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Serum persistent organic pollutants (POPs) and prostate cancer risk: A case-cohort study

Jung-eun Lim[a,b,c], Chungmo Nam[d], Jiyeon Yang[e], Koon Ho Rha[f], Kyung-Min Lim[c], Sun Ha Jee[a,b,*]

[a] Institute for Health Promotion & Department of Epidemiology and Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, South Korea
[b] Department of Public Health, Graduate School, Yonsei University, Seoul, South Korea
[c] College of Pharmacy, Ewha Womans University, Seoul, South Korea
[d] Department of Biostatistics, College of Medicine, Yonsei University, South Korea
[e] Institute for Environmental Research, Yonsei University Health System, Seoul, South Korea
[f] Department of Urology, Urological Science Institute, Yonsei University College of Medicine, Seoul, South Korea

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ABSTRACT

It is still unclear whether persistent organic pollutants (POPs) exposure increases the prostate cancer incidence risk. This prospective cohort study evaluated the associations between serum POPs concentrations and prostate cancer risk.

Within a case-cohort study, we identified 110 people diagnosed with prostate cancer and randomly selected 256 sub-cohort participants without prostate cancer. Serum concentrations of 32 polychlorinated biphenyl (PCB) congeners and 19 organochlorine pesticides (OCPs) were measured. The hazard ratios (HRs) and 95% confidence interval (95% CI) for determining the associations between POPs and risk of prostate cancer were estimated using the weighted Cox regression model.

Compared to the lowest tertile, increased risks of prostate cancer incidence were observed in the upper tertile of following PCBs: the moderately chlorinated (HR: 4.19; 95% CI: 1.30–13.54), the highly chlorinated (HR: 4.14; 95% CI: 1.75–9.79), biologically persistent as CYP1A and CYP2B inducers (HR: 4.44; 95% CI: 1.33–14.83), the sum of non- dioxin-like (HR: 3.47; 95% CI: 1.21–9.98), and $\sum$PCBs (HR: 4.29; 95% CI: 1.52–12.08). In dose-response curves, $\sum$PCBs was associated with the increased risk of prostate cancer.

Our findings suggested a possible role of POPs in the etiology of prostate cancer.

1. Introduction

Prostate cancer is the most common cancer and the second leading cause of death for U.S. men (American Cancer Society, 2016). In Korea, prostate cancer was ranked as the fifth most-common cancer in 2013. During the last 15-year time period, the incidence rate (per 100,000 people) increased 10.5% annually in Korea (National Cancer Information Center, 2015). Nevertheless, only few risk factors such as age, race, and family history of prostate cancer have been known.

Persistent organic pollutants (POPs) are endocrine disrupting chemicals that adversely affect health. The World Health Organization (WHO) and the United Nations Environment Programme (UNEP) raised awareness about their health and environmental impact (WHO/UNEP, 2013). Not only diabetes but also cancer is suggested as a possible POPs-related disease (Wu et al., 2013; Lim and Jee, 2015; Ruzzin et al., 2010; Emeville et al., 2015; Liu et al., 2015). Biologic plausibility and experimental evidence support the hypothesis that endocrine disruptors could induce endocrine-related cancer including prostate cancer (Pflieger-Bruss et al., 2006; Kimbrough, 1995). However, studies on human health are limited.

In 2015, we conducted a meta-analysis of POPs level and risk of prostate cancer (Lim et al., 2015). According to the meta-analysis,

Abbreviations: POP, persistent organic pollutants; PCB, polychlorinated biphenyl; OCP, organochlorine pesticide; TEQ, toxic equivalency; TEF, toxic equivalency factor; LOD, limit of detection; HCB, Hexachlorobenzene; HCH, hexachlorocyclohexane; DDT, dichlorodiphenyltrichloroethane; DDD, dichlorodiphenyl dichloroethane; DDE, dichlorodiphenyldichloroethylene; HR, Hazard ratio; CI, confidence interval.

* Corresponding author at: Department of Epidemiology and Health Promotion,Graduate School of Public Health, Yonsei University, Seoul, South Korea.
E-mail address: jsunha@yuhs.ac (S.H. Jee).

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we found only one prospective cohort study estimated the association between POPs and prostate cancer risk (Sawada et al., 2010). Until now, due to the difficulty and the high expense of constructing a cohort with human bio-monitoring POPs data, most of the previous human epidemiology studies were conducted as a case-control study design with a small number of participants. Case-control studies are less costly and less time-consuming. However, case-control studies are placed low in the hierarchy of evidence, because it is difficult to establish the timeline of exposure to disease outcome. The previous case-control study showed an inverted U-shape association between oxychlordane and prostate cancer risk and also linear positive associations between several polychlorinated biphenyls (PCBs) and the risk of prostate cancer (Ritchie et al., 2003, 2005). In 2015, a nested case-control study suggested a positive association between plasma oxychlordane level and metastatic prostate cancer risk in Norwegians (Koutros et al., 2015). The authors observed an elevated but non-significant risk for prostate cancer in the highest quartile compared with the lowest quartile of heptachlor epoxide, or hexachlorobenzene.

In Korea, although POPs have been regulated since 2008, their long half-lives have resulted in the residual presence in several foods and persistence in the human blood (Park et al., 2015, 2016). Nevertheless, the association between POPs and prostate cancer has not been studied in Korea.

Using a prospective cohort data, a case-cohort study was conducted to evaluate the association between serum concentrations of POPs and the risk of prostate cancer incidence in the Korean population.

2. Materials and methods

2.1. Study subjects

A total of 270,514 individuals who visited 11 health promotion centers nationwide from 1994 to 2013 were included in the Korean Cancer Prevention Study-II (KCPS-II) (Lim and Jee, 2015; Jo et al., 2012; Jee et al., 2010). The mean and maximum follow-up times were 7.62 and 18.60 years, respectively. Among the KCPS-II participants, 159,844 agreed to participate in this study.

We used a case–cohort design within the KCPS-II consisted of 1879 subjects that were randomly drawn from the full cohort. In this study, participants were excluded if they were 1) Women (N = 63,307); 2) Younger than 20 years (N = 61); 3) Missing anthropometric or clinical measurements (i.e. weight, height, body mass index (BMI), systolic/diastolic blood pressure, fasting blood sugar, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), or triglyceride) (N = 2951); or 4) Missing self-report questionnaire information (N = 3525) 5) Insufficient serum samples for POPs analysis (N = 89,169).

Among the left 831 subjects, 256 controls in the sub-cohort and 110 incident cases, among which three cases are already members in the sub-cohort, were involved in this study. The Institutional Review Board of Yonsei University approved the study protocol.

2.2. Anthropometric measurement

Weight and height of participants were measured and BMI was calculated as weight (kg) divided by the square of their height in meters (m^2). Blood pressure of participants was measured using a standard mercury sphygmomanometer or an automatic manometer. Information including demographic characteristics (age, sex, etc.), lifestyle characteristics (cigarette smoking status, alcohol consumption (nondrinkers and current drinkers), etc.) and past history of clinical disease were collected using the structured questionnaire that was validated in previous studies (Lim and Jee, 2015; Jo et al., 2012; Jee et al., 2010). For prostate cancer cases, age at prostate cancer diagnosis was collected.

2.3. Sample collection

Serum, separated from the peripheral venous blood, was obtained from each participant after 12 h of fasting, which was then further stored at −70 °C until analysis. These serum samples were used for POPs measurement as well as other clinical chemistry parameters, such as fasting blood glucose, total cholesterol, triglyceride, HDL-C, and LDL-C. Fasting serum glucose, total cholesterol, triglyceride, HDL-C, and LDL-C were measured with a COBAS INTEGRA 800 and a 7600 Analyzer (Hitachi, Tokyo, Japan) at each health promotion center.

The quality control of clinical chemistry lab was maintained in accordance with the procedures of the Korean Association of Laboratory Quality Control.

2.4. Persistent organic pollutants analyses

The serum samples collected from the KCPS-II were used to analyze 51 POPs including: (1) 32 PCBs (1, 3–4, 15, 19, 28, 37, 52, 54, 77, 81, 101, 104–105, 114, 118, 123, 126, 138, 153, 155–157, 167, 169, 180, 188–189, 202, 205–206, and 208), and (2) 19 organochlorine pesticides (OCPs) such as oxychlordane, nonachlor (*trans*-, *cis*-), chlordane (*trans*-, *cis*-), heptachlor, hepatachlor epoxide (*trans*-, *cis*-), hexachlorobenzene (HCB), hexachlorocyclohexane (HCH) (α-, β-, γ-, δ-) p,p′–dichlorodiphenyltrichloroethane (p,p′–DDT), o,p′–dichlorodiphenyltrichloroethane (o,p′–DDT), p,p′–dichlorodiphenyldichloroethane (p,p′–DDD), o,p′–dichlorodiphenyldichloroethane (o,p′–DDD), p,p–DDE, and o,p′–dichlorodiphenyldichloroethylene (o,p–DDE)) as shown in Table S1.

The detailed methodology of the POPs analyses was described previously (Park et al., 2015, 2016). Isotopic substitution method was used in this study (U.S. EPA, 1994; Dmitrovic et al., 2002; Muir and Sverko, 2006). Briefly, serum samples were spiked with isotopically labeled standards for OCPs (ES-5465, Cambridge Isotope Labs., USA) and PCBs (68C-LCS, Wellington Labs., Canada) as internal standards. A C18 solid-phase extraction (SPE) was used. Gas chromatography/high-resolution mass spectrometry (GC/HRMS) measurements were performed on a JMS-800D instrument (JEOL, Japan) interfaced with a 6890N gas chromatograph (Agilent Technologies, USA) at the laboratory of Labfrontier (Seoul, Korea). Measurements were carried out by using a DB-5MS capillary column (60 m × 0.32 m × 0.25 μm, Agilent Technologies, USA). Quality control serum samples were incorporated in each batch of 15 samples. The recoveries of the internal standards were satisfactory, in general ranging from 50 to 120% (Park et al., 2016). The relative standard deviation of the quality assurance/quality control (QA/QC) samples was <15% for all compounds that were presented above the limit of detection (LOD) in the QA/QC samples.

2.5. The definition of outcome

The principle outcome was the risk of prostate cancer incidence, based on the National Cancer Registry. Since 1980, the Korean Ministry of Health and Welfare has established a nationwide, hospital-based cancer registry data that covers approximately 99% of new cancer cases in Korea (Shin et al., 2005). Cancer cases were classified according to the International Classification of Diseases, 10th edition (ICD-10), and prostate cancer was coded as C61.