# CIGARETTE SMOKING AND INVASIVE PNEUMOCOCCAL DISEASE

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## ABSTRACT

*Background* Approximately half of otherwise healthy adults with invasive pneumococcal disease are cigarette smokers. We conducted a population-based case–control study to assess the importance of cigarette smoking and other factors as risk factors for pneumococcal infections.

*Methods* We identified immunocompetent patients who were 18 to 64 years old and who had invasive pneumococcal disease (as defined by the isolation of *Streptococcus pneumoniae* from a normally sterile site) by active surveillance of laboratories in metropolitan Atlanta, Baltimore, and Toronto. Telephone interviews were conducted with 228 patients and 301 control subjects who were reached by random-digit dialing.

*Results* Fifty-eight percent of the patients and 24 percent of the control subjects were current smokers. Invasive pneumococcal disease was associated with cigarette smoking (odds ratio, 4.1; 95 percent confidence interval, 2.4 to 7.3) and with passive smoking among nonsmokers (odds ratio, 2.5; 95 percent confidence interval, 1.2 to 5.1) after adjustment by logistic-regression analysis for age, study site, and independent risk factors such as male sex, black race, chronic illness, low level of education, and living with young children who were in day care. There were dose–response relations for the current number of cigarettes smoked per day, pack-years of smoking, and time since quitting. The adjusted population attributable risk was 51 percent for cigarette smoking, 17 percent for passive smoking, and 14 percent for chronic illness.

*Conclusions* Cigarette smoking is the strongest independent risk factor for invasive pneumococcal disease among immunocompetent, nonelderly adults. Because of the high prevalence of smoking and the large population attributable risk, programs to reduce both smoking and exposure to environmental tobacco smoke have the potential to reduce the incidence of pneumococcal disease. (N Engl J Med 2000;342:681-9.)
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T HE incidence of invasive pneumococcal disease is highest among young children and the elderly. Although the rates are lower among nonelderly adults, the absolute numbers of infections are highest in these adults, who may be at increased risk if they have chronic illness.[1] The data on conditions predisposing nonelderly adults to pneumococcal infection have come from clinical case series and community-based surveillance studies and were not adjusted for multiple risk factors.[2,3]

Up to one third of adults with invasive pneumococcal disease have no recognized risk factors.[4]

Cigarette smoking and exposure to environmental tobacco smoke increase the risk of certain respiratory tract infections.[5-9] Smokers account for approximately half of otherwise healthy adult patients with invasive pneumococcal disease.[4,10] Characteristics associated with pneumococcal disease among adults, particularly behavioral and socioeconomic factors, have not been evaluated in controlled, population-based studies. To assess the contribution of active and passive smoking and other factors to the risk of invasive pneumococcal disease, we conducted a population-based case–control study.

## METHODS

### Definition and Ascertainment of Cases

A case of invasive pneumococcal disease was defined as an illness in which *Streptococcus pneumoniae* was isolated from a normally sterile site, such as blood or cerebrospinal fluid. Cases were identified prospectively among residents of metropolitan Atlanta, metropolitan Baltimore, and the Peel region of Toronto (aggregate population in 1995, 8.3 million) through ongoing laboratory-based surveillance, as described previously.[11] The study patients were residents of the surveillance area who were 18 to 64 years of age, who had a telephone, and in whom an illness that met the case definition of invasive pneumococcal disease developed between January 1995 and May 1996. Only community-acquired cases were included. Patients were excluded if they had a recognized condition or treatment that led to immunocompromise or immunosuppression[1] (asplenia, immunoglobulin deficiency, dialysis, organ transplantation, the nephrotic syndrome, human immunodeficiency virus infection, the acquired immunodeficiency syndrome, hematologic cancer, radiation therapy, or immunosuppressive chemotherapy, including corticosteroids) or if they were residents of an institution, such as a correctional facility or a nursing home.

### Selection of Patients

Each month we systematically selected a sample of approximately 25 percent of all cases reported in each surveillance area. Of 513 patients included in the samples, 42 percent were ineligible for the following reasons: immunocompromise (25 percent), no telephone (16 percent), or residence in an institution (1 percent). Of 297 eligible patients, 228 (77 percent) agreed to participate in the

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study, 24 declined (8 percent), 6 had died (2 percent), and 39 were unreachable (13 percent). The rates of participation were similar in all three areas. The patients who were interviewed were similar with respect to age, race, and sex to the eligible patients who were not enrolled in the study.

### Selection of Control Subjects

Control subjects were selected from the general population in each surveillance area by random-digit telephone dialing.[12] They were frequency-matched to the patients according to the month of positive culture (to account for seasonal variation in the incidence of invasive pneumococcal disease), area, and age group (18 to 29, 30 to 49, and 50 to 64 years), on the basis of the number of patients in each age group in the previous month. Each month, we attempted to enroll an equal number of control subjects and patients, using the same exclusion criteria. We called 7267 telephone numbers, of which 1367 were residential numbers. The respondents in 26 percent of the residences declined to participate, and there was no eligible respondent in 52 percent of the residences. A total of 301 control subjects were interviewed.

### Data Collection

Trained investigators obtained informed consent from the study subjects and conducted interviews using a standard questionnaire. Participants were asked about chronic illnesses, environmental and occupational exposures, and socioeconomic factors. Questions concerning cigarette smoking and alcohol consumption were adapted from the Behavioral Risk Factor Surveillance System of the Centers for Disease Control and Prevention (CDC).[13] All questions referred to the month before the patient's illness. The median number of days between a positive culture and the interview with the subject was 47 days for patients and 58 days for controls. The study was approved by the CDC and by the review board of each institution.

### Definitions of Cigarette Smoking

The study subjects were classified according to their smoking status.[13] Current smokers reported having smoked at least 100 cigarettes in their lifetime and still smoked or had quit smoking within the preceding year. Former smokers had smoked at least 100 cigarettes in their lifetime but had quit smoking more than one year earlier. Subjects who had smoked less than 100 cigarettes or who had never smoked were considered never to have smoked. For former smokers and those who had never smoked, exposure to environmental tobacco smoke was estimated by determining the number of people living in the household who smoked at home, the number of cigarettes smoked in the home each day, and the number of hours the subject spent daily outside the home in a place where people were smoking. We divided the subjects into four categories of smoking status: current smokers, former smokers (with no passive exposure to smoke), persons with passive exposure to smoke (those who had never smoked or former smokers exposed to tobacco smoke for more than one hour daily), and persons who had never smoked and had no passive exposure to smoke (the reference group).

### Statistical Analysis

Data were analyzed with SAS software (version 6.12, SAS Institute, Cary, N.C.) and Epi Info software (version 6.04). We used the Mantel–Haenszel method to calculate summary odds ratios after adjustment for the frequency-matching variables age and study area.[14] To control for confounding and to identify independent risk factors, we used unconditional logistic-regression analysis. After assessing two-way interactions and collinearity among variables, we used hierarchical backward elimination to determine the best fit for the model.[15]

Smoking status was the main variable analyzed. The following covariates included in the initial model were significantly associated with illness in the primary analysis or were considered potential confounders: study site, age, sex, race, level of education, household income, presence or absence of chronic illness (heart failure, cirrhosis, diabetes, and chronic obstructive pulmonary disease, including chronic bronchitis and emphysema), presence or absence of asthma, level of alcohol consumption, presence or absence of children under six years of age in the household, presence or absence of household crowding, and health insurance status. The likelihood-ratio test was used to assess the statistical significance of each variable. All reported P values are two-sided.

We calculated adjusted population attributable risks for independent risk factors in the multivariable model.[16] To examine whether there was a dose–response relation, we included both dichotomous and continuous components for each variable related to smoking (the number of cigarettes smoked, pack-years of smoking, and the time since quitting) in the final model, simultaneously testing for an effect associated with smoking status (yes or no) and a dose–response relation.[17] These models provided a much better fit than did models that used only the continuous variables.

## RESULTS

### Characteristics of Patients and Control Subjects

Between January 1995 and May 1996, a total of 2888 cases of invasive pneumococcal disease were identified, of which 1248 (43 percent) occurred among persons who were 18 to 64 years of age. The annual incidence of invasive pneumococcal disease ranged from 7.5 per 100,000 in Toronto to 21.8 per 100,000 in Baltimore (Table 1). In Atlanta and Baltimore, where the surveillance data included information on race, the rates were 5 to 8 times as high among blacks as among nonblacks and 1.7 times as high among men as among women.

Among the 228 patients enrolled, 216 (95 percent) had bacteremia, 10 (4 percent) had meningitis, and 2 (1 percent) had infections at other normally sterile sites. The patients were similar to the 301 control subjects in age, but were more likely to be male or black (Table 2). Overall, 23 percent of patients had chronic illnesses (Table 3), and the proportion increased to 44 percent among patients who were 50 to 64 years of age. When persons classified as heavy drinkers were included (those who consumed 25 or more drinks per week), 28 percent of patients had an indication for the receipt of pneumococcal vaccine.[1] Current smokers accounted for 58 percent of all patients, 57 percent of the 164 patients who did not have an indication for the receipt of pneumococcal vaccine, and 24 percent of the control subjects. Although chronic obstructive pulmonary disease (P<0.001) and chronic illness (P<0.001) were strongly associated with smoking, only 13 percent of all smokers had chronic lung disease; 23 percent had at least one chronic illness. Among persons who had an indication for vaccination, six patients (9 percent) and three control subjects (11 percent) reported having received the vaccine.

Among the patients, 57 percent of the men, 59 percent of the women, 64 percent of the nonblacks, and 51 percent of the blacks were current smokers. Among the control subjects, 26 percent of the men, 26 percent of the women, 24 percent of the blacks,

**TABLE 1.** INCIDENCE OF INVASIVE PNEUMOCOCCAL DISEASE OVERALL AND AMONG PERSONS 18 TO 64 YEARS OLD, ACCORDING TO RACE AND SEX IN THREE POPULATION-BASED SURVEILLANCE AREAS IN 1995.*

| AREA | POPULATION | OVERALL INCIDENCE PER 100,000 POPULATION (95% CI) | INCIDENCE PER 100,000 POPULATION AMONG PERSONS 18 TO 64 YR OLD (95% CI) | | | | |
|---|---|---|---|---|---|---|---|
| | | | ALL | BLACKS | NONBLACKS | MEN | WOMEN |
| Atlanta | 2,669,146 | 30.9 (28.8–33.1) | 19.9 (17.9–22.1) | 45.7 (40.1–52.0) | 9.5 (7.9–11.4) | 24.9 (21.7–28.5) | 15.0 (12.6–17.8) |
| Baltimore | 2,431,131 | 27.8 (25.7–29.9) | 21.8 (19.5–24.3) | 60.7 (53.4–68.7) | 7.6 (6.1–9.4) | 27.7 (24.1–31.8) | 16.1 (13.4–19.2) |
| Toronto† | 3,196,600 | 15.0 (13.6–16.4) | 7.5 (6.4–8.8) | — | — | 8.4 (6.8–10.3) | 5.6 (4.3–7.1) |

*CI denotes confidence interval.

†Surveillance data for Toronto did not include race.

**TABLE 2.** DEMOGRAPHIC CHARACTERISTICS OF PATIENTS WITH INVASIVE PNEUMOCOCCAL DISEASE AND FREQUENCY-MATCHED CONTROL SUBJECTS.*

| CHARACTERISTIC | PATIENTS (N=228) | CONTROL SUBJECTS (N=301) |
|---|---|---|
| | no. (%) | |
| Geographic area | | |
| Atlanta | 111 (49) | 161 (53) |
| Baltimore | 77 (34) | 88 (29) |
| Toronto | 40 (18) | 52 (17) |
| Age group† | | |
| 18–29 yr | 34 (15) | 49 (16) |
| 30–49 yr | 123 (54) | 169 (56) |
| 50–64 yr | 71 (31) | 83 (28) |
| Sex | | |
| Male | 125 (55) | 70 (23) |
| Female | 100 (44) | 168 (56) |
| Unknown | 3 (1) | 63 (21) |
| Race | | |
| White | 122 (54) | 202 (67) |
| Black | 101 (44) | 68 (23) |
| Other or not specified | 5 (2) | 31 (10) |

*Because of rounding, not all percentages total 100.

†The median ages of the patients and control subjects were 42.5 and 42.0 years, respectively.

and 25 percent of the nonblacks were current smokers. Patients were as likely as control subjects to be former smokers (Table 3), but the average time since patients had stopped smoking was 11.3 years, as compared with 17.0 years for the control subjects (P= 0.005). Among 318 nonsmokers, 33 percent of patients and 17 percent of control subjects were exposed to environmental tobacco smoke. These patients and control subjects were similar with respect to the mean daily duration of passive exposure to smoke outside the home (3.7 vs. 3.1 hours, P=0.48) and the mean number of cigarettes smoked daily by others in their home (14 vs. 16, P=0.42).

**Stratified Analysis**

After adjustment for age and study area, current smoking was strongly associated with pneumococcal disease (Table 3). Passive smoking was also associated with illness, but the point estimate was lower; the odds ratios were similar for persons who were exposed to smoke only at home and those who were exposed to smoke only outside the home. Other characteristics associated with pneumococcal disease included chronic illness, particularly chronic obstructive pulmonary disease and cirrhosis, living with children under the age of six years who attended day-care centers, and characteristics associated with low socioeconomic status (low educational level and low income, lack of health insurance [or only Medicaid coverage], and household crowding). Patients were less likely than control subjects to consume moderate amounts of alcohol and were more likely to be heavy drinkers.

**Multivariable Analysis**

Covariates that were not significant (by the likelihood-ratio test) were removed from the initial model in the following sequence: household crowding, health insurance status, annual household income, level of alcohol consumption, and presence or absence of asthma. The elimination of these variables did not appreciably change the regression coefficients for the independent risk factors included in the final model (Table 4). Patients were 4.1 times as likely as control subjects to be current smokers (95 percent confidence interval, 2.4 to 7.3). Nonsmoking patients were 2.5 times as likely to be exposed to environmental tobacco smoke as nonsmoking controls (95 percent confidence interval, 1.2 to 5.1). When they were entered into the model individually, the effects of chronic obstructive pulmonary disease, heart failure, cirrhosis, and diabetes were not significant. However, when these variables were incorporated into the predefined variable of chronic illness, the presence of chronic illness was a significant independent risk factor (P=0.005). In addition, male sex, black race, and a low level of education were significantly associated

**TABLE 3.** DEMOGRAPHIC, MEDICAL, AND SOCIOECONOMIC CHARACTERISTICS
ASSOCIATED WITH INVASIVE PNEUMOCOCCAL DISEASE IN IMMUNOCOMPETENT ADULTS
18 TO 64 YEARS OLD.*

| CHARACTERISTIC | PATIENTS (N=228) | CONTROL SUBJECTS (N=301) | ODDS RATIO (95% CI)† |
|---|---|---|---|
| | no. (%) | | |
| Male sex | 125 (56) | 70 (29) | 3.1 (2.1–4.6) |
| Black race | 101 (44) | 68 (23) | 3.2 (2.1–4.8) |
| Chronic obstructive pulmonary disease‡ | 26 (12) | 11 (4) | 3.4 (1.6–7.0) |
| Heart failure | 3 (1) | 1 (<1) | 3.7 (0.4–36.1) |
| Cirrhosis | 8 (4) | 1 (<1) | 12.2 (1.5–101.7) |
| Diabetes | 23 (10) | 12 (4) | 2.5 (1.2–5.1) |
| Asthma (treated) | 32 (15) | 18 (6) | 2.5 (1.4–4.7) |
| Chronic illness§ | 53 (23) | 25 (8) | 3.3 (1.9–5.5) |
| Indication for receipt of pneumococcal vaccine¶ | 64 (28) | 27 (9) | 4.0 (2.4–6.5) |
| Pneumonia in past 5 yr | 32 (14) | 20 (7) | 2.3 (1.3–4.3) |
| Upper respiratory tract infection in past month | 146 (64) | 128 (43) | 2.4 (1.7–3.5) |
| Level of education‖ | | | |
|   Less than high school | 52 (25) | 23 (9) | 7.3 (3.8–13.9) |
|   High-school graduate | 121 (57) | 127 (48) | 3.0 (1.9–4.7) |
|   College graduate | 38 (18) | 117 (44) | 1.0 |
| Medical insurance status | | | |
|   No insurance, or Medicaid coverage | 66 (29) | 45 (15) | 2.7 (1.7–4.2) |
|   Private, HMO, or PPO | 161 (71) | 256 (85) | 1.0 |
| Annual household income | | | |
|   <$15,000 | 56 (28) | 34 (13) | 3.9 (2.2–6.9) |
|   $15,000–$45,000 | 99 (49) | 102 (40) | 2.6 (1.6–4.0) |
|   ≥$45,000 | 47 (23) | 119 (47) | 1.0 |
| Household crowding** | 67 (31) | 47 (16) | 2.4 (1.6–3.8) |
| Smoking status†† | | | |
|   Current smoker | 130 (58) | 72 (24) | 5.4 (3.4–8.5) |
|   Former smoker | 23 (10) | 61 (21) | 1.2 (0.7–2.3) |
|   Passive exposure to smoke | 31 (14) | 38 (13) | 2.5 (1.4–4.5) |
|   Never smoked and no passive exposure to smoke | 40 (18) | 125 (42) | 1.0 |
| Alcohol consumption‡‡ | | | |
|   Heavy | 15 (7) | 2 (1) | 7.1 (1.7–30.3) |
|   Moderate | 108 (48) | 181 (60) | 0.7 (0.5–1.0) |
|   None | 103 (46) | 118 (39) | 1.0 |
| Status of children in household | | | |
|   <6 yr old, in day care | 35 (15) | 24 (8) | 2.3 (1.3–4.1) |
|   <6 yr old, not in day care | 29 (13) | 34 (11) | 1.4 (0.8–2.4) |
|   No children <6 yr old | 163 (72) | 240 (81) | 1.0 |

*Only subjects on whom data were available are included. CI denotes confidence interval, HMO health maintenance organization, and PPO preferred-provider organization. Because of rounding, percentages do not always total 100.

†The Mantel–Haenszel method was used to calculate summary odds ratios for frequency-matched data in stratified analyses (adjusted for age and study area).

‡This category includes chronic bronchitis and emphysema.

§Chronic illness was defined as one or more of the following conditions: chronic obstructive pulmonary disease (including chronic bronchitis and emphysema), heart failure, cirrhosis, and diabetes.

¶The indications for receipt of vaccine are listed in the recommendations of the Advisory Committee on Immunization Practices.[1]

‖The level of education was determined for 211 patients and 267 control subjects who were at least 25 years old.

**Crowding was defined as more than 0.67 person per room (75th percentile of the distribution among controls).

††See the Methods section for definitions of smoking status. Because the number of former smokers with passive exposure to smoke (seven patients and eight control subjects) was too small for consideration as an independent group, these subjects were included in the "passive exposure to smoke" category.

‡‡Heavy drinking was defined as the consumption of at least 25 alcoholic drinks per week in the previous month. Moderate drinking was defined as the consumption of more than 0 and fewer than 25 alcoholic drinks per week in the previous month.

**TABLE 4.** INDEPENDENT RISK FACTORS FOR INVASIVE PNEUMOCOCCAL DISEASE AMONG IMMUNOCOMPETENT ADULTS 18 TO 64 YEARS OLD.

| VARIABLE | ODDS RATIO (95% CI)* | P VALUE |
|---|---|---|
| Male sex | 2.7 (1.7–4.3) | <0.001 |
| Black race | 3.4 (2.0–5.6) | <0.001 |
| Chronic illness† | 2.6 (1.4–5.1) | 0.005 |
| Smoking status | | |
|   Current smoker | 4.1 (2.4–7.3) | <0.001 |
|   Former smoker | 1.1 (0.5–2.2) | 0.91 |
|   Passive exposure to smoke | 2.5 (1.2–5.1) | 0.01 |
|   Never smoked and no passive exposure to smoke | 1.0 | |
| Level of education | | |
|   Less than high school | 2.8 (1.3–5.9) | 0.007 |
|   High-school graduate | 2.0 (1.2–3.4) | 0.006 |
|   College graduate | 1.0 | |
| Status of children in household | | |
|   <6 yr old, in day care | 3.0 (1.5–6.2) | 0.003 |
|   <6 yr old, not in day care | 1.0 (0.5–2.0) | 0.99 |
|   No children <6 yr old | 1.0 | |

*Odds ratios and 95 percent confidence intervals were calculated in an unconditional logistic-regression analysis and were adjusted for age, study site, and all other variables in the table. The Hosmer and Lemeshow goodness-of-fit statistic was used for the model, 8.30, 8 df; P=0.41.

†Chronic illness was defined as one or more of the following conditions: chronic obstructive pulmonary disease (including chronic bronchitis and emphysema), heart failure, cirrhosis, and diabetes.

with pneumococcal disease. Patients were 3.0 times as likely as control subjects to live in a household with children under the age of six years who were in day care (95 percent confidence interval, 1.5 to 6.2). This association was strongest among patients who were 18 to 49 years of age. The population attributable risks for independent risk factors in the multivariable model were 51 percent for cigarette smoking, 17 percent for passive smoking (among nonsmokers), 14 percent for chronic illness, 57 percent for chronic illness and smoking combined, and 11 percent for living with young children who were in day care.

### Dose–Response Relations

Among current smokers, the adjusted odds ratios for invasive pneumococcal disease increased steadily from 2.3 to 5.5 with increases in the number of cigarettes smoked daily, suggesting a dose–response relation (Table 5). As compared with not smoking, an increased risk of invasive pneumococcal disease was observed for smoking cigarettes, and the risk increased linearly with increases in the number of cigarettes smoked (P<0.001). Among current and former smokers, the multivariate adjusted odds ratios increased from 1.5 to 3.2 with increasing number of pack-years of smoking (P=0.002), a finding also consistent with a dose–response relation. Although former smokers were not at increased risk overall, an association was observed with the length of time since quitting (P= 0.001). The risk of pneumococcal disease decreased

by 14 percent per year after the subjects quit smoking, returning to the level of those who had never smoked after approximately 13 years. Among nonsmokers, the risk increased with an increasing duration of passive exposure to smoke.

## DISCUSSION

Our results indicate that cigarette smoking is the strongest independent risk factor for invasive pneumococcal disease among immunocompetent, nonelderly adults and that 51 percent of the disease burden in this population group can be attributed statistically by this modifiable risk factor. We found that the current number of cigarettes smoked per day, the number of pack-years of smoking, and the time since quitting showed clear dose–response relations with the risk of pneumococcal disease. Increased risk was also independently associated with exposure to environmental tobacco smoke, chronic illness, a low level of education, black race, male sex, and living with young children who were in day care.

Differences in the distribution of factors associated with both smoking and pneumococcal disease, such as chronic illness (particularly chronic lung disease), alcohol consumption, and low socioeconomic status, could confound the association with smoking. However, adjustment for multiple demographic, medical, and socioeconomic characteristics did not appreciably change the crude estimates, suggesting that confounding by these factors was relatively minor.

In most areas of the United States, more than 90 percent of adults live in households with telephones, and control subjects selected by random-digit dialing have been shown to be representative of the general population in most respects.[18] However, this method necessarily excludes people without telephones, such as the homeless. Although random-digit dialing may have resulted in overrepresentation of women, the selection of controls was unlikely to depend on exposure status, and the missing information on the sex of the control subjects was probably nondifferential. The effects of sex and race were controlled for in multivariable analysis. Among selected control subjects, the proportions of blacks, current smokers, former smokers, and persons who had never smoked (with stratification according to sex and race) were similar to those among adults in the general population of the surveillance areas,[13] suggesting that the sample was representative. In addition, the estimates of the effects of smoking were consistently similar in different demographic groups (data not shown). The prevalence of moderate alcohol consumption and of abstinence among the controls was also similar to that in the general-population estimates,[13] but underreporting and misclassification are possible, particularly among heavy drinkers. Heavy use of alcohol has been associated with pneumococcal infections in other studies.[3,10] Because of the small number of persons who

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**TABLE 5.** RELATION OF THE INTENSITY OF CIGARETTE SMOKING, CUMULATIVE EXPOSURE, REVERSIBLE EXPOSURE, AND PASSIVE SMOKING TO THE RISK OF INVASIVE PNEUMOCOCCAL DISEASE.*

| GROUP AND VARIABLE | PATIENTS | CONTROL SUBJECTS | ODDS RATIO ADJUSTED FOR AGE AND STUDY AREA (95% CI)† | ODDS RATIO ADJUSTED FOR MULTIPLE VARIABLES (95% CI)‡ | P VALUE |
|---|---|---|---|---|---|
| | no. (%) | | | | |
| **Current smokers** | | | | | |
| No. of cigarettes smoked§ | | | | | |
| Reference category (0/day) | 92 (42) | 224 (76) | 1.0 | 1.0 | |
| 1–14/day | 48 (22) | 39 (13) | 2.8 (1.7–4.6) | 2.3 (1.3–4.3) | 0.006 |
| 15–24/day | 41 (19) | 19 (6) | 5.3 (2.9–9.7) | 3.7 (1.8–7.8) | <0.001 |
| ≥25/day | 37 (17) | 13 (4) | 7.3 (3.7–14.5) | 5.5 (2.5–12.9) | <0.001 |
| P for trend | | | <0.001 | | |
| **Current and former smokers** | | | | | |
| Pack-years of smoking¶ | | | | | |
| Reference category (0 pk-yr) | 64 (30) | 155 (53) | 1.0 | 1.0 | |
| 1–14 pk-yr | 70 (33) | 85 (29) | 1.9 (1.2–3.0) | 1.5 (0.9–2.5) | 0.10 |
| 15–29 pk-yr | 29 (14) | 26 (9) | 2.8 (1.5–5.4) | 3.0 (1.4–6.6) | 0.006 |
| ≥30 pk-yr | 50 (23) | 24 (8) | 5.2 (2.8–9.6) | 3.2 (1.6–6.9) | 0.002 |
| P for trend | | | <0.001 | | |
| **Former smokers** | | | | | |
| Years since quitting smoking‖ | | | | | |
| Reference category (never smoked) | 64 (62) | 155 (76) | 1.0 | 1.0 | |
| <5 yr | 20 (19) | 11 (5) | 4.7 (2.1–10.4) | 3.5 (1.3–9.8) | 0.02 |
| 5–9 yr | 9 (9) | 11 (5) | 2.3 (0.9–6.1) | 3.7 (1.1–13.2) | 0.04 |
| ≥10 yr | 10 (10) | 28 (14) | 1.0 (0.4–2.2) | 0.6 (0.2–1.3) | 0.18 |
| P for trend | | | <0.001 | | |
| **Nonsmokers** | | | | | |
| Level of exposure to environmental tobacco smoke | | | | | |
| Reference category (no exposure) | 40 (59) | 125 (80) | 1.0 | 1.0 | |
| 1–4 hr/day | 16 (24) | 25 (16) | 2.0 (1.0–4.1) | 2.4 (0.9–6.3) | 0.08 |
| >4 hr/day | 12 (18) | 7 (4) | 4.9 (1.8–15.0) | 3.9 (1.0–16.1) | 0.05 |
| P for trend | | | <0.001 | | |

*Only subjects on whom data were available are included. CI denotes confidence interval. Because of rounding, percentages do not always total 100.

†The Mantel–Haenszel method was used to calculate summary odds ratios for frequency-matched data in stratified analyses (adjusted for age and study area).

‡Odds ratios and 95 percent confidence intervals were calculated by unconditional logistic-regression analysis and were adjusted for the following variables: age, study site, sex, race, presence or absence of chronic illness, level of education, and status of children under six years of age in the household.

§Information concerning the number of cigarettes smoked per day was available for 126 patients and 71 control subjects who were current smokers.

¶For current and former smokers, the number of pack-years of smoking was calculated as the number of packs (20 cigarettes per pack) per day multiplied by the years of smoking. Information concerning pack-years of smoking was available for 149 patients and 135 control subjects who were current or former smokers.

‖The risk of pneumococcal disease in former smokers equaled that of those who had never smoked approximately 13 years after they quit smoking, calculated from the following regression equation: Ln OR=1.7962 + years (−0.1368).

reported heavy drinking, our study did not have the statistical power to assess the relation between smoking and heavy consumption of alcohol.

The rates of disease in our study and in other studies[2,4,10] were higher among men and blacks. Male sex and black race remained independent risk factors even after adjustment for possible confounders. The reasons for geographic variation in the reported incidence of pneumococcal disease are unclear. Because the surveillance methods in each study area were standardized and had a high sensitivity,[11] the differences in rates between the U.S. sites and the Canadian site may reflect differences in clinical practice (such as the frequency of obtaining blood for

cultures from patients with pneumonia) or the racial or ethnic composition of the populations.

Exposure to environmental tobacco smoke is widespread in both the home and the workplace.[19] Among children, parental smoking has been linked with certain respiratory illnesses.[5,20-22] Among adults, passive smoking has also been implicated as a risk factor for meningococcal disease, but the association with pneumococcal disease has not been reported.[23,24]

The specific biologic mechanisms by which exposure to tobacco smoke increases the risk of pneumococcal disease are poorly understood. Cigarette smoke impairs mucociliary clearance, enhances bacterial adherence, and disrupts the respiratory epithelium.[25-28] In some studies, smokers had serum immunoglobulin levels that were 10 to 20 percent lower than those of nonsmokers.[29,30] However, smokers also had increased levels of pneumococcal antibodies, possibly as a consequence of frequent respiratory tract infections or higher rates of carriage.[31]

Higher rates of nasopharyngeal colonization with meningococcus have been observed among active and passive smokers than among nonsmokers.[32,33] Exposure to pneumococcus is common, and in some studies, smokers had higher rates of pneumococcal carriage than nonsmokers.[34,35] Smokers may be more susceptible than nonsmokers to viral infections of the respiratory tract, such as influenza,[36,37] and a recent history of an upper respiratory tract illness or a coexisting illness may increase the risk of invasive pneumococcal disease.[38,39]

Young children who attend day-care centers are at increased risk for invasive pneumococcal disease.[40,41] We found an increased risk of disease among adults who lived with children who attended day-care centers, and the risk is probably associated with increased exposure to colonizing bacteria. The carriage rates of *S. pneumoniae* are highest among young children and are higher among adults with preschool children than among adults without preschool children.[42] In some studies, children attending day-care centers had higher rates of carriage than those who were not in day care.[43,44]

The rates of pneumococcal disease are higher in low-income census tracts than in those with high incomes.[2,10,45,46] After adjustment for other covariates in the multivariable model, a low household income was not significantly associated with the risk of illness, but a low level of education was a strong independent risk factor. The prevalence of smoking varies inversely with the level of education,[47-49] which is the most commonly used measure of socioeconomic status.[50] The level of education is more consistently associated with illness and risk factors (such as cigarette smoking) than is income or occupation.[51]

Smoking is the most common cause of chronic obstructive pulmonary disease, and the rate of pneumococcal disease is high among patients with chron-ic obstructive pulmonary disease,[10,52] probably because of defective clearance mechanisms. Although chronic lung disease is an important confounder, the numbers of study subjects with chronic obstructive pulmonary disease or other specific chronic medical conditions were too small for an independent analysis in the multivariable model. In our study, only 13 percent of current smokers had chronic lung disease. The presence of any chronic illness for which pneumococcal vaccine is recommended was an independent risk factor for invasive pneumococcal disease, but the population attributable risk was relatively low because of the low prevalence in the age group studied.

Fewer than one third of the patients had a condition for which pneumococcal vaccine is recommended.[1] Although our study was not specifically designed to ascertain vaccination status or evaluate the efficacy of vaccination,[53] the self-reported prevalence of pneumococcal vaccination was similar to that in national surveys in this age group (CDC: unpublished data). Because the vaccine is effective against bacteremia among immunocompetent adults,[53,54] persons with underlying chronic illnesses should be vaccinated.[1] Our results support the evaluation of persons 50 years of age for indications for pneumococcal vaccine,[1,55] because of the high prevalence of risk factors in this group. Although the risk of pneumococcal disease decreased with time since quitting smoking, former smokers appear to be at increased risk for at least 10 years after they quit. Therefore, it may be reasonable to incorporate the pneumococcal vaccine into smoking-cessation programs as well as to consider vaccinating those who continue to smoke.

Our study documents yet another example of an adverse health effect linked to active and passive smoking. In 1995, 47 million adult Americans, about one fourth of the U.S. adult population, smoked cigarettes.[49] Because of the high prevalence of smoking and the high population attributable risk for smoking, the implications of our results for prevention are important. Reducing the prevalence of cigarette smoking to 15 percent[56] could reduce the incidence of invasive pneumococcal disease among nonelderly adults by approximately 18 percent, preventing approximately 4000 cases in the United States annually (CDC: unpublished data). Studies should be conducted to determine how the incidence of pneumococcal disease is affected by programs to prevent people from starting smoking and to encourage smoking cessation,[57] as well as by regulatory approaches intended to reduce both smoking and exposure to environmental smoke.[19] Our findings may also be of interest to advisory bodies that are responsible for formulating recommendations for pneumococcal vaccination.

## APPENDIX

The members of the Active Bacterial Core Surveillance Team are as follows: Atlanta Veterans Affairs Medical Center, Atlanta — W.S. Baughman and L. Rhodes; Johns Hopkins University School of Hygiene and Public Health, Baltimore — L. Billmann; Maryland Department of Health and Mental Hygiene, Baltimore — D.M. Dwyer; Princess Margaret Hospital, Toronto — E. Goldenberg; Centers for Disease Control and Prevention, Atlanta — A. Kraus, B. Plikaytis, K. Robinson, and A. Schuchat.

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