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RESEARCH NOTE

Long-term ambient air pollution exposure and risk of sinonasal inverted papilloma

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Sinonasal inverted papilloma (IP) is a benign tumor with a propensity for malignant transformation in 5% to 7% of cases.[1] Although its pathogenesis remains uncertain, recent epidemiologic studies have implicated environmental and occupational exposures, such as organic solvents and welding fumes as potential contributors to IP.[2–4] A meta-analysis has showed that occupational exposure would increase the risk of developing sinonasal cancer.[5] Sham et al performed a case-control study on patients with IP and reported a higher incidence with outdoor occupations, such as construction.[4] They concluded this higher incidence is likely due to outdoor air pollution, but this effect has not been directly studied. Airborne fine particulate matter (particulate matter $\leq$2.5 μm in aerodynamic diameter [$PM_{2.5}$]) is the most noxious component of air pollution and has been associated with the development of nasopharyngeal and lung carcinoma among others.[6] Although $PM_{2.5}$ air pollution has been associated with eosinophilic chronic rhinosinusitis in mouse models, its role has not been studied previously in the pathogenesis of sinonasal IP.[7] Thus, the purpose of this study was to determine whether airborne $PM_{2.5}$ air pollution exposure is associated with the development of sinonasal IP. Data were extracted from a large academic, tertiary care medical center and analyzed ising a case-control approach.

PATIENTS AND METHODS

Cases were defined as new patients age $\geq$18 years of age and diagnosed with sinonasal IP according to *International Classification of Diseases*—ninth/tenth revision coding by a board-certified otolaryngologist based on pathology reports. Four controls without such diagnosis codes and with clear sinus computed tomography (CT) scans were selected for each case using the nearest neighbor strategy to match for age, gender, race, and IP diagnosis dates. Clinical characteristics (demographics and medical conditions) were extracted, along with the onset of IP, defined

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as the diagnosis date. Ambient $PM_{2.5}$ exposure levels were estimated based on validated prediction models.[8] Briefly, deep learning neural networks that incorporated meteorologic measurements, land-use terms, satellite-based measurements, and simulation outputs from a chemical transport model were used to predict daily concentrations of $PM_{2.5}$. We calculated the mean $PM_{2.5}$ exposures for each patient based on their residential address postal code at 12, 24, and 36 months before the diagnosis date.

This study aims to detect a large clinically relevant effect size with a Cohen's $d = 2.5$. A power analysis using two-tailed Student's t test, with an alpha of 0.05 and a power of 0.8, was performed. From this analysis, we found that 82 patients in each group would be required.

Conditional logistic regression models were used to determine the association between long-term $PM_{2.5}$ exposure and risk of developing IP. Adjusted odds ratios (ORs) and associated 95% confidence intervals (CIs) were obtained by adjusting for a priori confounding factors. Statistical analyses were conducted using STATA version 16.0 (StataCorp) and R version 4.1 (R Development Core Team).

This study was approved by the institutional review board of the Johns Hopkins University School of Medicine.

RESULTS

The characteristics of cases and their matched controls by age, sex, race, and diagnose date are shown in Table 1. We included 87 patients with IP pathogenesis and controls for the present analyses. The mean (standard deviation [SD]) ages of cases and control were 59.3 (SD, 15.8) years and 58.4 (SD, 15.3) years, respectively. A larger proportion of cases and controls were male and white. The mean PM air pollution levels of cases were significantly higher than for controls. Among cases, diabetes was the most prevalent comorbid disease (40.2%), followed by hypertension (13.8%) and asthma (10.3%). We adjusted for all these factors in the multivariate analysis.

In fully adjusted models, the ORs for the development of sinonasal IP associated with a 5-$\mu g/m^3$ increase in 12-, 24-, and 36-month $PM_{2.5}$ exposure were 2.65 (95% CI, 1.10-6.38), 2.68 (95% CI, 1.18-6.09), and 2.77 (95% CI, 1.25-6.11), respectively (Table 2).

DISCUSSION

Using sophisticated exposure estimates and a well-characterized cohort of patients, we have demonstrated that airborne $PM_{2.5}$ exposure may correlate with the presence of sinonasal IP. Previous studies examining environmental or occupational exposures have implicated increased rates of IP formation with an exposure to organic solvents, welding fumes, and organic solvents. Deitmer and Wiener performed a case-control study on 47 patients and found a significantly higher degree of occupational exposure to different kinds of smoke, dust, and aerosol in their case group.[9]

The mechanisms underlying the association between long-term air pollution and sinonasal IP are unclear. Inhalation of PM and absorption of its constituents into the bloodstream could result in high levels of reactive oxygen species, systemic inflammation, and epithelial barrier dysfunction as seen in previous studies.[7] The link between $PM_{2.5}$ and neoplasms is an evolving area of research with a primary focus on lung cancer. $PM_{2.5}$ is associated with epigenetic and microenvironmental alterations in lung cancer, including tumor-associated signaling pathway activation, DNA methylation, and increased levels of cytokines and inflammatory cells.[10] Similar changes may account for how $PM_{2.5}$ may be involved in the pathogenesis of IP formation even though it is a benign neoplasm, but further research is warranted.

Strengths of this study include a large, well-defined patient population (objective testing, otolaryngologist diagnosis), sophisticated matching for controls, who had clear sinus imaging, adjustment for confounding variables, and assessment of exposure with high spatial and temporal resolution. Study limitations include the retrospective design, which has inherent weaknesses related to coding accuracy, inability to assess causality, lack of residents' moving, detail smoking status, alcohol consumption and occupational information, lack of disease severity and transformation information, and potential sampling bias. Our $PM_{2.5}$ exposure model relied on mapping to the patient's residential address but did not account for other exposures (commuting, work) nor indoor ambient exposures. In addition, this study could be subject to bias and confounding due to the factors, which have not been measure and the diagnosis date usually after the initiation and development of the diseases.

To our knowledge, this is the first study to address the relationship between long-term exposure to fine particulate matter air pollution and sinonasal IP. We found that airborne $PM_{2.5}$ exposure was associated with the development of sinonasal IP. Further research into the effects of air pollution, including particulate matter, ozone, and NO_2, is warranted, especially in locations with a wider range of air pollution.

AUTHOR CONTRIBUTIONS

Z.Z. and M.R. contributed to data analysis, reporting, and drafting the work. W.K.M., N.R.L., S.B., and M.R.

TABLE 1 Demographics and clinical characteristics of participants

Characteristics	Controls, n = 348	Cases, n = 87	*p* Value
Age (year)	59.3 (15.8)	58.4 (15.3)	0.65
Male	227 (65.2)	58 (66.7)	0.90
Race			0.57
White	250 (71.8)	58 (66.7)	
Black	68 (19.5)	18 (20.7)	
Hispanic/Latino ethnicity	17 (4.9)	5 (5.7)	
Other	13 (3.7)	6 (6.9)	
12-month $PM_{2.5}$ average ($\mu g/m^3$)	9.2 (5.9-11.0)	9.6 (4.5-13.6)	0.03
24-month $PM_{2.5}$ average ($\mu g/m^3$)	9.4 (5.8-12.2)	9.9 (4.9-15.4)	0.02
36-month $PM_{2.5}$ average ($\mu g/m^3$)	9.6 (5.8-12.7)	10.1 (4.9-16.2)	0.01
BMI (kg/m^2)			0.51
Underweight (BMI <18.5)	6 (1.7)	1 (1.1)	
Normal weight (BMI 18.5 to ≤25)	116 (33.3)	23 (26.4)	
Overweight (BMI 25 to ≤30)	119 (34.2)	30 (34.5)	
Obese (BMI >30)	107 (30.7)	33 (37.9)	
Current smoking status (%)			0.95
Never smoker	188 (54.0)	46 (52.9)	
Current smoker	38 (10.9)	9 (10.3)	
Former smoker	122 (35.1)	32 (36.8)	
Current alcohol consumption	151 (43.4)	36 (41.4)	0.83
Hypertension	41 (11.8)	12 (13.8)	0.74
Diabetes mellitus	139 (39.9)	35 (40.2)	1.00
COPD	16 (4.6)	2 (2.3)	0.51
Asthma	27 (7.8)	9 (10.3)	0.57
Environmental allergy	9 (2.6)	3 (3.4)	0.94

Data expressed as mean (SD), mean (minimum-maximum), or count (%). Values calculated using the chi-square test for categorical variables and the Mann-Whitney *U* test for continuous variables.

BMI = body mass index; COPD = chronic obstructive pulmonary disease; PM = particulate matter; SD = standard deviation.

TABLE 2 Conditional logistic regression analyses for association between exposure to air pollution and sinonasal IP

Air pollution	Model 1	Model 2	Model 3
$PM_{2.5}$ 1 year	2.46 (1.03-5.86)	2.62 (1.09-6.30)	2.65 (1.10-6.38)
$PM_{2.5}$ 2 years	2.52 (1.12-5.67)	2.70 (1.19-6.17)	2.68 (1.18-6.09)
$PM_{2.5}$ 3 years	2.61 (1.20-5.72)	2.81 (1.27-6.22)	2.77 (1.25-6.11)

Data expressed as odds ratio (95% confidence interval). Model 1: adjusted for age, sex, and race; Model 2: additionally adjusted for BMI, current alcohol consumption status, and current smoking status; Model 3: additionally adjusted for the medical history of hypertension, diabetes, chronic obstructive pulmonary disease, and asthma.

BMI = body mass index; CI = confidence interval; IP = inverted papilloma; OR = odds ratio; PM = particulate matter.

contributed to revision and final approval of the work. All authors listed made substantial contributions to this work.

POTENTIAL CONFLICT OF INTEREST

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