Proportion of Community-Acquired Pneumonia Cases Attributable to Tobacco Smoking*

Jordi Almirall, PhD; Carlos A. González, PhD; Xavier Balanzó, PhD; and Ignasi Bolíbar, MD

Study objectives: To assess the population-attributable risk (PAR) of smoking and the effect of tobacco smoking on the development of community-acquired pneumonia (CAP) in adults.

Design: A population-based case-control study. Information on history of smoking and other risk factors was obtained by a questionnaire administered by interview.

Setting: Mixed residential-industrial area having 74,610 adult inhabitants in Barcelona, Spain.

Participants: Two hundred five male and female patients (age, 15 to 74 years old) with CAP diagnosed between 1993 and 1995. They were matched to 475 control subjects randomly selected from the municipal census.

Results: Smoking any type of tobacco had an odds ratio (OR) of CAP of 2.0 for ever smokers (95% confidence interval [CI], 1.24 to 3.24); 1.88 for current smokers (95% CI, 1.11 to 3.19); and 2.14 for ex-smokers (95% CI, 1.26 to 3.65). A positive trend for increased risk of CAP was observed for an increase in the duration of the habit, the average number of cigarettes smoked daily, and cumulative cigarette consumption. Former smokers had a 50% reduction in the OR 5 years after the cessation of smoking. The risk of CAP attributable to the consumption of any type of tobacco in this population was 32.4% of cases (95% CI, 14.8 to 50.1%). In subjects without a history of COPD, the PAR of tobacco was 23.0% (95% CI, 3.3 to 42.7%).

Conclusion: This study gives better quantitative and qualitative evidence about the effects of tobacco smoking on the occurrence of pneumonia in the adult community.

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Key words: attributable risk; case-control study; community-acquired pneumonia; smoking

Abbreviations: CAP = community-acquired pneumonia; CI = confidence interval; OR = odds ratio; PAR = population-attributable risk

Cigarette smoking is the most important single risk factor of morbidity and mortality in developed countries. Although community-acquired pneumonia (CAP) is a major cause of hospitalization and a common cause of death in developed countries, few epidemiologic studies have investigated the association between smoking and lower respiratory infections. Tobacco has been identified as a cause of CAP in adults, but uncertainty remains about several aspects of the relationship between smoking habits and CAP.

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Pneumonia is the result of several factors that favor the entrance, establishment, and multiplication of pathogenic organisms, as well as factors that decrease the respiratory defense mechanisms in the host. Numerous studies have shown alterations in the immune and inflammatory functions in smokers. Tobacco smoking is the most important risk factor for the development of COPD, and it is recognized as a risk factor for other respiratory infections. Both smoking and COPD are predisposing factors for CAP.

Most of the previous findings concerning risk factors associated with pneumonia have been derived from studies based on selected groups of patients (pneumonia cases requiring hospitalization, pneumonia acquired in the hospital, or pneumonia caused by specific pathogenic agents). To our knowledge, the only previous population-based study on true CAP was that by Koivula et al., but it was a cross-sectional study on the elderly, and information...
on smoking was not available. In this analysis, we used data obtained in a population-based case-control study of CAP to estimate the population-attributable risk (PAR) percent of smoking, as well as the risk related to the intensity and the duration of the pattern of tobacco consumption.

**Materials and Methods**

Further details on cases and controls and methods of collecting information have been reported elsewhere. Briefly, the study was conducted in a mixed residential-industrial urban area having 74,610 inhabitants > 14 years of age in the Maresme county (Barcelona, Spain), which is situated on the Mediterranean coast. This area was selected because all of its physicians who are first contacted by patients having symptoms of CAP (ie, primary care and hospital emergency departments) undertook to collaborate in the study. A case-by-case assessment was organized on a daily basis to identify all clinically suspected CAP patients living in the area. Predefined criteria for registration were based on acute lower respiratory tract infections for which antibiotics were prescribed, associated or not with new focal signs on examination of the chest, and radiographic indicative of pneumonia (required for all suspected cases). This register involved all physicians working in public (covering 95.2% of the population) and private health-care facilities in the study area (medical consulting rooms, primary health-care centers, and three regional hospitals), as well as reference hospitals outside the area. Periodic meetings and weekly phone contacts were held to improve the system of reporting cases.

From December 1, 1993, to November 30, 1995, 292 patients with clinically suspected CAP who fulfilled the entry criteria were reevaluated using chest radiography on the fifth day of illness and at monthly intervals until they had complete recovery. Cases of suspected pneumonia were discarded after finding a secondary concurrent disease or a noninfectious origin (51 respiratory disorders, 17 acquired immunodeficiency virus infections, and 5 active cancers). After inclusion, 14 patients could not be interviewed because 6 had died, 5 had dementia, and 3 could not be contacted. Finally, 205 patients with CAP (112 men and 93 women; mean age, 56.1 and 51.1 years old, respectively) remained in the study.

For each case, three control subjects matched by gender and age (± 5 years) were recruited within the subsequent 21 days. These were selected at random, using a computerized system, from the same section of the municipal register as that of the patient, being the easiest and quickest procedure for the selection and recruitment of control subjects. Most of the control subjects who were contacted and did not participate in the study were replaced following the same sampling and matching criteria. A total of 685 control subjects were contacted by phone to participate in the study; of these, 13.3% declined to answer the questionnaire: 8.8% were not present because of work, leisure, or health reasons; and 8.6% had other or unknown reasons for not participating. Finally, 475 control subjects participated in the study.

Information on each patient’s life smoking history and other background data were obtained by a questionnaire that was administered by trained physicians or nurses at home directly to all study participants; self-reported factors included weight, height, alcohol consumption, life conditions, medical history, and regular treatments during the previous year. Some of the participants who were inpatients were interviewed at the end of their hospital stay. Information on smoking was collected in separate sections for consumption of cigarettes, cigars, and pipes. Any change in the characteristics of the habit, including a variation of ± 20% in the amount smoked, was reported as a separate period. Information on the type of tobacco (blond or dark), use of a filter, and depth of inhalation was collected for cigarette smoking in each period. An “ever smoker” was defined as anyone who had at some time smoked at least one cigarette per day or one cigar or pipe per week for at least 1 year; an ex-smoker was defined as a smoker who had given up the habit at least 1 year before the diagnosis (for patients) or the date of interview (for control subjects).

To assess the reliability of the questionnaire, 36 interviews (14 patients and 22 control subjects) were repeated by the same interviewer within a period of 3 weeks. Results of the reliability study showed elevated proportions of agreement for most variables (82.9 to 100.0%). The weighted k index of agreement was 0.82 for status of smoker and 0.74 for chronic bronchitis.

As a measure of association between risk factors and the occurrence of CAP, we used estimations of the relative risk through odds ratios (ORs) using a standard program of epidemiologic analysis. The effect estimate was made by conditional logistic regression, with 95% confidence intervals (CIs). For the analysis of the effect in subjects (matched sets of cases and controls) without COPD, in order not to lose too much data, an unmatched analysis was done with the matching variables included in the model. Ordered variables were analyzed with the test for trend. PAR percentsages have been estimated using the method termed by Miettinen as the etiologic fraction. The CI of the attributable risk of smoking was calculated by the method proposed by Greenland.

**Results**

Among the patients with CAP, 64.9% were current smokers of cigarettes (Table 1) or had smoked at some time during their life; among the control subjects, 56.2% were current smokers or had smoked at some time during their life. Of these, 15 patients and 24 control subjects had also smoked cigars, and 4 control subjects had also smoked pipes. The OR for ever smokers of any type of tobacco was 2.0 (95% CI, 1.24 to 3.24), for current smokers was 1.88 (95% CI, 1.11 to 3.19), and for ex-smokers was 2.14 (95% CI, 1.26 to 3.65). The proportion of CAP cases attributable in that population to ever having consumed any type of tobacco was 32.4% of cases (95% CI, 14.8 to 50.1%).

The number of cigarettes smoked by day and the lifetime pack-years showed a positive dose-response relationship, with a significant trend. The risk of smokers who smoked > 38 pack-years of cigarettes was 3.15. The risk of ex-smokers was similar to current smokers, but after 5 years of the cessation of smoking exposure, the risk of pneumonia was reduced. A higher risk of nonfilter (OR, 2.43) and dark cigarettes (OR, 2.68) was found when compared with filter (OR, 2.16) and blond types (OR, 1.53) of cigarettes, but this difference disappeared when intensity and cumulative exposure were included in the model. An inconsistent pattern of risk was observed with relation to the depth of inhalation.
The distribution of patients and control subjects according to smoking status and the simultaneous presence of previous diagnoses of COPD is presented in Table 2. The observed risk of current smokers without the presence of COPD was 1.68 (95% CI, 1.02 to 2.80). The proportion of CAP cases attributable in that population to ever having consumed any type of tobacco, in subjects without a history of COPD, was 23.0% of cases (95% CI, 3.3 to 42.7%).

### Table 1—The Relationship of CAP With Tobacco and Cigarette Smoking in Adults*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control Subjects (n = 475)</th>
<th>Patients (n = 205)</th>
<th>OR (95% CI)</th>
<th>p Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status of smoker</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked (reference category)</td>
<td>208</td>
<td>72</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ever smoker</td>
<td>267</td>
<td>133</td>
<td>2.00 (1.24–3.24)</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>133</td>
<td>68</td>
<td>2.14 (1.26–3.65)</td>
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</tr>
<tr>
<td>Current smoker</td>
<td>134</td>
<td>65</td>
<td>1.58 (1.11–3.19)</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarettes/d†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>208</td>
<td>72</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1–9</td>
<td>83</td>
<td>25</td>
<td>1.24 (0.67–2.29)</td>
<td></td>
</tr>
<tr>
<td>10–20</td>
<td>108</td>
<td>62</td>
<td>2.36 (1.37–4.07)</td>
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</tr>
<tr>
<td>&gt; 20</td>
<td>57</td>
<td>38</td>
<td>2.97 (1.52–5.81)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Lifetime smoking, pack-years‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>208</td>
<td>72</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1–4.9</td>
<td>62</td>
<td>23</td>
<td>1.28 (0.68–2.42)</td>
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<tr>
<td>5–16.4</td>
<td>62</td>
<td>31</td>
<td>2.06 (1.10–3.85)</td>
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<tr>
<td>16.5–38</td>
<td>62</td>
<td>35</td>
<td>2.83 (1.45–5.48)</td>
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<tr>
<td>&gt; 38</td>
<td>62</td>
<td>36</td>
<td>3.15 (1.52–6.51)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Years of ex-smokers§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>208</td>
<td>72</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>119</td>
<td>59</td>
<td>1.84 (1.07–3.16)</td>
<td></td>
</tr>
<tr>
<td>1–4</td>
<td>26</td>
<td>23</td>
<td>3.52 (1.72–7.17)</td>
<td></td>
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<tr>
<td>5–9</td>
<td>27</td>
<td>8</td>
<td>1.21 (0.48–3.04)</td>
<td></td>
</tr>
<tr>
<td>&gt; 10</td>
<td>78</td>
<td>36</td>
<td>1.84 (0.95–3.55)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

*Risk related to status, intensity, and time aspects.
†By conditional regression analysis (matching variables: age, gender, and municipality of residence).
‡Excluding 19 control subjects and 8 patients who had smoked exclusively cigars or pipes and 6 subjects with missing information.
§Excluding 17 control subjects and 7 patients who had smoked exclusively cigars or pipes and 3 subjects with missing information.

The distribution of patients and control subjects according to smoking status and the simultaneous presence of previous diagnoses of COPD are presented in Table 2. The observed risk of current smokers without the presence of COPD was 1.68 (95% CI, 1.02 to 2.80). The proportion of CAP cases attributable in that population to ever having consumed any type of tobacco, in subjects without a history of COPD, was 23.0% of cases (95% CI, 3.3 to 42.7%).

### Discussion

One of the major advantages of our case-control study is that it is population based, and one in which all CAP cases occurring in the entire population of a defined area within a 2-year period were included. Thus, we avoided the potential selection biases that affect studies restricted to hospitalized patients or selected groups of patients with pneumonia. The geographic area is relatively small, and it enabled the identification and the study of all suspected pneumonia cases registered by physicians through a prospective case-identification system. The estimated incidence rate of CAP, according to our study, is lower than those reported in other countries,4 but similar to a previous incidence study in the same area.14 Furthermore, we achieved a high participation rate of population control subjects.

An increase in the risk of CAP was found to be associated with smoking status, number of cigarettes smoked per day, and lifetime smoking. A trend toward increased risk was observed for increase in duration, average intensity, and cumulative exposure. Smokers of ≥ 20 cigarettes per day had a risk of 2.97 (95% CI, 1.52 to 5.81) in relation to never smokers. All of these estimates are based on an adjustment for gender, age group, and residence. After adjusting for several other factors related to medical history (underweight, overweight, respiratory infection in the previous month, previous pneumonia, diabetes, chronic bronchitis, asthma, lung

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*OR by unconditional regression analysis adjusted by gender, age, and residence.
tuberculosis, and chronic liver disease) and medical treatment associated with CAP (benzodiazepines, aminophylline, aerosols, and plastic pear-spacers), the observed multivariate OR for smokers of > 20 cigarettes per day was almost the same (OR, 2.75; 95% CI, 1.14 to 6.68). According to our results, no difference of risk was observed in relation to the use of filter cigarettes, dark cigarettes, and the depth of inhalation.

Smoking is a well-known and important risk factor for CAP through alterations in mechanisms of the host defense system. Oxidative stress and alterations in responsiveness of inflammatory cells are associated with the physical and chemical properties of tobacco smoke. There is consistent evidence that shows a higher vulnerability of people with cigarette-related diseases to respiratory infections in smokers compared to nonsmokers, and studies on selected groups of pneumonia patients have observed an association with smoking habits. Several longitudinal studies have previously shown an increase in the mortality rate from pneumonia in smokers, and that mortality from pneumonia increased with the amount smoked.

We examined the effect of smoking cessation and found a reduction in the risk of CAP in ex-smokers. Former smokers of any amount have approximately a 50% reduction in the OR after 5 years of abstinence. Regarding mortality from pneumonia, it has been observed before that former male smokers of > 21 cigarettes per day have mortality ratios after 10 years of abstinence that are approaching unity. Studies on animals and humans have shown a return to normal immune and inflammatory functions after the cessation of exposure to cigarette smoke.

The PAR of smoking in our study was 32.4% of CAP cases. Our estimation suggests that approximately one of every three observed pneumonia cases in adults would have been avoided if no one in the population had smoked. The attributable risk is a measure of the burden of disease that is caused by an exposure. It depends on the relative risk and the prevalence of exposure. Because the misclassification of exposure can reduce the estimate of attributable risk, we compared the pattern of tobacco consumption by groups of age and gender in our control subjects with that observed in another survey on lifestyle habits, from a representative sample of the general population in the same area. We found a similar pattern of consumption. However, the estimate of PAR according to Miettinen is based on the prevalence of exposure in the patients only, and the use of matched control subjects does not interfere with this approach, although such control subjects are not a representative sample of the population. Nevertheless, PAR depends on the level of exposure in the studied population. Inasmuch as the level of exposure is likely to vary from country to country, the results are not able to be directly extrapolated without taking into account the prevalence of exposure. The estimated smoking prevalence among men and women ≥ 15 years old in Spain were in a middle-high position (48.0% in men and 25.0% in women) in comparison to other countries.

COPD was associated with the risk of CAP in our study, and it has been observed as a risk factor in other studies of CAP and nosocomial pneumonia. COPD is recognized as a condition causally associated with smoking, representing a potential confounder of the estimate of attributable risk for smoking. However, because COPD can be considered an intermediate state in the disease process between smoking exposure and CAP, it should not be considered as a confounding factor. Therefore, the estimation of an attributable risk of smoking adjusted for the effects of COPD is not appropriate, but a subject restriction with respect to that variable is possible, and we estimated the PAR of smoking in subjects without a history of COPD. According to our results, the proportion of CAP cases that are attributable to ever smoking without the mediating actions of COPD, was 23.0%.

This study gives new and better established evidence on smoking as a factor associated with the community occurrence of pneumonia in adults. Although it gives support to previous findings, it contributes new quantitative and qualitative aspects of the effect of tobacco smoking.

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APPENDIX

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