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Serum persistent organic pollutants levels and stroke risk☆

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ABSTRACT

Knowledge of environmental risk factors for stroke and their role are limited. We performed a case-cohort study to evaluate the association between serum persistent organic pollutants (POPs) level and stroke risk.

526 subcohort members and 111 stroke incidence cases were identified from the Korean Cancer Prevention Study-II. Serum levels of POPs were measured using gas chromatography/high-resolution mass spectrometry. The hazard ratios (HRs) for stroke (ischemic, hemorrhagic, and all stroke types) were estimated using the weighted Cox regression model. Age, sex, body mass index, smoking status, physical activity, family history of cardiovascular disease, and hypertension were adjusted in the weighted Cox regression model.

After adjusting for potential confounding factors, increased risk for stroke was observed among participants with serum concentration of p,p'-DDE in the highest tertile compared to those in the lowest tertile (HR = 4.10, 95% CI: 1.58, 10.59). A similar association was estimated for PCB118 (HR = 2.33, 95% CI: 1.04, 5.22), PCB156 (HR = 3.42, 95% CI: 1.42, 8.23), and PCB138 (HR = 3.80, 95% CI: 1.48, 9.76). For TEQ, stroke was three times as likely to occur among subjects with TEQ in the highest tertile compared to those in the lowest tertile (HR = 3.12, 95% CI: 1.27, 7.65). PCBs were positively associated with ischemic stroke, but not with hemorrhagic stroke.

Elevated serum POPs levels were associated with an increased risk of stroke, especially ischemic stroke.

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1. Introduction

According to the World Health Organization (WHO), stroke is the second leading cause of death worldwide (WHO, 2014). Although conventional risk factors for stroke such as obesity and aging were described, knowledge of other environmental risk factors and their role in stroke are unclear.

Persistent organic pollutants (POPs) are endocrine disrupting chemicals which are persistent, bioaccumulative, toxic and long-range transportable (WHO, 2013). The United Nations Environment Programme (UNEP) and WHO published a document entitled 'State of the Science of Endocrine Disrupting Chemicals' to address concerns about the potential adverse health effects of chemicals on humans and wildlife in 2013 (WHO, 2013). Until now, many epidemiological studies have suggested the association between POPs and hypertension. In 2016, our research team conducted a meta-analysis to summarize the existing epidemiological studies of POPs concentration and risk of hypertension (Park et al., 2016b). The result of meta-analysis showed that exposure to certain POPs, especially dioxin-related compounds, was associated with risk of hypertension. Because high blood pressure is one of the most important risk factors for stroke (CDC, 2014), previous epidemiological studies of POPs and hypertension imply the possibility of an association between POPs and stroke. However, prospective cohort studies of POPs and stroke are scarce.

Three studies were conducted to observe whether or not living near a source of POP contamination was associated with increased risk of stroke (Sergeev and Carpenter, 2010, 2011; Shcherbatykh et al., 2005). However, in these studies, POP exposure status was

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indirectly assessed based on residency in a zip code containing environmental sources of POPs. In 2012, an epidemiological study suggested a positive association between plasma POPs concentration and the risk of stroke (Lee et al., 2012). However, the whole participants were limited to the elderly (70 years old), and only 35 stroke patients were involved in the analysis. They were not able to conduct analyses stratified by sex or of the association of POPs on type of stroke (ischemic stroke, hemorrhagic stroke).

Therefore, using a large prospective cohort data, we performed this case-cohort study to evaluate the association between serum POPs level and type of stroke risk.

2. Methods

2.1. Study population

This study is based on the data from the Korean Cancer Prevention Study-II (KCPS-II). Detailed description of KCPS-II is available in the previous studies (Lee et al., 2017; Lim et al., 2017; Lim and Jee, 2015). The Korean Cancer Prevention Study-II (KCPS-II) Biobank Cohort was initiated in 2004. Participants in routine health assessments at 11 health promotion centers across Seoul and Kyong-gi Province were included in KCPS-II. Among them, 159,844 subjects agreed to participate in this study. In this study, individuals who visited health promotion centers from years 2004–2011 were followed up until year 2013.

Following a case–cohort design (Prentice, 1986), we randomly seclected 1879 participants from the whole cohort population to define the sub-cohort. During the follow-up period 826 stroke incidence cases occurred in the full cohort. Among the sub-cohort members, three stroke incident cases occurred. In this study, we excluded participants who were younger than 20 years old (N = 151). Participants with missing anthropometric measurements (weight, height, body mass index (BMI), total cholesterol, systolic blood pressure, diastolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, or fasting blood sugar) or participants with missing self-report questionnaire information (smoking status or family history of CVD) were also excluded (N = 14,820). We further excluded subjects with weight under 30 kg or height under 130 cm or BMI under 16 kg/m^2 (N = 216) and subjects with missing data on serum POPs measurement (N = 143,821). Participants who already had stroke at enrollment (N = 199) were also excluded. Consequently, 526 controls in sub-cohort and 111 stroke cases were included in the final case-cohort analysis.

The Institutional Review Board of Yonsei University approved this study protocol, and all participants provided written informed consent.

2.2. Chemistry and anthropometric measurement

BMI was calculated as weight (kg) divided by the square of height in meters (m^2). Demographic characteristics (age, sex, and education level), lifestyle characteristics (cigarette smoking status, cigarette smoking duration, cigarette smoking amount, alcohol consumption frequency, alcohol consumption amount, and physical exercise) and family history of disease (cancer, diabetes, and cardiovascular disease) were surveyed using the structured questionnaire validated in previous studies (Lim and Jee, 2015a; Jo et al., 2012; Jee et al., 2010).

All participants were asked to maintain a minimum fasting period of 12 h before they visited health promotion centers for serum sample collection. Samples are stored at -70 °C until it was analyzed. Fasting blood glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride were measured in the collected samples.

The quality control of data was achieved in accordance with the procedures of the Korean Association of Laboratory Quality Control.

2.3. Persistent organic pollutants analyses

In the sample collected from the KCPS-II, serum levels of 51 POPs including 32 PCBs and 19 organochlorine pesticides (OCPs) were measured by isotopic substitution method using gas chromatography/high-resolution mass spectrometry (GC/HRMS) (U.S. EPA, 1994; Dmitrovic et al., 2002; Muir and Sverko, 2006). The detailed methodology of the POPs analyses and quality control procedures were described in previous studies (Park et al., 2015, 2016a,b; Lim et al., 2017). Quality control serum samples were incorporated in each batch. Every batch included both samples of prostate cancer patients and samples of controls. The internal standard recoveries were satisfied with the desirable range, 50% - 120%, that was announced by the Korean Ministry of Environment (Park et al., 2016a,b; Lim et al., 2017). The relative standard deviation of the quality assurance/quality control samples was less than 15%.

2.4. The definition of outcome

Incidence of stroke and its subtypes (ischemic, hemorrhagic) were recorded in hospital admission discharge records. We ascertained these outcomes of stroke from health insurance claim data from the National Health Insurance Corporation and checked fatal cases from the national death certification data (Kim et al., 2005; Jee et al., 2006; Kimm et al., 2009).

The International Classification of Diseases 10th Revision codes were used to define ischemic (I63-I639), hemorrhagic (I60-I629), and all stroke types (I60-I699). For participants with more than one event occurrence during the follow-up period, we considered only the first event in our statistical analyses.

2.5. Statistical analysis

Both lipid-unadjusted serum POPs concentrations (pg/mL) and lipid adjusted serum POPs concentrations (ng/g lipid) were collected in this study. Total lipid was calculated using the following calculation: total lipid (mg/dL) = 2.27 × total cholesterol + triglycerides + 62.3 (Phillips et al., 1989; Bernert et al., 2007). Because POPs are accumulated in lipid, many previous studies used the lipid adjusted POPs concentration in statistical analysis. In this study, the results from the analyses using lipid adjusted POPs concentrations were described (Koutros et al., 2015; Itoh et al., 2014; Xu et al., 2010). POPs concentrations were categorized into tertiles according to the distributions of each analyte concentration among subcohort (Koutros et al., 2015; Lim et al., 2017). Exposure levels equal to or below the limit of detection (LOD) were included in the first (lowest) tertile. The lowest tertile was considered as the reference group. Natural log–transformed POPs concentrations were modeled continuously.

Analyses were conducted for individual analytes, total OCPs, and total PCBs. Because recent epidemiological studies provided the health effect of POPs group that have similar properties (Koutros et al., 2015; Wolff et al., 1997), we also considered a priori groupings of PCB congeners based on previously suggested grouping methods for epidemiological stidies (low chlorinated: PCBs 1, 3, 4, 15, 19, 28, 37, 52, 54, 77, and 81; moderately chlorinated: PCBs 101, 104, 105, 114, 118, 123, 126, 138, 153, 155, 156, 157, 167, 169, 180, 188, and 189; highly chlorinated: PCBs 202, 205, 206, and 208; Wolff 1 (potentially estrogenic): PCBs 52 and 101; Wolff 2 (potentially antiestrogenic and immunotoxic, dioxinlike): PCBs 105, 118, 156,

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