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## **Lung cancer in the county of Gävleborg – Epidemiology and importance of infection with *Chlamydia pneumoniae***

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Stockholm 2001

## ABSTRACT

At the beginning of the 20th century lung cancer was a rare malignancy. It is in Sweden the second most common cause of cancer death in both men and women. The purpose of the studies was to investigate whether chronic infection with *C. pneumoniae* can contribute to cancer development; to describe a complete material of lung cancer in a geographically limited area; to try to find the "hidden cases", i.e. all those cases which would "normally" never be diagnosed or reported; and to investigate the delays in diagnosis, both from the patient and from the doctors.

In the county of Gävleborg, Sweden, with a population 290 000, practically all cases of lung cancer will be seen by the lung department. Beginning in 1998, meetings with all the general practitioners of the county were organized, asking them to refer all suspected cases of lung carcinoma as early as possible to the lung department, also including those with a dismal prognosis.

**Study I and II:** the aim was to investigate the occurrence of chronic Chlamydia pneumoniae infection in patients with lung cancer. In study I, sera from 33 women and 64 men were compared to healthy civil servants and a group who underwent coronary angiography. In Study II, 136 men and 74 women with lung cancer were included. Consecutive blood donors and currently smoking or ex-smoking 70-year olds were used as controls. Blood was obtained and a swab was taken from the posterior part of the retropharyngeal mucosa for detection of *C. pneumoniae* by PCR. The prevalence of specific *C. pneumoniae* IgG antibody titer of  $\geq 512$  was 57 % in male lung cancer patients compared to 27 % in male 70-year olds and 17 % in male blood donors. The prevalence figures for specific *C. pneumoniae* IgA antibody titers  $\geq 64$  were 69 % for lung cancer patients compared to 25 and 20 % for the respective control groups. The difference between patients and controls was highly significant ( $p < 0.000001$ ). The throat specimens had a low sensitivity.

**Study III:** patient's and doctors' delays in an unselected material of patients with lung cancer were investigated. A questionnaire recorded symptoms and when they first occurred. All dates for visits to doctors and investigations were recorded. The mean delay of the patients was 43 days (median 21) days. The GP delay was a mean of 56 days, median 33, and the specialist doctor's delay was a mean of 33 days (median 9). The time from first symptom until treatment or decision not to treat was in the mean 203 days (median 189).

**Study IV:** is a descriptive analysis of cancer type, stage, symptoms, smoking habits etc. The first symptoms were cough and dyspnea. 60 % were smokers, 27 % ex-smokers. Only 12.8 % had never smoked. Of the men, 91.9 % were smokers or ex-smokers, and of the women, 78.4 %. The difference between the sexes were statistically highly significant ( $p < 0.0001$ ). Squamous cell carcinoma was seen in 30.4 % of the men but only 19.8 % of the women. Adenocarcinoma was seen in one third of the women but only 19 % of the men. 18 % were Stage I, 2 % II, 10 % IIIa, 28 % IIIb and 42 % IV.

**Study V** was made to study how big the proportion of all lung cancer patients which "normally" never are diagnosed or reported to official cancer registries is, in other words try to find "the hidden cases of lung cancer". The incidence of lung cancer, as published by the official cancer registries from the County of Gävleborg and four neighbouring counties from 1985 to 1998, were compared. For the four neighbouring counties there was an average of 86 new cases per year and county prior to 1997 and an average of 96 new cases per year during 1997 and 1998, thus a slight increase ( $p < 0.045$ ). Comparable figures for the county of Gävleborg were 87 new cases per year prior to 1997 and 124 cases for 1997 and 1998. After 1997 the incidence in the county remained high and in year 2000, 140 new cases were diagnosed. The number of cases in the county of Gävleborg from 1997 onwards is significantly higher both compared to the number of cases in the four neighbouring counties during the same period of time ( $p < 0.000$ ) and compared to the number of cases prior to 1997 in the county of Gävleborg ( $p < 0.000$ ). Thus, the implementation of the new routines in the county of Gävleborg in 1997 caused a considerable increase in the incidence of lung cancer. One can thus conclude that around 20 % of all lung cancers were never registered earlier. The figures are probably similar for most Sweden.

**Conclusions:** There is a correlation between antibodies to *C. Pneumoniae* and lung cancer. There can be a considerable number of patients with lung cancer who are never "normally" diagnosed. Both patients' and doctors' delays are in most instances fairly long. Adenocarcinoma incidence is increasing. A distressingly large proportion of patients is diagnosed in high stages.

**Keywords:** lung cancer, Chlamydia pneumoniae, chronic infection, patient's delay, doctors' delay, epidemiology, reservoir, microimmunofluorescence, polymerase chain reaction