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ORIGINAL RESEARCH & CONTRIBUTIONS

Passive Cigarette Smoke Exposure and Other Risk Factors for Invasive Pneumococcal Disease in Children: A Case-Control Study

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ABSTRACT

Objective: To investigate whether passive cigarette smoke exposure increases the risk of invasive pneumococcal disease in children.

Methods: In a population-based case-control study, 171 children aged 0 to 12 years with culture-confirmed invasive pneumococcal disease during the years 1994 to 2004 were identified. Two controls were matched to each case on age and patterns of Health Plan membership. We reviewed medical records of subjects and family members for information on household cigarette smoke exposure within 2 years of the diagnosis of invasive pneumococcal disease. We collected information on sex, race, pneumococcal vaccination, selected medical conditions, and medications in the 3 months before the diagnosis.

Results: Similar proportions of cases (25%) and controls (30%) had definite or probable passive smoke exposure (odds ratio [OR] = 0.76, 95% confidence interval [CI] = 0.47-1.2). Cases of invasive pneumococcal disease were more likely to be nonwhite than controls (OR = 4.4, 95% CI = 2.3-8.2). Elevated risk of invasive pneumococcal disease was found in subjects with recent pulmonary diagnoses (OR = 2.2, 95% CI = 1.2-4.0) and recent antibiotic use (OR = 1.6, 95% CI = 1.1-2.3).

Conclusions: Passive cigarette smoke exposure was not associated with invasive pneumococcal disease in this pediatric population. Invasive pneumococcal disease was associated with recent pulmonary diagnoses and recent antibiotic use.

INTRODUCTION

Streptococcus pneumoniae commonly causes bacterial infections among children. It is the predominant bacterial agent of acute otitis media, the most common pediatric outpatient diagnosis and reason for antibiotic prescriptions.[1] It causes bacterial pneumonia among patients of all ages. Before routine immunization of US children with pneumococcal conjugate vaccine began in 2000, S pneumoniae was the most common bacteria in blood cultures from young febrile pediatric outpatients.[2] Invasive pneumococcal disease, defined as isolation of S pneumoniae from a normally sterile site (eg, blood, cerebrospinal fluid, synovial fluid, pericardial fluid, pleural fluid, or peritoneal fluid), is more common among children younger than age 2 years.[3]

The potential relationship in children between environmental smoke exposure and pneumococcal disease has been reported. In The Gambia, invasive pneumococcal disease was associated with secondhand exposure to tobacco or cooking fire smoke.[4] In Alaskan children, invasive pneumococcal disease was associated with a tobacco smoker living in the child's household.[3] In Finland, invasive pneumococcal disease among children was associated with smoking by the child's mother.[5] In a 2000 US case-control study of immunocompetent adults, invasive pneumococcal disease was associated with cigarette smoking and with passive smoking.[6]

To investigate whether passive exposure to cigarette smoke increases the risk of invasive pneumococcal disease among children aged 0 to 12 years, we performed a population-based case-control study among members of a US integrated health care plan using Health Plan medical records.

METHODS

Subjects

This study was conducted in the population of the Kaiser Permanente Northwest (KPNW) Health Plan, which numbered 404,778 persons in 1994, including 9362 persons aged 0 to 2 years and 65,735 children aged 3 to 12 years. Cases of invasive pneumococcal disease were identified from a microbiology laboratory database or from medical records with the International Classification of Diseases, Ninth Revision (ICD-9) codes corresponding to invasive pneumococcal disease (038.x and 320.x). Cases identified through ICD-9 codes were not considered eligible unless the medical record documented that the *S pneumoniae* infection was confirmed by culture. Cases were collected from 1994 to 2004. These subjects were aged 0 to 12 years when the culture that yielded *S pneumoniae* was collected, and they had at least 1 month of Health Plan coverage before culture collection. The reference date was defined as the date of culture collection.

Two controls per case were randomly selected from KPNW membership files and were matched to cases by age, Health Plan membership on the reference date, and length of membership in KPNW before the reference date. We matched on Health Plan membership patterns to equalize access to past

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medical history. Because our study design involved collecting information from the medical records of family members, we also matched cases and controls on whether the Health Plan account included the child alone (indicative of Medicaid and other publicly funded members) or the child plus others. KPNW's institutional review board approved the study design and procedures. In our statistical power calculation assuming 170 cases with $\alpha = 0.05$ and a 2-tailed test, we estimated that we would have excellent power to detect an odds ratio (OR) of 2 or above and fair power to detect an association of 1.8.

Data Collection

Trained medical record abstractors reviewed the outpatient medical records of each case, each control, and all other individuals on their respective Health Plan account. Unless otherwise noted, we assumed that all persons listed on a Health Plan account were from one household. Persons eligible to enroll in a Health Plan account include the subscriber, a spouse or domestic partner, their children, their grandchildren, and other children for whom an eligible adult is the legal guardian.

We collected information about household exposure to passive cigarette smoke from birth through the reference date and, if documented, smoking history for all adults in the household. Information on household smoking is routinely collected by a nurse at the mother-baby visit, occurring approximately three days after nursery discharge. From each sibling's chart, information on household cigarette smoking was collected from two years before the subject's birth through the reference date. From the subjects' charts, we also collected other information, including sex, race, height, weight, pneumococcal vaccination, medical conditions associated with increased risk of invasive pneumococcal disease,[1,7] medical history, medications in the three months before the reference date, history of being breastfed, and daycare attendance. From the chart of each adult, we collected smoking history from two years before the subject's birth through the reference date. The accuracy of smoking history documentation for adults using the same electronic medical record system was validated in a recent study from Kaiser Permanente Southern California.[8]

We defined passive cigarette smoking as any secondhand exposure to cigarette smoke within two years up to and including the reference date. Using this definition, we developed exposure categories for the subjects on the basis of information in family members' charts about the smokers in the home and whether they smoked outside (Table 1). Three study investigators (CC, KR, SW) reviewed all smoking information collected from the medical records of all family members and manually coded the passive smoking variable for each subject.

We categorized subjects as being at high-risk of invasive pneumococcal disease if they had any of the following diagnoses from birth to the reference date: chronic cardiac disease, chronic pulmonary disease, diabetes mellitus, immunodeficiency, sickle cell anemia, cancer, chronic kidney disease, functional or anatomic asplenia, cerebrospinal fluid leak, and cystic fibrosis. Medical diagnoses in the three months before diagnosis of invasive pneumococcal disease were classified as ophthalmologic, ear/nose/throat (ENT), pulmonary, gastrointestinal, genitourinary, musculoskeletal, skin, neurologic, systemic, and infectious disease. Infectious disease was subclassified as viral, bacterial, and fungal.

Subjects with missing information on race were coded as white. The KPNW membership is 94% white and 6% African American, Hispanic, Asian, Native American, or other races and ethnicities.

Statistical Analysis

For the main analysis, we compared subjects classified as either "definitely exposed" or "probably exposed" to passive cigarette smoke with those classified as either "definitely not exposed" or "probably not exposed." A secondary analysis

Table 1. Definitions of passive smoke exposure categories

Exposure category	Definition
Definitely exposed	All 3 of the following: At least 1 person smokes recorded within 2 years of RD No conflicting information from family members' charts No mention in child's chart that smoker smokes outside
Probably exposed	Conflicting information on smoking in household but at least 1 record stating there is a smoker in household *or* Meets criteria for "definitely exposed" and child's record mentions that all smokers smoke outside *or* Meets criteria for "definitely exposed" and only available information is recorded > 2 years before RD
Probably not exposed	One parent is nonsmoker. No smoking information on other parent *or* Child's record states household is nonsmoking and 1 or more adults quit smoking within the last 5 years or quit at an unknown date *or* Any family member's record states that no one in household smokes *or* Both parents documented as nonsmokers or former smokers but information on at least one parent is > 2 years before RD
Definitely not exposed	Unequivocal information from child's record within 2 years before RD that no one in household smokes *or* Information within 2 years before RD that both parents are nonsmokers. Any former-smoker parents quit more than 5 years before RD.
Unknown	No smoking-related information found in subject's or any family member's medical record

RD = reference date (date of culture collection).

compared subjects classified as "definitely exposed" with those classified as "definitely not exposed"; although statistical power for this comparison was smaller, fewer misclassification errors were expected.

We evaluated the relationship between passive smoke exposure and invasive pneumococcal disease using conditional and unconditional logistic regression analysis; although controls were individually matched to cases, the general nature of the demographic matching variables permitted unconditional analysis.[9] Results were very similar, and we report conditional results here for all analyses except the subanalysis comparing "definitely exposed" to "definitely not exposed," for which we used unconditional logistic regression to retain subjects whose matched cases or controls had been excluded. For that analysis, conditional logistic regression produced a similar but less precise result because of exclusion of discordant cases and controls in the estimation. Conditional logistic regression results were adjusted for months of membership in the Health Plan during the last unbroken period of membership (linear) and earlier membership in the Health Plan (yes/no). The unconditional logistic regression model was further adjusted for the matching variables age (linear), Health Plan area (Portland, OR/Vancouver, WA metropolitan area vs Kelso/Longview, WA, and Salem, OR, areas), and whether family members were in the Health Plan (yes/no).

Because we did not know passive smoke exposure status for a substantial number of study subjects, we performed sensitivity analysis by bracketing exposure and comparing results. First, we put all subjects with unknown smoking history in the "definitely or probably exposed" group and ran the main logistic model; then we put all subjects with missing data in the "definitely not or probably not" exposed group and ran the main model again. We compared these results with a model in which we excluded subjects with unknown smoke exposure history. Results were similar, and we present the models excluding unknowns.

We evaluated for confounding by adding other potential risk factors one at a time to the smoke/invasive pneumococcal disease logistic models. We defined confounding as a change of more than 10% in the OR for smoke exposure/invasive pneumococcal disease with the potential confounder added to the model. Using multiplicative interaction terms and comparison of stratum-specific ORs, we assessed whether the smoke/invasive pneumococcal disease results differed according to the following characteristics: sex, race (white vs nonwhite), age group (0-2 years vs 3-12 years), high-risk status (yes/no), family members in Health Plan (yes/no), and years of conjugate vaccine availability (2000-2004 vs 1994-1999).

RESULTS

We identified 171 culture-confirmed invasive pneumococcal disease cases, all of whom presented with fever (Table 2). One hundred sixty-eight cases were identified from the laboratory database, and 3 were identified from ICD-9 codes. More than three-fourths of the cases (78%) were aged 2 years or younger. Cases were more likely than controls to be nonwhite (26% vs 10% of subjects with known race). During 1994-1999, the incidence of invasive pneumococcal disease was 26.8 cases per 100,000 person-years; 0.8% of cases and 0.4% of controls had received the pneumococcal polysaccharide vaccine, and the median number of invasive pneumococcal disease cases per year was 20. During 2000 to 2004, the incidence of invasive pneumococcal disease was 14.3 cases per 100,000 person-years; 19% of cases and 24% of controls had received pneumococcal conjugate vaccine, and the median number of annual cases decreased to 6.

Similar proportions of cases (25%) and controls (30%) had definite or probable passive smoke exposure (OR = 0.76, 95% confidence interval [CI] = 0.47-1.23; Table 3). For 20% of cases and 14% of controls, we were unable to find smoke exposure information. When we compared the "definitely exposed" group with the "definitely not exposed" group, results were similar (OR = 0.97, 95% CI = 0.50-1.88; Table 3); sensitivity analysis showed no material change in results (data not shown). These results were not confounded by sex, race, high-risk status, or other health conditions. Because of incomplete information in the medical record, we had insufficient information to assess confounding by history of being breastfed, daycare attendance, and number of household members.

Table 2. Characteristics of cases and controls

Factor	Cases (n = 171) No. (%)	Controls (n = 342) No. (%)
Source of case		
Laboratory database	168 (98)	NA
ICD-9 diagnoses	3 (2)	NA
Year of diagnosis or reference date		
1994-1999	119 (70)	238 (70)
2000-2004	52 (30)	104 (30)
Age group (years)		
0-2	134 (78)	270 (79)
3-5	19 (11)	36 (11)
6-12	18 (11)	36 (11)
Male sex	83 (49)	184 (54)
Race		
White	95 (56)	148 (43)
African American	11 (6)	8 (2)
Asian	9 (5)	4 (1)
Hispanic	9 (5)	4 (1)
Other	5 (3)	3 (1)
Not in medical chart	42 (25)	175 (51)
Family medical records available	147 (86)	294 (86)
Any pneumococcal vaccination (1994-2004)	11 (6)	26 (8)
Polysaccharide (1994-2004)	1	1
Conjugate (2000-2004)	10	25
4 doses	6	12
1-3 doses	4	13

ICD-9 = International Classification of Diseases, Ninth Revision; NA = not applicable.

We computed ORs for the association between invasive pneumococcal disease and other measured factors (Table 4). Cases of invasive pneumococcal disease were 4 times more likely to be nonwhite than controls. Children with the diagnosis of chronic asthma did not have a significantly elevated risk of invasive pneumococcal disease. However, a medical visit for asthma in the 3 months before the reference date was the most common pulmonary diagnosis. Of the 47 pulmonary diagnoses, the most common besides asthma were cough and bronchiolitis. During the 3 months before the reference date, subjects with pulmonary diagnoses had an elevated risk of invasive pneumococcal disease (OR = 2.2, 95% CI = 1.2-4.0).

The data also suggest an association between invasive pneumococcal disease and gastrointestinal diagnoses (OR = 1.8, 95% CI = 0.96-3.4), as well as with ENT conditions (OR = 1.33, 95% CI = 0.92-1.93). The association with ENT conditions was not substantially influenced by the specific diagnosis of otitis media (OR = 1.20, 95% CI = 0.78-1.84); the OR for the association of invasive pneumococcal disease with ENT conditions other than otitis media was 1.34 (95% CI = 0.80-2.23).

Antibiotic use during the 3 months before the reference date was related to invasive pneumococcal disease (Table 4). We observed higher ORs in children with 2 or more prescriptions during this period (OR = 2.1, 95% CI = 1.2-3.8) than in those with 1 prescription (OR = 1.4, 95% CI = 0.88-2.3). When we examined the timing of the most recent prescription, ORs for 0 to 30 days, 31 to 60 days, and 61 to 90 days before the reference date were 1.9 (95% CI = 1.1-3.2), 1.6 (95% CI = 0.89-3.0), and 1.2 (95% CI = 0.60-2.5), respectively.

Overall, few subjects had received pneumococcal vaccination (6% of cases, 8% of controls). During a nationwide shortage of pneumococcal conjugate vaccine from November 2003 to September 2004, many children 0 to 2 years of age received only the first 1 to 3 doses of the 4-dose series per recommendations from the Centers for Disease Control and Prevention in Atlanta, GA.

DISCUSSION

Parental cigarette smoking has been associated with increased nasopharyngeal carriage of pneumococci in children.[10] Cigarette smoke exposure decreases mucociliary clearance,[11] enhances bacterial adherence to the respiratory epithelium,[12] and increases the permeability of the respiratory epithelium.[13] Passive smoke exposure is also associated with an increased incidence of viral upper respiratory tract infections,[11] which have been related to increased occurrence of invasive pneumococcal disease[14]; near doubling of the risk of developing a serious lower respiratory tract infection requiring hospitalization, especially in children younger than 2 years of age[15]; and a 28% increase in hospitalization for pneumonia and bronchitis in infants of mothers who smoke.[16]

Cigarette smoking is associated with alterations in immune system function, including decreased levels of circulating immunoglobulins, decreased natural killer cell activity, depressed neutrophil chemotaxis and phagocytic activity, and decreased release of proinflammatory cytokines.[17] Further research is

Table 3. Relation between cigarette smoke exposure and invasive pneumococcal disease

Smoke exposure category	Cases No. (%)	Controls No. (%)	Odds ratio (95% CI)
All subjects			
Definitely not exposed or probably not exposed	94 (55)	191 (56)	Reference
Definitely exposed or probably exposed	43 (25)	103 (30)	0.76 (0.47-1.23)[a]
No information in chart	34 (20)	48 (14)	—
Subjects classified as "definite"			
Definitely not exposed	35 (60)	85 (63)	Reference
Definitely exposed	23 (40)	50 (37)	0.97 (0.50-1.88)[b]

[a] Conditional logistic regression odds ratio adjusted for receipt of any pneumococcal vaccine and patterns of Health Plan membership. This analysis used 132 case-control sets with smoke exposure data on the case (n = 132, 30% exposed) and at least 1 of the 2 matched controls (n = 239, 35% exposed).

[b] Unconditional logistic regression odds ratio adjusted for age, presence of family members in Health Plan, area of residence, receipt of any pneumococcal vaccine, and patterns of Health Plan membership.

CI = confidence interval.

Table 4. Demographics and medical history in relation to invasive pneumococcal disease

Factor	Cases (n = 171) No. (%)	Controls (n = 342) No. (%)	Odds ratio[a] (95% CI)
Demographic			
Male sex	83 (49)	184 (54)	0.84 (0.58-1.22)
Nonwhite race[b]	34 (20)	19 (6)	4.37 (2.32-8.22)
Chronic conditions			
High-risk for IPD[c]	18 (11)	24 (7)	1.51 (0.77-2.94)
Chronic asthma	13 (8)	22 (6)	1.18 (0.57-2.45)
Pneumococcal vaccination	11 (6)	26 (8)	0.49 (0.12-2.03)
Diagnoses/events at visit < 3 months before reference date			
Antibiotic use	66 (39)	97 (28)	1.57 (1.06-2.33)
Ophthalmologic ICD-9	10 (6)	22 (6)	0.92 (0.42-1.99)
ENT ICD-9	76 (44)	128 (37)	1.33 (0.92-1.93)
Otitis media	46 (27)	81 (24)	1.20 (0.78-1.84)
Nonotitis media ENT ICD-9	30 (18)	47 (14)	1.34 (0.80-2.23)
Pulmonary ICD-9	24 (14)	23 (7)	2.20 (1.20-4.02)
Gastrointestinal ICD-9	19 (11)	21 (6)	1.81 (0.96-3.41)
Genitourinary ICD-9	6 (4)	7 (2)	1.77 (0.58-5.41)
Musculoskeletal ICD-9	5 (3)	6 (2)	1.59 (0.48-5.23)
Skin disease ICD-9	11 (6)	46 (13)	0.45 (0.22-0.90)
Neurologic ICD-9	4 (2)	10 (3)	0.79 (0.24-2.61)
Systemic disease ICD-9	8 (5)	10 (3)	1.69 (0.62-4.61)
Any infectious disease	85 (50)	146 (43)	1.33 (0.92-1.92)
Infectious disease: viral ICD-9	14 (8)	21 (6)	1.33 (0.65-2.72)
Infectious disease: fungal ICD-9	1 (1)	4 (1)	0.52 (0.06-4.70)
Infectious disease: bacterial ICD-9	5 (3)	5 (1)	1.80 (0.51-6.34)

[a] Conditional logistic regression odds ratios adjusted for patterns of Health Plan membership.

[b] Subjects with missing data on race (25% of cases and 51% of controls) were considered as white in this analysis.

[c] Includes asthma, chronic cardiac disease, chronic pulmonary disease, diabetes mellitus, immune deficiency, sickle cell anemia, cancer, chronic kidney disease, functional/anatomic asplenia, cerebrospinal fluid leak, and cystic fibrosis.

CI = confidence interval; ENT = ear/nose/throat; ICD-9 = International Classification of Diseases, Ninth Revision; IPD = invasive pneumococcal disease.

needed to investigate whether similar immune alterations occur among children with passive smoke exposure.

Epidemiologic research on cigarette smoke exposure and invasive pneumococcal disease in children is limited. Among Alaskan Native children aged 0 to 2 years, the risk of invasive pneumococcal disease was associated with presence of at least 1 tobacco smoker in the household and smokeless tobacco use by a household contact.[3] The small study size (29 cases, 85 controls) limited statistical power to evaluate these associations, particularly in multivariate analysis. Among children in Finland, daycare attendance and frequent otitis media were significantly associated with invasive pneumococcal disease in 0- to 2-year-old children, and among children aged 2 to 15 years, having a preschool-aged sibling was a risk factor.[5] Presence of a parent smoking daily inside the home did not increase the risk of invasive pneumococcal disease.[5] In a study of 0- to 15-year-old children in Spain, the risk of invasive pneumococcal disease was associated with siblings younger than age 15 years and with day nursery attendance. There was no significant association with smokers living in the child's home or with the number of cigarettes smoked in the home.[18] Our finding of no association between passive smoke exposure and invasive pneumococcal disease agrees with 2 of the aforementioned studies and a meta-analysis of the 1975-2009 literature.[19]

A large case-control study demonstrated that asthma was a risk factor for invasive pneumococcal disease among 2- to 17-year-old children.[20] Our study's association of a pulmonary diagnosis during the 3 months before the reference date with invasive pneumococcal disease may reflect asthma as a risk factor because the most common pulmonary diagnosis was asthma. Among the many 0- to 2-year-old subjects, an age group in whom asthma can be difficult to diagnose, some subjects diagnosed with cough or bronchiolitis may have been asthmatic.

Our finding that a higher proportion of cases of invasive pneumococcal disease than controls are nonwhite was previously described. In the US, African Americans, Alaskan Natives, and certain American Indians have a twofold to threefold higher rate of invasive pneumococcal disease compared with whites.[7] Possible reasons for more invasive pneumococcal disease among nonwhites include differences in medical care-seeking behavior and factors related to low socioeconomic status, such as transmission of respiratory diseases in crowded housing.

Other reported risk factors for invasive pneumococcal disease in children 2 to 59 months of age in North America include underlying illnesses (immunodeficiency HIV infection, sickle cell disease, cancer, kidney disease, asplenia, or splenic dysfunction); daycare attendance in the preceding 3 months; antibiotic use within the preceding 3 months; and lack of breastfeeding.[1,5,7,18] Our finding of a positive association with recent antibiotic use agrees with the findings of Takala et al[5] and Levine et al[1] and is expected because an antibiotic prescription is a surrogate marker for likely bacterial infection. Few children in our study had high-risk medical conditions, so we had little power to explore that association.

Limitations of our analysis include possible exposure misclassification. Health Plan members could share a Health Plan account yet live in different households, or children could be exposed to smoke from caregivers outside the home. Another limitation is that medical records may contain underreporting of smoking activity. We lacked information to adjust for breastfeeding, daycare attendance, or number of household members.

The relationship between invasive pneumococcal disease and recent pulmonary diagnoses is probably because of *S pneumoniae* causing bacterial pneumonia, bronchitis, sinusitis, and otitis media in children. Subjects with asthma may be more susceptible to invasive pneumococcal disease because of corticosteroid treatment of reactive airway disease or injured lower respiratory tract epithelium.

It is difficult to speculate on reasons for the possible association between recent gastrointestinal conditions and invasive pneumococcal disease. To our knowledge, our study is the first to report this association.

CONCLUSION

In this largest study to date examining whether passive smoke exposure increases the risk of invasive pneumococcal disease in children, we did not observe a positive association, as has been described in adults.[6] Ascertainment of passive smoke exposure from medical records was incomplete for 16% of subjects; however, sensitivity analysis confirmed that results were unchanged when subjects with unknown smoke exposure were classified as exposed or as unexposed. Given the incidence of smoking and the morbidities associated with passive smoke exposure, improved documentation of smoke exposure in the child's medical record is needed to facilitate better assessment of the patient's disease risk, target smoke avoidance advice, and counsel household contacts regarding tobacco cessation. The association of invasive pneumococcal disease with recent pulmonary diagnoses and with recent antibiotic use should be investigated further. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Who Could Stay and Not Perish

Smoking is … markedly impolite, an impertinent unsociability. Smokers poison the air near and far and suffocate every honest person who cannot defend himself by smoking in his turn. Who on earth can enter the room of a smoker without getting nauseated? And who could stay and not perish?

— Johan Wolfgang von Goethe, 1749-1832, German writer and statesman