgA cutoff (e.g., ≥64) was used, the ORs were farther from the null (OR range, 2.1-9.9). There was only limited agreement between the results of subgroup analyses; identified higher-risk subgroups included current smokers (26), former smokers (29), those younger at diagnosis (23, 25, 26), and men (25, 27). Two studies observed higher C. pneumoniae-associated risks for squamous cell or small cell carcinomas (23, 29).

**Limitations of Studies**

Potential limitations of these studies include selection bias, exposure misclassification, and inadequate control for confounding. Selection bias is a concern in the hospital-based case-control studies (25, 27) because cases included in these studies may not be representative of all those occurring in the general population, and because appropriate control selection is more challenging. An ideal control group would consist of individuals selected from a population whose prevalence of chronic C. pneumoniae infection is the same as the population from which the cases arose. Furthermore, ideal controls would be identical to the cases with respect to the distribution of lung cancer risk factors that are associated with the likelihood or degree of C. pneumoniae infection (30). Blood donors, relatives, and hospital staff may not fulfill these criteria.

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### Table 1. Summary of nested case-control studies of *C. pneumoniae* and lung cancer risk with blood collected before lung cancer diagnosis in cases and a comparable time in controls

<table>
<thead>
<tr>
<th>First author, year, location</th>
<th>Population</th>
<th>Number of subjects</th>
<th>Time between blood sampling and lung cancer diagnosis/censoring (y)</th>
<th>Variables adjusted for in multivariate models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laurila, 1997 (23) Finland</td>
<td>Male smokers involved in a randomized trial of β-carotene and α-tocopherol</td>
<td>230 cases/230 controls</td>
<td>3-8 (median = 6.1)</td>
<td>Years of smoking and cigarettes smoked per day</td>
</tr>
<tr>
<td>Anttila, 2003 (28) Finland</td>
<td>Women in 1st trimester of pregnancy in Finnish Maternity Cohort</td>
<td>58 cases/287 controls</td>
<td>1.6-16.7 (mean = 9.1)</td>
<td>Current smoking defined by serum cotinine levels</td>
</tr>
<tr>
<td>Jackson, 2004 (29) USA</td>
<td>Men and women involved in a randomized trial of β-carotene and retinol</td>
<td>508 cases/508 controls</td>
<td>0-16 (median = 9)</td>
<td>Years of smoking, cigarettes smoked per day, education, and body mass index (kg/m²)</td>
</tr>
</tbody>
</table>

### Table 2. Summary of case-control studies of *C. pneumoniae* and lung cancer risk with blood sampled at or after lung cancer diagnosis and at a comparable time in the controls

<table>
<thead>
<tr>
<th>First author, year, location</th>
<th>Number of cases/controls</th>
<th>Case population/selecton</th>
<th>Control population/selecton</th>
<th>Matching factors</th>
<th>Confounders adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jackson, 2000 (26) USA</td>
<td>148 cases/148 controls</td>
<td>Men in WA state diagnosed with LC between 5/93 and 7/96, identified through the SEER cancer registry. Population based.</td>
<td>Men without LC identified through random digit dialing.</td>
<td>Age (5-y categories) and gender</td>
<td>Smoking status (current or former), pack-years (&lt;40 or ≥40) and education</td>
</tr>
<tr>
<td>Koyi, 2001 (25) Sweden</td>
<td>177 cases/ C1 = 68, C2 = 111</td>
<td>Diagnosed with LC at a single hospital between 2/97 and 2/98. Hospital based.</td>
<td>C1: Consecutive blood donors who were former or current smokers presenting at the same hospital during spring 1998 (exclusions: history of MI, medication for hypertension, or other CV diseases). C2: Participants in a study of current and ex-smokers &gt;70 y old</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Kocazeybek, 2003 (27) Turkey</td>
<td>123 cases/123 controls</td>
<td>Smokers admitted to an Istanbul hospital with a diagnosis of LC between 6/98 and 7/2000. Hospital based.</td>
<td>Healthy hospital staff, relatives of the patients, blood donors, or persons with similar age, sex, and smoking habits and not having any medical treatment for a local or systemic disease and not admitted to the hospital in the previous 2 months</td>
<td>Age (5-y age group), sex, living environment (i.e., province), smoking status (former or current), duration (10-y categories), and quantity of cigarettes smoked (4 categories)</td>
<td>In primary analyses, none.</td>
</tr>
</tbody>
</table>

**Abbreviations:** WA, Washington; LC, lung cancer; MI, myocardial infarction; CV, cardiovascular; SEER, Surveillance, Epidemiology, and End Results; C1, control group 1; C2, control group 2.
Selection bias is also a concern in the study by Jackson et al. (26). While the cases were drawn from a population-based cancer registry, and the controls were selected at random from the population, many of the cases had died by the time the study began and thus were unable to participate. It is unknown whether seropositivity rates of those who survived long enough to participate in the study reflect those of the individuals who were eligible but unable or unwilling to participate. Accurate assessment of serologic markers of past C. pneumoniae infection is a concern in all studies and is difficult for the following reasons: (a) there is no serologic test to specifically identify persons with chronic infection; (b) the reliability of the existing serologic tests is questionable; and (c) the etiologically relevant time period has not been established. We will discuss each of these points below.

First, it is unclear what type or titer levels of antibodies accurately reflect chronic infection, although serologic criteria have been used in all studies that have investigated a link between C. pneumoniae and lung cancer, as well as in many studies assessing a link between C. pneumoniae and atherosclerosis (16). In the lung cancer studies, a variety of measures and cutoff levels were used (Table 3), making it difficult to assess how these measures relate to each other. Furthermore, cutoffs may have been chosen post hoc, possibly resulting in a bias away from the null.

Second, there is evidence suggesting that methods used to measure antibody levels may not be reliable. Our group recently conducted an intralaboratory reliability study in which the same serum samples were tested for C. pneumoniae between the case and control groups.

### Table 3. Selected results from studies on C. pneumoniae infection and lung cancer risk

<table>
<thead>
<tr>
<th>First author, year, location</th>
<th>Definition of chronic infection</th>
<th>Overall results</th>
<th>Findings by age at diagnosis/reference</th>
<th>Other subgroup findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laurila, 1997 (23), Finland</td>
<td>“Strong or moderate” evidence*</td>
<td>1.6 (1.0-2.3)</td>
<td>50-59 y: OR, 2.9; 95% CI, 1.5-5.4 ≤60 y: OR, 0.9; 95% CI, 0.5-1.6</td>
<td></td>
<td>Squamous or small cell cancer: OR, 1.7; 95% CI, 1.0-2.8 Follow-up &lt;5 y: OR, 2.0; 95% CI, 1.1-3.6 ≥5 y: OR, 1.2; 95% CI, 0.5-2.5</td>
</tr>
<tr>
<td>Jackson, 2000 (26), USA</td>
<td>IgA ≥ 16</td>
<td>1.4 (0.9-2.3)*</td>
<td>&lt;60 y: OR, 2.7; 95% CI, 1.2-5.9 ≥60 y: OR, 0.7; 95% CI, 0.3-1.4</td>
<td>Association stronger among current smokers &lt;60 y at diagnosis than former smokers: Current: OR, 4.6; 95% CI, 1.4-13.7 Former: OR, 1.5; 95% CI, 0.5-4.8</td>
<td>Blood specimens were obtained from only 47% of cases who completed interviews in counties where blood was collected, mainly because of death or illness. Possible confounding by age, which differed between the case and control groups</td>
</tr>
<tr>
<td>Koyi, 2001 (25), Sweden</td>
<td>IgA ≥ 64*</td>
<td>9.9 (4.6-22.2)*</td>
<td>Cases vs. C1: OR, 2.9; 95% CI, 1.2-6.3 Cases vs. C2: OR, 2.5; 95% CI, 1.3-4.9</td>
<td></td>
<td>Possible selection bias; possible exposure misclassification due to use of higher value in cases only</td>
</tr>
<tr>
<td>Kocayebek, 2003 (27), Turkey</td>
<td>IgG ≥ 512; IgA ≥ 40*</td>
<td>4.6 (2.3-10.2)*</td>
<td>Men &lt; 55 y: OR, 18.0; 95% CI, 4.6-154 Men ≥ 55 y: OR, 1.0; 95% CI, 0.3-3.3</td>
<td></td>
<td>Mean age of cases at diagnosis was 41 y (range 22-53 y)</td>
</tr>
<tr>
<td>Anttila, 2003 (28), Finland</td>
<td>IgA ≥ 16; IgG ≥ 64*</td>
<td>1.6 (0.9-2.8)</td>
<td>ORs for IgG antibody titers (≥32 and ≥128) and IC (&gt;2 and &gt;4) were of similar magnitude (1.7 to 2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Littman, 2004 (29), USA</td>
<td>IgA ≥ 16</td>
<td>1.2 (0.9-1.6)</td>
<td>Male asbestos-exposed workers: OR, 1.9; 95% CI, 0.9-3.7; former smokers: OR, 2.1; 95% CI, 1.1-4.1; squamous cell carcinoma: OR, 1.7; 95% CI, 1.1-2.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IC, immune complexes; OR, odds ratio; CI, confidence interval; C1, control group #1 (see Table 2); C2, control group #2 (see Table 2).

*Blood sampled at baseline and at 3-y follow-up used to assess exposure. Strong evidence defined as IgA antibodies ≥16 in both samples and IgG ≥ 4 in both samples.

†Final titer defined as higher value of blood sampled at diagnosis (all) or 3 months later (n = 127).

‡Final titer defined as higher value of blood sampled at diagnosis or 1 month later.
observed *C. pneumoniae*-lung cancer associations may underestimate the true association.

Finally, assuming there was an accurate method to identify persons with chronic lung infection, it would also be necessary to establish that the infection was in the lungs at the etiologically relevant time period. In the case-control studies (25-27), investigators measured *C. pneumoniae*—specific antibodies or immune complexes after diagnosis. If antibody levels change in response to cancer or its treatment, then case-control studies where blood is sampled after diagnosis may obtain biased results. Moreover, although samples were collected before diagnosis in the study by Laurila et al. (23), follow-up was relatively short and the association was stronger for those followed for 5 years or less, a point in time when cancer may have already been present (but undiagnosed). Thus, it is uncertain, even in the prospective studies, whether *C. pneumoniae* infection (as measured by elevated antibody levels) increased the risk of lung cancer, or whether the presence of lung cancer increased the likelihood of *C. pneumoniae* infection and/or *C. pneumoniae* IgA or IgG antibody titer levels.

Different sampling time frames for cases and controls (25) and repeated measurement of antibodies for cases, but not controls (27), are other sources of potential bias. In one study, blood was collected from cases throughout the year, whereas blood was collected from controls in a single season only (25). If antibody titers fluctuate throughout the year, this could lead to bias in either direction. One study sampled blood from the cases at two time points, using the higher of the antibody measurements, but only sampled blood once from controls, potentially biasing results away from the null (27).

A final concern is whether results reflect adequate control for confounding factors. Because age and cigarette smoking are strongly associated with lung cancer, and are potentially also associated with *C. pneumoniae* antibody titers (10, 34, 35), elevated antibody titers in cases relative to controls in unadjusted analyses may be explained in whole or in part by differences in these factors. For example, in one study (25), controls were younger than cases, but the authors did not adjust for age. As both *C. pneumoniae* seropositivity (1, 10) and lung cancer risk increase with age, confounding by age is possible. In addition, residual confounding by cigarette smoking is a concern even in studies that controlled for smoking. In one study, only current smoking was adjusted for (28), whereas in others, there was no adjustment for smoking duration or frequency (25, 27).

**Potential Mechanisms**

Despite limitations, the relative consistency of results across studies in different populations using different study designs and methods suggests that there may truly be an association between chronic *C. pneumoniae* infection and lung cancer. Several mechanisms have been proposed to explain how chronic infection with *C. pneumoniae* could increase the risk of lung cancer. One mechanism is through mediators of inflammation (23). Inflammation results in reactive oxygen species that can cause damage to DNA. Furthermore, inflammation causes cell injury and consequent repair, increasing the rate of cell division. Even a fixed rate of DNA damage, higher cell turnover will increase the risk of a mutation conferring a selective advantage to cells that may lead to cancer (36). The association between *Helicobacter pylori* and gastric cancer is an excellent example of bacterium-induced chronic inflammation playing a role in the development of cancer (37).

Infection with *C. pneumoniae* could also act synergistically with cigarette smoking to increase the risk of lung cancer. Smoking impairs lung immunity and increases the secretion of interleukin (IL)-4. IL-4 production is associated with a predominantly Th2-repertoire (10), whereas in others, there was no adjustment for smoking. In one study, only current smoking was adjusted for (28), whereas in others, there was no adjustment for smoking duration or frequency (25, 27).

**Summary and Conclusions**

We identified six epidemiologic studies that investigated whether persons with serologic evidence of past infection with *C. pneumoniae* had higher lung cancer risks than those without such evidence. All reported positive results (23, 25-29). Although measurement error is a concern in these studies, results were relatively consistent, suggesting a potentially novel and interesting association.

Future progress into understanding this association can best be accomplished by employing methods other than serology, which can help us to understand when the critical time period for infection is, and how eradication of the organism in adults might affect disease risk. Animal models present a potentially useful tool for demonstrating how *C. pneumoniae* infection may lead to initiation or progression of cancer, particularly in the presence of cigarette smoke. Analysis of existing data from completed randomized controlled trials (18) of patients with atherosclerosis may also be informative. Investigators could compare lung cancer incidence rates in treatment groups relative to the rates in placebo groups. Observational studies using other methods (such as PCR or immunohistochemistry) to detect *C. pneumoniae* in relevant tissues (such as sputum or lung biopsies) in samples taken before diagnosis could also provide useful information by showing that *C. pneumoniae* is more likely to localize in tumor tissue relative to normal tissue and that organisms found in tumor tissues are viable. Findings from these studies, in combination with the existing serologic studies, may help scientists to better understand the role that *C. pneumoniae* may play in the etiology of lung cancer, and potentially lead to earlier detection or prevention.

**References**

**Chlamydia pneumoniae** DNA in respiratory specimens with four conventional PCR assays. J Clin Microbiol 2003;41:392–600.


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