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Exposure to daily ambient particulate polycyclic aromatic hydrocarbons and cough occurrence in adult chronic cough patients: A longitudinal study

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HIGHLIGHTS

- Exposure to ambient particulate PAHs may evoke cough in adult chronic cough patients.
- Non-asthma patients have marginally stronger associations.
- Effects may occur several days after exposure.

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ABSTRACT

The specific components of airborne particulates responsible for adverse health effects have not been conclusively identified. We conducted a longitudinal study on 88 adult patients with chronic cough to evaluate whether exposure to daily ambient levels of particulate polycyclic aromatic hydrocarbons (PAH) has relationship with cough occurrence. Study participants were recruited at Kanazawa University Hospital, Japan and were physician-diagnosed to at least have asthma, cough variant asthma and/or atopic cough during 4th January to 30th June 2011. Daily cough symptoms were collected by use of cough diaries and simultaneously, particulate PAH content in daily total suspended particles collected on glass fiber filters were determined by high performance liquid chromatography coupled with fluorescence detector. Population averaged estimates of association between PAH exposure and cough occurrence for entire patients and subgroups according to doctor's diagnosis were performed using generalized estimating equations. Selected adjusted odds ratios for cough occurrence were 1.088 (95% confidence interval (CI): 1.031, 1.147); 1.209 (95% CI: 1.060, 1.379) per 1 ng/m^3 increase for 2-day lag and 6-day moving average PAH exposure respectively. Likewise, 5 ring PAH had higher odds in comparison to 4 ring PAH. On the basis of doctor's diagnosis, non-asthma group had slightly higher odds ratio 1.127 (95% CI: 1.033, 1.228) per 1 ng/m^3 increase in 2-day lag PAH exposure. Our findings suggest that ambient PAH exposure

Abbreviations: PM, particulate matter; DEPs, diesel exhaust particles; PM_{10}, particulate matter less than 10 μm in aerodynamic diameter; $PM_{2.5}$, particulate matter less than 2.5 μm in aerodynamic diameter; PAH, polycyclic aromatic hydrocarbons; TNF-α, Turmor necrosis factor-alpha; IL-8, interleukin-8; TRPA1, transient receptor potential Ankyrin 1; CYP1A1, cytochrome P450 family 1 subfamily A member 1; NO, nitric oxide; HPLC, high performance liquid chromatography; IQR, interquartile range; CI, confidence interval; CVA, cough variant asthma; AC, atopic cough; TSP, total suspended particles; GEE, generalized estimating equation; Lag 0, 24-h before health outcome; MA-2, 2-day moving average (average of lag 0–2).

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is associated with cough occurrence in adult chronic cough patients. The association may be stronger in non-asthma patients and even at low levels although there is need for further study with a larger sample size of respective diagnosis and inclusion of co-pollutants.

1. Introduction

Exposure to ambient particulate matter (PM) increases mortality and morbidity related to respiratory diseases especially among susceptible individuals such patients with pre-existing chronic disease, children and the elderly (Anderson et al., 2012; McCreanor et al., 2007). Despite the strong association, it still remains to be determined which specific constituents of PM are responsible for the observed effects (Heo et al., 2014). Polycyclic aromatic hydrocarbons (PAH) are group of organic chemical compounds containing two or more benzene rings. PAH are widely spread in the environment and are closely linked to diesel exhaust particles (DEPs), $PM_{2.5}$ and PM_{10}. Exposures to PAH emitted from vehicular sources, cigarette smoking, cooking and space heating have been associated with various adverse health effects in children (Al-Daghri et al., 2013; Gale et al., 2012; Jung et al., 2015; Padula et al., 2015). In particular, exposure to PAH such as benz[*a*]anthracene, benzo[*a*]pyrene, benzo[*b*]fluoranthene, benzo[*g*,*h*,*i*]perylene, chrysene and dibenz[*a*,*h*]anthracene are linked to increased cough and wheeze at age of 12 months (Miller et al., 2004). However, few longitudinal studies have been done, on its association with cough occurrence in adult chronic cough patients. Besides studies that have investigated its effects among occupationally exposed workers (Clark et al., 2012), and volunteers in controlled experiments (Behndig et al., 2006), some have reported links to wheezing and lung function in non-smoking women (Jedrychowski et al., 2007), cough and bronchial hyperreactivity among firefighters (Landrigan et al., 2004). More studies are needed to elucidate on effects of ambient exposures whose levels might be lower than those encountered in experiments or occupationally, with regard to susceptible persons such as adult chronic cough patients.

PAH may exert adverse health effects by increasing production of pro-inflammatory mediators (e.g., TNF-α, IL-8) in lung cells via oxidative stress as well as stimulation of IgE production among other mechanisms (Koike et al., 2014; Li et al., 2002; Takenaka et al., 1995). Alternatively, recent studies have shown correlation between responses to environmental PM that contains PAH, with activation of airway sensory neurons that express Transient Receptor Potential Ankyrin-1 (TRPA1), and substance P (Deering-Rice et al., 2012; Shapiro et al., 2013). This has led to the suggestion that activation of TRPA1 considered as a probable target for DEP and DEP-associated electrophilic combustion by-products in the respiratory tract may mediate responses such as cough, dyspnea, neurogenic inflammation (Deering-Rice et al., 2012). However, epidemiological evidence that supports the hypothesis is scarce with only one study performed among adult workers (Smit et al., 2012).

Chronic cough is a common reason for seeking medical consultation with a primary care or respiratory physician, and can lead to decreased quality of life in the event of unsuccessful control (Chung and Pavord, 2008). Asthma, post-nasal drip or rhinosinusitis, and gastro-oesophageal reflux disease are recognizable clinical conditions that are related to chronic cough (Groneberg et al., 2004). Asthma is a chronic airway inflammatory condition characterized by repetitive cough, wheezing, dyspnea, reversible airway narrowing and airway hyperresponsiveness (Ohta et al., 2011). Furthermore, cough variant asthma (CVA) considered as a precursor of asthma (Corrao et al., 1979), and atopic cough (AC) are major causes of non-productive cough in Japan (Fujimura et al., 2003). With the prevalence of asthma is said to have increased over the past decade (Ohta et al., 2011) as well as rising cases of cough variant asthma and atopic cough amongst Japanese adults (Higashi et al., 2014), there is need to assess whether exposure to ambient PAH is related to cough occurrence in such subgroup of patients. It is suggested that chronic cough may result from hypersensitive response to environmental factors such as chemicals, cold air, smoke and Asian dust (Higashi et al., 2014; Matsumoto et al., 2012; Ternesten-Hasséus et al., 2011). Currently limited information is available about susceptibility of adult patients with asthma, cough variant asthma and/or atopic cough to ambient PAH. Information of any association with aggravating factors could be helpful during evaluation of patient history as well as in management of the condition (Pavord and Chung, 2008).

In the present study we hypothesized that exposure to ambient particulate PAH may activate TRPA1 in the lung cells of patients with chronic cough that could lead to increased cough occurrence. To test our hypothesis, a group of adult patients in Kanazawa city diagnosed with asthma, CVA and or AC were followed for a period of 6 months. Kanazawa is the headquarters of Ishikawa prefecture located in the central area bordering the Sea of Japan on the west side. Previous studies have suggested automobiles and long-range transport as the major contributors of atmospheric PAH (Tang et al., 2005; Yang et al., 2007). It has also been reported higher concentrations occur in winter attributable to temperature inversion phenomenon. However, it could be considered among the regions that records fairly low air pollution levels throughout the year. For these reasons assessment on relation between exposure to daily ambient PAH level with information on daily cough symptoms, atopy and exhaled nitric oxide (marker of airway inflammation) was performed.

2. Methods

2.1. Participants

Data used was from a longitudinal study performed from 4th January–30th June 2011 on 88 out of 99 (89%) patients who had given informed consent before participating in the study. Participants were recruited from outpatients receiving treatment at Kanazawa University Hospital, Ishikawa Prefecture, Japan. Medical Ethics Committee of Kanazawa University issued study approval. All were adult patients aged over 20 years and were physician-diagnosed to have at least asthma, CVA and/or AC during the study period. The composition included asthma (56%), asthma and AC (6%), CVA (9%), AC (18%), and both CVA and AC (11%). We divided them into two; asthma group (asthma, asthma and AC) and non-asthma group (CVA, AC, CVA and AC).

Diagnosis of asthma patients was made on basis of the Japan Asthma Prevention and Management Guidelines 2011 (Ohta et al., 2011). Cough variant asthma was diagnosed using the criteria of the Japanese Cough Research Society (Kohno et al., 2006). Atopic cough was diagnosed according to previously reported criteria