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Original Article

Association between serum concentrations of persistent organic pollutants and smoking in Koreans: A cross-sectional study

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ABSTRACT

Background: Studies on the associations between persistent organic pollutants (POPs) and smoking according to gender and smoking amount (cigarettes/day) are limited, and the results regarding the relationship between POPs and smoking are not completely consistent across studies.
Objectives: The smoking rate in Korea is one of the highest among the Organization for Economic Cooperation and Development (OECD) countries. We investigated the association between serum concentrations of POPs and cigarette smoking in Koreans by smoking status (never-smoker/ever-smoker) and smoking amount (cigarettes/day) according to gender.
Methods: Serum concentrations of 32 polychlorinated biphenyls (PCBs) and 19 organochlorine pesticides (OCPs) were measured in 401 participants (232 men and 169 women) who received health examinations during the Korean Cancer Prevention Study-II. We compared POP levels in ever-smokers and never-smokers and conducted multivariate logistic regression analyses to identify associations between POPs and smoking.
Results: Among women, the concentrations of PCB 156, PCB 167, and PCB 180 were significantly higher in ever-smokers than in never-smokers. After adjustments for age, body mass index, gamma-glutamyl transpeptidase, and alcohol intake, serum PCB 157 concentration was positively associated with male ever-smokers (OR 2.26; 95% CI, 1.01–5.04). In addition, *trans*-nonachlordane in OCPs as well as PCBs was significantly positively related with female ever-smokers (OR 3.21; 95% CI, 1.04–9.86). We found that subjects who smoked fewer than 15 cigarettes/day had a higher risk of having high POP concentrations than never-smokers.
Conclusions: These results indicate that smoking may be associated with human serum POPs levels.

1. Introduction

Persistent organic pollutants (POPs), including polychlorinated biphenyls (PCBs) and organochlorine pesticides (OCPs), are chemical substances that persist in the environment and accumulate in adipose tissue.[1,2] Many studies have suggested that POPs may increase health risks.[2] Therefore, to decrease the risks of high body burden, many countries are trying to eliminate or restrict POPs through legal regulations. Bioaccumulation through the food chain and intake of food are known as major exposure factors for POPs.[3–5] However, it has been reported that smoking may also affect POP concentrations.[6]

Some scientists have studied the influence of smoking on POP levels in humans, but the results have been inconsistent.[7–10] In a study based on samples of Swedish males, CB-153, and p,p′-DDE was correlated with smoking when 2000 and 2004 data were pooled.[10] Also, Fierens et al. reported that serum dioxin levels in male smokers were higher than in male non-smokers, while serum dioxin concentrations of female smokers were lower than female non-smokers.[7] In a review study, it was reported that seven studies published between 1980 and 1995 reported that smoking was not associated with levels of organochlorines, while five studies published in a similar period (1985–1994) reported that smoking was correlated with concentrations of organochlorine residues.[8] In addition, another review study suggested that the associations

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between POPs and smoking were different by district.[9] Furthermore, in an epidemiologic study based on samples of male Inuit in Greenland, smoking was an important determinant of POP bioaccumulation.[11] In a epidemiologic study using NHANES data, smoking increased the mortality of subjects with high serum POP levels. However, Jain and Wang found that the levels of polychlorinated dibenzo-p-dioxins/polychlorinated dibenzofurans (PCDD/PCDF) were significantly lower in smokers than in nonsmokers.[12]

In studies of populations in East-Asian countries, it has been reported that PCDD/F levels were higher in nonsmokers and passive smokers than in active smokers among Taiwanese[13] and that maternal smoking history was associated with a decrease of POP concentrations among Japanese.[14] Despite the fact that Korea has banned most OCPs since 1969, several OCPs were still detected in Korean human samples. In addition, the level of OCPs was higher than has been reported in several other countries.[15]

The smoking rate of Korean men was the highest among the OECD countries in 2012. In addition, the smoking rate of Korean women was the lowest among the OECD countries in 2012 but has been increasing continuously.[16] Therefore, it is necessary to determine the accumulation of POPs by smoking amount in Koreans. To our knowledge, a study on the associations of POPs and smoking aimed at the Korean population has not yet been conducted. Also, studies analyzing the associations between POPs and smoking according to gender and smoking amount are scarce.

The purpose of this study was to investigate the associations between serum concentrations of POPs and cigarette smoking among Koreans by smoking status and smoking amount according to gender.

2. Materials and methods

2.1. Study population

The study population was selected from the Korean Cancer Prevention Study-II (KCPS-II). KCPS-II included 270,514 individuals who visited 21 health examination centers in the Seoul and Gyeonggi districts of Korea from April 1994 to December 2013. In the process of health examination, a researcher who was educated about Institutional Review Board (IRB) requirements explained the KCPS-II and received a signed written consent form from participants. In total, 159,844 participants provided a signed written consent form.[17,18] Of these, 1,050 subjects with anthropometric data (height, weight, and body mass index [BMI]), blood test information (total cholesterol, high-density lipoprotein cholesterol [HDL-C], triglyceride, and gamma-glutamyl transpeptidase), self-reported questionnaire information (age, smoking status, smoking amount, and alcohol intake) obtained during the health examination and POPs values obtained during 2013–2014 were eligible.[17,18] We excluded 601 participants with prostate cancer, breast cancer, or stroke, 44 participants who were missing body mass index (BMI) values or smoking status, and 4 participants who had outlying values for OCPs ($\geq$1,000 ng/g lipid). Thus, the final study subjects consisted of 401 participants (232 men and 169 women) aged 21–73 years who had health examination from 2001 to 2011 (Fig. 1).

This study was approved by Yonsei University Health System, Severance Hospital, Institutional Review Board (Approval Number 4-2013-0119).

2.2. Measurements

In the collected blood samples, total-cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride, and gamma-glutamyl transpeptidase were measured. Weight and height were measured in light clothing after the participants removed their shoes.[18]

Information on cigarette smoking (smoking status and smoking amount [cigarettes/day and packs/year]) and alcohol intake was obtained from self-reported questionnaires. Packs/year was calculated as smoking amount (cigarettes/day) divided by 20 (cigarettes/pack) and multiplied by smoking period.[19]

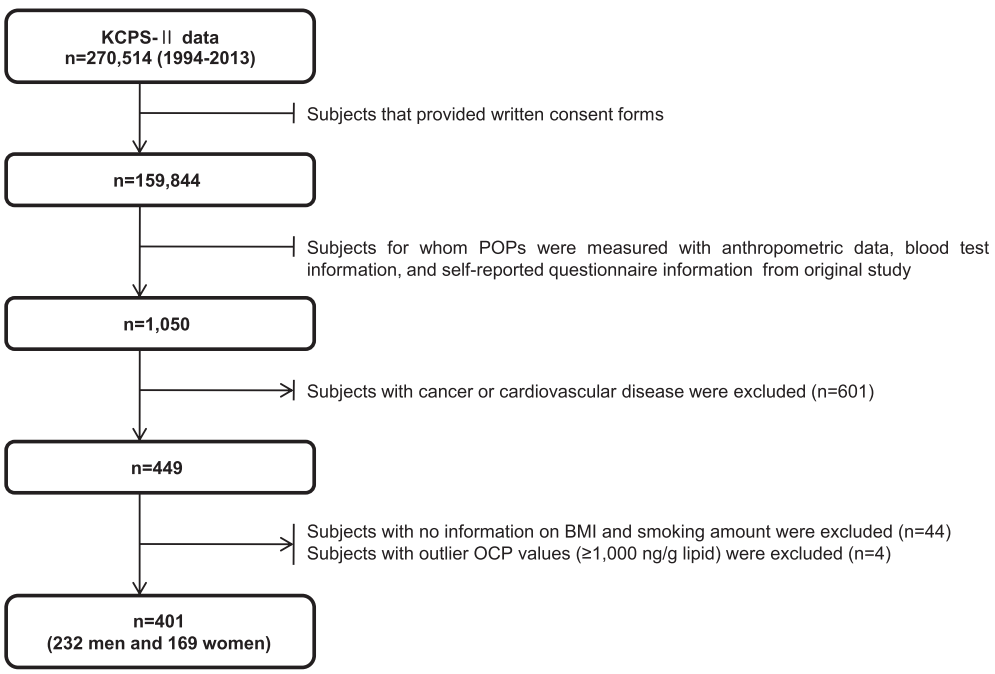

Fig. 1. Flow chart for selection of the study population. KCPS, Korean Cancer Prevention Study; POPs, persistent organic pollutants; OCPs, organochlorine pesticides.

Serum POPs were measured in 0.5–1 mL samples of peripheral venous blood from each participant collected at the health examination after 12 h of fasting. Serum samples were stored at −70 °C and analyzed after thawing and homogenization. We measured 33 PCBs and 19 OCPs as individual chemicals and used analytical methods for POPs used in previous research.[20]

Internal standard materials for refinement were added to the sample, stirred for 15–20 s, and left for 15 min. The mixture was then added to 1 mL ultrapure water and stirred. To remove air, 2 mL formic acid was added and stirred. After air was released for 30 min, ultrapure water was added again. To analyze the amount of POPs in 0.5–1 mL of human blood, a solid-phase extraction method was used to simultaneously pretreat PCBs and OCPs. For efficient extraction of all organic materials except for soluble materials, and to remove C_{18} cartridge and fats, an NH_2 cartridge was used. In the extracted solvent, the sample was refined with Silica-gel (1 g) and Florisil (0.5 g) cartridge to remove interfering substances, using 50% DCM/n-Hexane 16 mL as the elution solvent. Because the refinement efficiency or recovery factor differs by the amount of elution solvent used, the adequate amount of elution solvent was determined through a fraction test. After that, the elution solution was collected in a glass tube and condensed to below 1 mL using a nitrogen concentrator at temperatures below 35 °C and pressure of 8–10 psi. Internal standard materials were added using a syringe and included nitrogen gases condensed to roughly 50–100 μL. A gas chromatograph (6890 Series; Agilent, Palo Alto, CA, USA) and high resolution mass spectrometry (JMS-800D; Jeol, Tokyo, Japan) were used for analyses.

To ensure reliable results, we performed a base experiment by repeatedly measuring the same pool of serum every batch (20 samples) whenever the samples were analyzed. In addition, we confirmed the coefficient of variation (CV) for each chemical and identified the linearity of the calibration-curve. The same method of validation (n = 20) was used in two independent laboratories to verify the suitability of the analysis method. The detection limit was calculated by spiking using 2–5 times the expected detection limit and then multiplied by 3.143 (t-value, a = 99%), the standard deviation derived from seven repetitions. The detection limit was 0.04–0.15 ng/g lipid for PCBs and 0.25–0.94 ng/g lipid for OCPs.

We selected 10 PCBs (PCB 52, PCB 101, PCB 105, PCB 118, PCB 138, PCB 153, PCB 156, PCB 157, PCB 167, and PCB 180) and 6 OCPs (β-hexachlorocyclohexane, p,p′-dichlorophenyldichloroethylene, *cis*-heptachlor epoxide, *trans*-nonachlordane, p,p′-dichlorodiphenyltrichloroethane, and p,p′-dichlorodiphenyldichloroethane), which have 70% or above detection rate according to a preceding study.[21]

This study used lipid-adjusted POP concentrations (ng/g lipid) for analyses based on previous epidemiologic studies.[22] Total lipids were calculated using a formula described in previous studies[23,24]: total lipid (mg/dL) = 2.27 × total cholesterol + triglycerides+62.3.

2.3. Statistical analyses

Smoking status consisted of never-smoker, ex-smoker, and current smoker. Participants that had stopped smoking were classified as ex-smokers, while those that were smokers during the study period were classified as current smokers. We combined ex-smokers and current smokers in the ever-smoker group and classified smoking status as never-smoker and ever-smoker for comparison. In addition, we stratified subjects by gender in accordance with a previous study showing that the association between dioxin body burden and tobacco smoking is different for men and women.[7]

The general characteristics of subjects are presented as means and standard deviations. Student's *t*-test and Chi-square test were used for comparison between never-smokers and ever-smokers by sex. In women, only 8 subjects of 18 ever-smokers had available information on smoking amount (cigarettes/day); therefore, we only analyzed the relationship between POPs and smoking amount in men. The smoking amount for men was divided into two groups (<15 cigarettes/day and ≥15 cigarettes/day) according to the median value. We categorized POP as high or low using a threshold of 75% for logistic regression analyses. Cut-off levels of high or low POPs are presented in eTable 1.

Humans are concurrently exposed to various POP chemicals, not just a single POP. Therefore, we classified POPs as dioxin-like PCBs that interact with AhR (mono-ortho-substituted planar PCB and congeners 105, 118, 156, 157, and 167), and non-dioxin-like PCBs (congeners 52, 101, 138, 153, and 180)[25] according to their toxicological and chemical properties. We also summed the concentrations of dioxin-like PCBs, non-dioxin-like PCBs, total PCBs, and OCPs to calculate the concentration of the POPs mixture and examined the relationship between the POPs (sum of dioxin-like PCBs, sum of non-dioxin-like PCBs, total PCBs, and total OCPs) in each analysis.

The POP concentrations did not satisfy a normal distribution, so a non-parametric test was used. The Mann-Whitney *U* test was used for comparison of never-smokers and ever-smokers. Also, multivariable logistic regression analyses were conducted to demonstrate the associations between POPs, smoking status, and smoking amount. For logistic regression analyses, factors that potentially affect POP levels, such as age, BMI, gamma-glutamyl transpeptidase, and alcohol intake, were adjusted. Statistical significance was considered as a p-value <0.05, and all statistical analyses were performed with SAS 9.2 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Study subjects characteristics according to cigarette smoking status

General characteristics according to the cigarette smoking status are shown in Table 1. Comparing ever-smokers with never-smokers of both sexes, ever-smokers tended to be younger and had lower total cholesterol but higher gamma-glutamyl transpeptidase and alcohol intake than never-smokers. Among men, ever-smokers were likely to have higher BMI and triglyceride than never-smokers, in contrast to women. Statistically significant differences in the general characteristics between never-smokers and ever-smokers were found only for alcohol consumption in males.

3.2. POP levels according to the smoking status

Table 2 indicates the median concentrations of serum POPs according to cigarette smoking status. Among women, the concentrations of PCB 156, PCB 167, and PCB 180 were significantly higher in ever-smokers than in never-smokers. Moreover, the sum of dioxin-like PCBs, the sum of non-dioxin-like PCBs, and the total amount of PCBs showed the same trend. However, a difference was not observed in OCP levels by smoking status. Among men, higher POP concentrations for ever-smokers compared with never-smokers were observed in PCB 105, PCB 167, PCB 101, PCB 153, and PCB 180, but these were not statistically significant.

3.3. POP levels and smoking status and smoking amount

Table 3 shows the results of logistic regression analyses for high POPs (≥75%) by smoking status and smoking amount. Among men, the adjusted odds ratio for a high concentration of PCB 157 was 2.26 for ever-smokers (95% CI, 1.01–5.04) and 4.31 for subjects in the

Table 1
General characteristics according to cigarette smoking status.

	Men (n = 232)			Women (n = 169)		
	Never-smoker (n = 60)	Ever-smoker (n = 172)	p-value	Never-smoker (n = 151)	Ever-smoker (n = 18)	p-value
Age, years	43.2 (10.33)	40.87 (8.92)	0.0957[e]	39.32 (10.84)	35.28 (7.52)	0.1265[e]
Body mass index, kg/m^2	23.86 (3.09)	24.27 (2.65)	0.3273[e]	21.78 (2.83)	21.35 (3.3)	0.5553[e]
Total-cholesterol, mg/dL	199.05 (32.24)	193.34 (36.74)	0.2867[e]	174.67 (33.91)	170.56 (30.1)	0.6235[e]
HDL cholesterol, mg/dL[a]	49.98 (7.99)	48.82 (8.65)	0.3632[e]	57.15 (9.6)	55.25 (10.53)	0.4326[e]
LDL cholesterol, mg/dL[b]	122.25 (30.65)	115.88 (29.59)	0.1568[e]	99.19 (31.53)	100.38 (26.86)	0.8783[e]
Triglyceride, mg/dL	142.58 (70.56)	162.27 (182.02)	0.4154[e]	97.97 (59.44)	81.28 (44.12)	0.2505[e]
GGT, mg/dL	41.82 (44.54)	45.48 (39.14)	0.5476[e]	18.68 (18.28)	19.33 (16.05)	0.8841[e]
Cigarettes/day[c]	–	16.33 (6.53)	–	–	7.13 (5.25)	–
Pack/years[d]	–	14.23 (10.16)	–	–	3.8 (3.34)	–
Alcohol, n (%)	47 (78.33)	154 (89.53)	0.0353[f]	78 (51.66)	10 (55.56)	0.7539[f]

GGT, gamma-glutamyl transpeptidase; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a] 4 missing male ever-smokers and 2 missing female never-smokers.
[b] 1 missing male ever-smoker and 2 missing female never-smokers.
[c] 38 missing male ever-smokers, 10 missing female ever-smokers.
[d] 46 missing male ever-smokers, 10 missing female ever-smokers.
[e] Student's *t*-test was used.
[f] Chi-square test was used.

group that smoked <15 cigarettes/day (95% CI, 1.48–12.50) compared with never-smokers. In addition, PCB 153, PCB 180, the sum of non-dioxin-like PCBs, and total PCBs were more likely to be higher in the <15 cigarettes/day group. In women, *trans*-nonachlordane as well as PCBs (PCB 118, PCB 156, PCB 157, PCB 167, PCB 180, and total PCBs) showed statistically significantly higher odds of having high concentrations. When we analyzed the influence of confounding variables on all subjects, age was the most influential variable on the associations of POPs and smoking status (followed by alcohol consumption and GGT) (eTable 3).

4. Discussion

This study demonstrated that serum POP concentrations were positively associated with smoking status and smoking amount in members of the Korean general population who had health examinations. Among women, the levels of PCBs and *trans*-nonachlordane were significantly higher in ever-smokers than in never-smokers, while male ever-smokers were significantly associated with only PCB 157, which is a dioxin-like PCB.

These results are partially consistent with those of some previous studies. In a study conducted among Norwegian women, smoking was significantly associated with higher levels of PCBs, p,p′-DDE, and β-HCH in breast milk.[3] Some studies in Greenland populations reported that cigarette smokers had higher levels of POPs.[26–28] Also, a previous small study of a German population (n = 80) showed that children born to smoking mothers had higher POP concentrations than children of nonsmoking families.[29]

On the other hand, some researchers have reported negative associations between POPs and smoking.[30,31] In a short report evaluating the relationship between tobacco smoking and dioxin accumulation in Belgium, serum dioxin and coplanar PCBs were

Table 2
Serum median (interquartile range) concentrations of persistent organic pollutants according to cigarette smoking status.

	Men			Women		
	Never-smokers (n = 60)	Ever-smokers (n = 172)	p-value[a]	Never-smokers (n = 151)	Ever-smokers (n = 18)	p-value[a]
DL-PCBs, ng/g lipid						
PCB 105	0.55 (0.20–1.04)	0.60 (0.20–0.95)	0.7003	0.61 (0.2–0.94)	0.81 (0.57–1.48)	0.0614
PCB 118	2.93 (1.99–5.00)	2.93 (1.76–4.53)	0.3879	2.80 (2.08–4.76)	3.58 (2.59–7.10)	0.0878
PCB 156	0.96 (0.62–1.81)	0.92 (0.62–1.66)	0.7477	0.87 (0.55–1.63)	1.44 (0.91–3.00)	0.0039
PCB 157	0.34 (0.18–0.45)	0.31 (0.14–0.51)	0.9570	0.32 (0.15–0.54)	0.50 (0.27–0.96)	0.0930
PCB 167	0.54 (0.39–0.85)	0.55 (0.34–0.82)	0.4568	0.54 (0.38–0.86)	0.78 (0.57–1.61)	0.0124
Sum of DL-PCBs	5.53 (3.68–8.99)	5.34 (3.28–8.45)	0.4072	5.10 (3.47–9.02)	7.49 (5.04–13.22)	0.0159
Non DL-PCBs, ng/g lipid						
PCB 52	2.47 (1.10–4.67)	2.47 (1.40–3.75)	0.9243	2.50 (1.50–3.96)	2.56 (1.54–3.35)	0.9756
PCB 101	1.16 (0.84–2.06)	1.23 (0.83–2.04)	0.7308	1.18 (0.83–1.85)	1.12 (0.89–2.05)	0.9594
PCB 138	5.55 (4.06–7.43)	5.49 (3.54–8.74)	0.9111	5.00 (3.23–8.48)	6.35 (3.29–9.94)	0.3445
PCB 153	12.02 (8.63–20.26)	12.36 (6.75–24.77)	0.9421	10.24 (6.56–20.15)	14.64 (9.42–32.42)	0.0534
PCB 180	8.55 (5.49–14.47)	8.79 (4.61–19.35)	0.8442	6.95 (4.46–15.36)	15.89 (8.29–42.24)	0.0088
Sum of non DL-PCBs	32.85 (22.56–50.81)	32.01 (19.47–60.70)	0.9448	26.53 (20.19–48.80)	36.17 (27.80–81.15)	0.0325
Total PCBs	38.47 (26.36–61.88)	37.04 (22.36–70.01)	0.8442	32.14 (24.26–56.57)	43.58 (31.79–90.97)	0.0272
OCPs, ng/g lipid						
β-HCH	12.36 (7.86–17.66)	11.53 (7.94–18.27)	0.6737	17.23 (12.86–26.32)	21.64 (16.76–26.66)	0.1673
p,p′-DDE	99.91 (70.76–161.29)	94.11 (58.40–154.67)	0.4066	100.73 (59.15–165.26)	100.66 (67.28–223.45)	0.5803
cis-heptachlor epoxide	1.85 (0.90–3.49)	1.71 (0.87–3.44)	0.8729	1.72 (1.00–3.13)	2.40 (1.70–3.09)	0.1376
trans-nonachlordane	4.20 (2.50–6.44)	3.53 (2.13–6.48)	0.2953	2.93 (1.99–5.26)	3.57 (2.94–5.71)	0.1219
p,p′-DDD	2.07 (0.86–3.72)	1.70 (0.78–3.46)	0.2880	1.30 (0.28–2.57)	1.83 (0.71–3.85)	0.1688
p,p′-DDT	10.17 (6.99–14.10)	10.11 (6.19–15.73)	0.9599	7.73 (5.33–11.14)	7.43 (6.09–15.94)	0.4771
Total OCPs	132.56 (90.76–213.56)	123.10 (78.53–198.65)	0.3770	128.18 (87.39–219.39)	132.56 (100.14–286.25)	0.4311

DL-PCBs, dioxin-like polychlorinated biphenyls; OCPs, organochlorine pesticides; β-HCH, β-hexachlorocyclohexane; p,p′-DDE, p,p′-dichlorophenyldichloroethylene; p,p′-DDD, p,p′-dichlorodiphenyldichloroethane; p,p′-DDT, p,p′-dichlorodiphenyltrichloroethane.
[a] Mann-Whitney *U* test was used.

Table 3
Adjusted odds ratios (95% confidence intervals)[a] of high levels of persistent organic pollutants[b] according to smoking factors.

	Men				Women	
	Never-smoker (n = 60)	Ever-smoker (n = 172)	<15 cigarettes/day (n = 37)	≥15 cigarettes/day (n = 97)	Never-smoker (n = 151)	Ever-smoker (n = 18)
DL-PCBs, ng/g lipid						
PCB 105	1.00	0.94 (0.47, 1.91)	1.87 (0.71, 4.92)	0.60 (0.27, 1.37)	1.00	2.75 (0.95, 7.97)
PCB 118	1.00	0.81 (0.40, 1.62)	1.30 (0.48, 3.51)	0.57 (0.25, 1.27)	1.00	2.96 (1.00, 8.71)
PCB 156	1.00	1.09 (0.53, 2.25)	1.92 (0.70, 5.22)	0.82 (0.36, 1.86)	1.00	3.52 (1.19, 10.42)
PCB 157	1.00	2.26 (1.01, 5.04)	4.31 (1.48, 12.50)	1.74 (0.70, 4.29)	1.00	3.52 (1.17, 10.55)
PCB 167	1.00	0.99 (0.49, 2.00)	2.13 (0.82, 5.51)	0.61 (0.27, 1.39)	1.00	3.53 (1.22, 10.21)
Sum of DL-PCBs	1.00	1.06 (0.52, 2.19)	1.63 (0.58, 4.53)	0.82 (0.36, 1.85)	1.00	2.70 (0.92, 7.89)
Non DL-PCBs, ng/g lipid						
PCB 52	1.00	0.68 (0.33, 1.37)	0.71 (0.26, 1.97)	0.47 (0.20, 1.08)	1.00	0.77 (0.24, 2.55)
PCB 101	1.00	1.12 (0.55, 2.28)	1.35 (0.51, 3.57)	1.02 (0.47, 2.23)	1.00	1.08 (0.36, 3.29)
PCB 138	1.00	1.69 (0.79, 3.61)	2.49 (0.88, 7.01)	1.30 (0.55, 3.03)	1.00	1.25 (0.40, 3.89)
PCB 153	1.00	1.84 (0.83, 4.10)	2.98 (1.03, 8.66)	1.30 (0.54, 3.13)	1.00	2.98 (0.99, 8.96)
PCB 180	1.00	1.69 (0.76, 3.76)	3.60 (1.25, 10.36)	0.97 (0.40, 2.37)	1.00	5.49 (1.80, 16.76)
Sum of non DL-PCBs	1.00	2.19 (0.96, 4.99)	3.52 (1.18, 10.50)	1.36 (0.55, 3.37)	1.00	2.73 (0.92, 8.09)
Total PCBs	1.00	1.90 (0.85, 4.23)	3.16 (1.08, 9.19)	1.13 (0.46, 2.75)	1.00	3.98 (1.34, 11.88)
OCPs, ng/g lipid						
β-HCH	1.00	1.17 (0.56, 2.44)	1.44 (0.51, 4.08)	1.02 (0.45, 2.31)	1.00	1.37 (0.43, 4.37)
p,p′-DDE	1.00	1.04 (0.50, 2.15)	1.96 (0.73, 5.29)	0.81 (0.36, 1.85)	1.00	1.52 (0.47, 4.91)
cis-heptachlor epoxide	1.00	0.94 (0.46, 1.90)	1.28 (0.48, 3.46)	0.77 (0.35, 1.70)	1.00	1.69 (0.49, 5.86)
trans-nonachlordane	1.00	1.28 (0.59, 2.79)	1.54 (0.50, 4.74)	1.18 (0.50, 2.78)	1.00	3.21 (1.04, 9.86)
p,p′-DDD	1.00	0.78 (0.40, 1.53)	0.75 (0.27, 2.05)	0.81 (0.38, 1.71)	1.00	1.83 (0.62, 5.43)
p,p′-DDT	1.00	1.54 (0.73, 3.26)	1.76 (0.64, 4.89)	1.45 (0.64, 3.26)	1.00	2.53 (0.86, 7.40)
Total OCPs	1.00	1.04 (0.50, 2.16)	1.73 (0.63, 4.76)	0.86 (0.38, 1.96)	1.00	1.67 (0.51, 5.44)

DL-PCBs, dioxin-like polychlorinated biphenyls; OCPs, organochlorine pesticides; β-HCH, β-hexachlorocyclohexane; p,p′-DDE, p,p′-dichlorophenyldichloroethylene; p,p′-DDD, p,p′-dichlorodiphenyldichloroethane; p,p′-DDT, p,p′-dichlorodiphenyltrichloroethane.
[a] Adjusted for age, body mass index, gamma-glutamyl transpeptidase, and alcohol intake.
[b] High levels of persistent organic pollutants were ≥quartile 3 of each chemical.

lower in current female smokers but higher in current male smokers than in never-smokers.[7] This inconsistency has also been observed in some other studies.[8–10] While Greenland male residents were positively correlated with OCPs and plasma cotinine (ng/mL) in one study,[11] statistically significant associations with OCPs and male ever-smokers were not apparent. In the present study, we only found significant positive associations between PCBs and male ever-smokers, while no association was observed in women.

Increased POP concentrations may be associated with enzymes of the p-450 cytochrome oxidase system, including CYP1A1, CYP1A2, and phenobarbital-CYP, which metabolize POPs, nicotine, and nicotine's breakdown products. POPs affect the expression of these enzymes and may cause competitive and feedback reactions.[11,32,33] Constituents from cigarette smoke, such as Cd and CO, influence the activity of the enzymes, and Cd from cigarettes was reported to stimulate PCB uptake in quail.[27,34]

In our study, the risk of high POP concentrations was lower in the group that smoked ≥15 cigarettes/day than in the <15 cigarettes/day group (Table 3). Although the difference was not statistically significant, the lower risk of high POP concentrations in heavy smokers (who smoked more than 15 cigarettes/day) may be due to the strong stimulation of dioxin biotransformation by polycyclic aromatic hydrocarbons (PAHs) or other chemicals in cigarette smoke.[7] Some studies indicated that the compounds contained in cigarette smoke have affinity for aryl hydrocarbon receptors (AhR) and could be potent inducers of cytochrome P450 enzymes.[7,35,36] POPs undergo enzymatic hydroxylation, which involves several cytochrome P-450 enzymes to varying extents, and the POPs bind to the AhR to upregulate the activity of CYP1A.[37] Additionally, CYP2B enzymes metabolize ortho-substituted PCB, including mono-ortho PCB. Upregulation of these enzymes causes receptor binding that results in an increase in the distribution of POPs to the liver from the central compartment.[12,38] In addition, a certain amount of smoking may affect metabolism of POPs in the body, and the metabolic ability of POPs by smoking may differ by individual. To date, obvious causes of inconsistency in the associations between POPs and smoking amount were not revealed. In women, more strong positive associations between POPs and smoking were shown than in men. This gender difference may be due to the low metabolic ability of POPs in women compared to men.

In this study, age, alcohol consumption, and GGT influenced the association between POPs and smoking (eTable 3). This could be because age may be one of the major factors of POPs accumulation.[24] Also, alcohol consumption and GGT levels are related to liver function, so they may affect POPs metabolism.

We propose that cigarette smoking leads to the bioaccumulation of POPs through the action of cytochrome P-450, one of the hepatic microsomal enzymes. However, as smoking frequency increases, cytochrome P-450 may trigger some metabolizing action by the POPs. These interactions between POPs and smoking should be further studied through a large-scale cohort study and through animal experiment.

Our study has the following strengths. First, we measured POPs concentrations in human samples directly within the Korean population rather than using a survey to collect exposure data. Second, we analyzed the relation between serum POPs and smoking using smoking amount (cigarettes/day) as well as smoking status according to gender. Third, 32 PCBs and 19 OCPs were analyzed, and associations were observed between a variety of POPs and smoking. Fourth, not only single materials but also POP mixtures were used for analyses. This method was meaningful, as humans are exposed to many POP materials simultaneously.

On the other hand, there are some limitations in our study. First, due to the nature of cross-sectional studies, it is difficult to describe the cause of the relationship between POPs and smoking. Second, we could not evaluate female smokers with smoking amount because of the limited sample size. Third, self-reported smoking habits may not be accurate, so further studies need to include

biological biomarkers, such as cotinine, in order to represent more exact information about smoking habits. Finally, there may be potential discrepancies in the timing of POPs measurements. Further study to clarify inconsistencies in the relations between POPs and smoking amount and gender is needed.

5. Conclusion

Our results suggest that POP concentrations may be higher in smokers than in never-smokers and that smoking is probably a confounding variable in studies of POPs. Additional in vivo and in vitro experimental studies, as well as larger prospective studies in humans, would help to elucidate the relationship between POPs and smoking.

Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.je.2016.09.006.

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