Environment International 143 (2020) 105925

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Impact of environmental exposure to persistent organic pollutants on lung cancer risk

Eun Young Park[a], Eunjung Park[a], Jinsun Kim[a], Jin-Kyoung Oh[a,b], Byungmi Kim[a], Yun-Chul Hong[c,d,e], Min Kyung Lim[a,b,*]

[a] Division of Cancer Prevention & Early Detection, National Cancer Control Institute, National Cancer Center, Goyang-si, Gyeonggi-do 10408, Republic of Korea
[b] Department of Cancer Control and Population Health, National Cancer Center Graduate School of Cancer Science and Policy, Goyang-si, Gyeonggi-do 10408, Republic of Korea
[c] Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea
[d] Institute of Environmental Medicine, Seoul National University Medical Research Center, Seoul, Republic of Korea
[e] Environmental Health Center, Seoul National University College of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Handling Editor: Adrian Covaci

Keywords:
Environmental exposure
Persistent organic pollutants
Chlordane
Polychlorinated biphenyls
Lung cancer

ABSTRACT

Background: Recent studies suggest that high pre-diagnostic serum concentrations of persistent organic pollutants (POPs) might result in the development of cancers in the general population. However, the association between pre-diagnostic serum POP concentrations and lung cancer risk has not been studied. Here, we evaluated associations between low-dose environmental exposure to POPs and risk of lung cancer using pre-diagnostic serum samples in a case-cohort study based on a population-based prospective cohort.

Methods: We conducted a case-cohort study based on the Korean National Cancer Center Community Cohort, from which we included 118 lung cancer cases and 252 controls. Serum concentrations of POPs were measured by high resolution gas chromatography/high-resolution mass spectrometry, and data were analyzed using multivariable Cox proportional-hazards regression models.

Results: Risk of lung cancer increased per unit increase in the natural log-transformed concentrations of the sum of chlordane congeners, total PCBs, and all PCBs subgrouped by the number of chlorines or *ortho*- substituted chlorines on the molecules, except for tri/tetrachlorobiphenyls, in all models. Among individual POP analytes with a detection rate > 80%, after Bonferroni adjustment, only *trans*-nonachlor was associated with lung cancer risk. In categorical models, risk of lung cancer was associated with serum concentration of chlordane (4th vs. 1st quartile, hazard ratio [95% confidence interval], 8.79 [2.77–27.97]). Dose-dependent relationships were also found between risk of lung cancer and serum concentrations of PCBs regardless of their degree of chlorination, substitution pattern, or binding affinity to receptors (total PCBs, $P = 0.002$; mid-chlorinated PCBs, $P = 0.004$; high-chlorinated PCBs, $P < 0.001$; non- and mono-*ortho* PCBs, $P = 0.031$; di-*ortho* PCBs, $P = 0.003$; PCBs with dioxin-like activity, $P = 0.011$; non-dioxin-like non-/mono-*ortho* PCBs, $P = 0.060$).

Conclusions: Serum concentrations of chlordane and PCBs are associated with risk of lung cancer in the general population, even decades after the ban on their production and use.

1. Introduction

Lung cancer is the leading cause of cancer-related death worldwide, accounting for 18% of all cancer-related deaths and constituting 17% and 8% of new cancer cases among men and women, respectively (Bray et al., 2018). The rate of lung cancer death is similar in Korea (11.6% of all cancer-related deaths, KOSIS, 2020). Tobacco smoking and other environmental factors (e.g., ionizing radiation, asbestos, metals, silica,

Abbreviations: AhR, aryl hydrocarbon receptor; BMI, body mass index; CI, confidence interval; DDD, dichlorodiphenyldichloroethane; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; HR, hazard ratio; LOD, limit of detection; NDMA, N-nitrosodimethylamine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; OCs, organochlorine pesticides; PCBs, polychlorinated biphenyls; POPs, persistent organic pollutants; TEQs, total dioxin equivalents; TEFs, toxic equivalence factors

* Corresponding author at: Division of Cancer Prevention & Early Detection, National Cancer Control Institute, Department of Cancer Control and Population Health, National Cancer Center Graduate School of Cancer Science and Policy, National Cancer Center, 323, Ilsan-ro, Ilsandong-gu, Goyang-si, Gyeonggi-do 10408, Republic of Korea.
E-mail address: mickey@ncc.re.kr (M.K. Lim).

https://doi.org/10.1016/j.envint.2020.105925
Received 17 December 2019; Received in revised form 2 June 2020; Accepted 21 June 2020
Available online 02 July 2020

polycyclic aromatic hydrocarbons, and air pollution) are well-documented major risk factors for lung cancer (Malhotra et al., 2016).

Persistent organic pollutants (POPs) are toxic chemicals used in agricultural, industrial, and manufacturing processes that disturb the endocrine system and damage the immune system in humans (UN (United Nations), 2019). POPs production and use have been banned internationally since the 1970s due to their harmfulness, persistence in the environment, bioaccumulation, and long-range transport ability (UN (United Nations), 2019). The major point of concern is that POPs readily bioaccumulate in human fat tissue after consumption of contaminated foods or water (Malisch and Kotz, 2014; UN (United Nations), 2019), and they persist in the body even decades after their release into the environment.

Environmental and occupational exposure to POPs has decreased over recent decades due to the ban on their production and use. However, low-dose environmental exposure to POPs is an ongoing public health issue worldwide. Previous studies provide evidence that low-dose circulating concentrations of POPs are associated with diabetes (Lee et al., 2011; Lee et al., 2014; Lee et al., 2010; Zong et al., 2018), cardiovascular diseases (Henríquez-Hernández et al., 2017; Kim et al., 2015; Lim et al., 2018), and death (Fry and Power, 2017; Lind et al., 2019). Moreover, the Halifax project reports that low-dose environmental exposure to mixtures of chemicals may contribute to cancer development; that is, the combined and cumulative effects of individual chemicals acting on a variety of organs, tissues, and cells through different pathways could produce carcinogenic synergies (Goodson et al., 2015).

Although some recent studies performed using pre-diagnostic serum samples suggest that environmental exposure to POPs leads to the development of prostate cancer, breast cancer, liver cancer, non-Hodgkin's lymphoma, and acute myeloid leukemia (Bassig et al., 2019b; Emeville et al., 2015; Engel et al., 2019; Koutros et al., 2015), most of these studies evaluated cancer risk using serum samples collected during active POPs exposure. To the best of our knowledge, no published studies have prospectively evaluated associations between pre-diagnostic serum POP concentrations and lung cancer risk in the general population, although some studies investigated the association between lifetime occupational pesticide use and risk of lung cancer (Bonner et al., 2017; Purdue et al., 2007).

Here, we hypothesized that low-dose environmental exposure to individual or mixtures of POPs increases risk of lung cancer. To test this hypothesis, we conducted a case-cohort study based on a prospective general population cohort to evaluate associations between low-dose environmental exposure to POPs and risk of lung cancer using pre-diagnostic serum samples.

2. Methods

2.1. Study population

The Korean National Cancer Center Community (KNCCC) cohort was a community-based prospective cohort between 1993 and 2010 that investigated associations between environmental factors and cancer risk in the Republic of Korea (Oh et al., 2017). A total of 16,304 men and women aged over 30 years who resided in the rural areas of Changwon-si, Chuncheon-si, Chungju-si, Sancheong-gun, or Hamangun were included in the cohort. Baseline demographic, environmental, and lifestyle characteristics were collected using a structured questionnaire. Anthropometric measurements and clinical laboratory tests were also conducted. Serum samples collected between 1993 and 2008 were stored at −70 °C in a deep freezer, and samples collected between 2009 and 2010 were stored at −140 °C in a liquid nitrogen tank. Participants were linked to national cancer incidence data from the Korea Central Cancer Registry and national mortality data from Statistics Korea and were followed up through 2015.

This study was approved by the KNCC institutional review board (no. NCC2017-0217), and informed consent forms were signed by all participants. The reporting of this cohort study followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

2.2. Case-cohort study design and outcome definition

We designed a case-cohort study to evaluate associations between pre-diagnostic serum concentrations of POPs on lung cancer risk. We randomly selected a representative subcohort of 342 participants who entered the cohort between 2001 and 2010 for whom there was serum for the analysis of POPs. During the follow-up period, 178 participants were diagnosed with primary lung cancer (10th revision of the International Classification of Diseases (ICD-10) codes: C33 or C34), and six cases of lung cancer were found in the random subcohort. We excluded participants diagnosed with lung cancer within 1 year of sample collection (n = 13), participants with insufficient serum volume for dual analysis (< 800 μL) to assess POPs exposure (n = 73), and participants with missing data for total cholesterol or triglyceride values (for calculating total lipid levels) or other covariates (education, cigarette smoking, alcohol consumption status, obesity, previous pesticide use; n = 64). As a result, we included 118 lung cancer cases (113 cases plus 5 cases in the random subcohort) and 252 controls in the statistical analysis. A flow diagram showing the derivation of the study sample is presented in Supplementary Fig. 1.

2.3. Measurement of serum POPs

Serum concentrations of 19 organochlorine pesticides and metabolites (OCs) [hexachlorobenzene (HCB; α-, β-, γ-, δ-), hexachlorocyclohexane (HCH), heptachlor, *cis*-heptachlor epoxide, *trans*-heptachlor epoxide, *cis*-chlordane, *trans*-chlordane, oxychlordane, *cis*-nonachlor, *trans*-nonachlor, *o,p′*-dichlorodiphenyltrichloroethane (DDT), *p,p′*-DDT, *o,p′*-dichlorodiphenyldichloroethylene (DDE), *p,p′*-DDE, *o,p′*-dichlorodiphenyldichloroethane (DDD), and *p,p′*-DDD] and 32 polychlorinated biphenyl (PCB) congeners (1, 3, 4, 15, 19, 28, 37, 52, 54, 77, 81, 101, 104, 105, 114, 118, 123, 126, 138, 153, 155, 156, 157, 167, 169, 180, 188, 189, 202, 205, 206, and 208) were measured using an isotopic substitution method involving high resolution gas chromatography/high-resolution mass spectrometry (HRGC/HRMS) according to POPs Korean standard method, 'ES 10910.1 Official Method of Persistent Organic Pollutants(POPs) in Blood' (Ministry of Environment of the Republic of Korea, 2017). Precision and accuracy for POP measurements are reported in Table S1.

Selection of the 19 OCs and 32 PCBs was based on the Stockholm Convention list (UN (United Nations), 2019), and PCBs were further selected based on the number of chlorines and *ortho*-substituted chlorines on their molecules and their dioxin-like activity to evaluate carcinogenesis in relation to their structure.

Analytical values of POPs are reported as wet-weight concentrations (pg/mL) with total serum lipids as a covariate based on evidence that traditional lipid adjustment can create bias (Schisterman et al., 2005). Total lipids were calculated for each sample using the following equation: total lipids (mg/dL) = 2.27 × [total cholesterol (mg/dL) + triglycerides (mg/dL)] + 62.3) (Phillips et al., 1989). Concentrations below the limit of detection (LOD) were imputed as the LOD divided by the square root of 2. Table S2 provides detailed information on LODs, serum concentrations of the 19 OCs and 32 PCBs, and the percentage of samples with concentrations below the LODs. To compare POP concentrations between present and previous studies, their lipid-adjusted concentrations (ng/g lipids; Table S3) were calculated as POP wet-weight concentration divided by total lipid concentration.

2.4. Statistical analyses

As the 19 OCs and 32 PCBs measured in this study are lipophilic

chemicals and migrate as mixtures, it is difficult to identify the individual POPs responsible for observed associations (Aminov et al., 2016; Lee et al., 2018). Thus, serum concentrations of the 19 OCs and 32 PCBs were pooled into single variables labeled "total OCs" and "total PCBs", respectively. For more comprehensive analysis and evaluation, we subgrouped PCBs by the number of chlorines and *ortho*-substituted chlorines on their molecules as follows: DDTs (*o,p′*-DDT, *p,p′*-DDT, *o,p′*-DDE, *p,p′*-DDE, *o,p′*-DDD, *p,p′*-DDD); chlordanes (*cis*-chlordane, *trans*-chlordane, oxychlordane, *cis*-nonachlor, *trans*-nonachlor); mono- and di-chloro biphenyls (1, 3, 4, 15); tri- and tetra-chloro biphenyls (19, 28, 37, 52, 54, 77, 81); penta- and hexa-chloro biphenyls (101, 104, 105, 114, 118, 123, 126, 138, 153, 155, 156, 157, 167, 169); hepta-, octa-, nona-, and deca-chloro biphenyls (180, 188, 189, 202, 205, 206, 208); non- and mono-*ortho* biphenyls (1, 3, 15, 28, 37, 77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, 189); di-*ortho* biphenyls (4, 52, 101, 138, 153, 180); and tri- and tetra-*ortho* biphenyls (19, 123, 206). We also re-subgrouped non- and mono-*ortho* PCBs as dioxin-like PCBs (77, 81, 126, 169, 105, 114, 118, 123, 156, 157, 167, 189) to evaluate whether the effects of non- and mono-*ortho* biphenyls (105, 114, 118, 123, 156, 157, 167, 189) are due to dioxin-like or non-dioxin-like PCBs. To determine total dioxin equivalents (TEQs), toxic equivalence factors (TEFs) and serum concentrations of each dioxin-like PCB congener were incorporated using the following formula (Van den Berg et al., 2006): TEQ = (PCB-77) × 0.0001 + (PCB-81) × 0.00003 + (PCB-126) × 0.1 + (PCB-169) × 0.03 + (PCB-105) × 0.00003 + ((PCB-114) × 0.00003 + (PCB-118) × 0.00003 + (PCB-123) × 0.00003 + (PCB-156) × 0.00003 + (PCB-157) × 0.00003 + (PCB-167) × 0.00003 + (PCB-189) × 0.00003. Subgrouping for hexachlorobenzene and heptachlor were not considered, as their concentrations were below the LOD in several cases; however, we evaluated a subset of individual analytes with values > 80% of the LOD (β-HCH, *cis*-heptachlor epoxide, *trans*-nonachlor, *p,p′*-DDT, *p,p′*-DDE, *p,p′*-DDD, PCB-52, PCB-101, PCB-105, PCB-118, PCB-138, PCB-153, PCB-156, and PCB-180).

Wet-weight serum POP concentrations were natural log-transformed due to their skewed distribution and categorized into quartiles, yielding results in terms of easily interpretable hazard ratios (HRs) depending on the distribution of POPs among controls (or divided into two groups by the median value when their values were ≥ 50% of the LOD).

We examined differences in the following characteristics at baseline between lung cancer and controls: age, gender, region, year of entry into the cohort, education (elementary school or less, middle school, high school, or college or higher), cigarette smoking (pack-years), alcohol consumption status (non-consumers, former consumers, or current consumers), body mass index (BMI), total lipid concentration, and lifetime pesticide use (self-reported as "yes" or "no").

To examine associations between serum POP concentrations and risk of lung cancer, we conducted Cox proportional-hazards regression analyses weighted by Barlow's method as appropriate for our case-cohort design (Barlow et al., 1999). To assess the validity of the proportional-hazards assumption, Schoenfeld residuals were calculated, which showed no violation of assumptions. Three separate models were evaluated: the first model was adjusted for age (continuous variable), gender, and total lipids (continuous variable); the second model was further adjusted for year of entry into the cohort, region, education, cigarette smoking (continuous variable), alcohol consumption status, BMI (continuous variable), and history of pesticide use; and the third model was further adjusted for serum concentrations of "total OCs" or "total PCBs" (continuous variables). Associations were also evaluated using Bonferroni adjustment.

Sensitivity analyses excluding lung cancer cases diagnosed within 3 or 5 years of entry into the cohort were conducted to determine whether serum concentrations of lipids and POPs were influenced by weight loss, which could be caused by undiagnosed or preclinical lung cancer (Lee et al., 2017a; Lee et al., 2018).

Table 1
Baseline characteristics of case-cohort study participants.

	Lung cancer cases (n = 118)	Controls (n = 252)
Age, years, mean ± SD	66.1 ± 6.8	58.9 ± 10.4
Gender, n (%)		
Men	82 (69.5)	106 (42.1)
Women	36 (30.5)	146 (57.9)
Region, n (%)		
San-cheong	46 (39.0)	121 (48.0)
Ui-ryeong	10 (8.5)	8 (3.2)
Chang-won	13 (11.0)	37 (14.7)
Choon-cheon	8 (6.8)	24 (9.5)
Choong-joo	15 (12.7)	30 (11.9)
Ham-an	26 (22.0)	32 (12.7)
Year of entry into the cohort, n (%)		
2001	20 (17)	21 (8.3)
2002	4 (3.4)	5 (2)
2003	23 (19.5)	44 (17.5)
2004	27 (22.9)	51 (20.2)
2005	11 (9.3)	30 (11.9)
2006	18 (15.3)	39 (15.5)
2007	3 (2.5)	10 (4)
2008	7 (5.9)	25 (9.9)
2009	1 (0.9)	13 (5.2)
2010	4 (3.4)	14 (5.6)
Educational achievement, n (%)		
None	37 (31.4)	57 (22.6)
Middle school	74 (62.7)	146 (57.9)
High school	6 (5.1)	41 (16.3)
College or more	1 (0.9)	8 (3.2)
Cigarette smoking, pack-years, mean ± SD[a]	38.0 ± 23.4	27.1 ± 19.3
Nonsmoker, n (%)	26 (22.0)	154 (61.1)
< 30 pack-years, n (%)	36 (30.5)	59 (23.4)
≥30 pack-years, n (%)	56 (47.5)	39 (15.5)
Alcohol consumption status, n (%)		
Never	50 (42.4)	136 (54)
Former	10 (8.5)	11 (4.4)
Current	58 (49.2)	105 (41.7)
Obesity (BMI), mean ± SD	22.5 ± 2.9	23.8 ± 3.2
No (BMI < 25 kg/m^2), n (%)	99 (83.9)	162 (64.3)
Yes (BMI ≥ 25 kg/m^2), n (%)	19 (16.1)	90 (35.7)
Total lipids (mg/dL), mean ± SD	595.9 ± 136.0	606.5 ± 172.7
Total cholesterol (mg/dL), mean ± SD	192.9 ± 39.3	201.6 ± 41.1
High (≥240 mg/dL), n (%)	15 (12.7)	43 (17.1)
Borderline high (200–239 mg/dL), n (%)	33 (28.3)	85 (33.7)
Optimal (< 200 mg/dL), n (%)	70 (59.3)	124 (49.2)
Triglycerides (mg/dL), mean ± SD	157.4 ± 87.9	148.3 ± 117.1
High (≥200 mg/dL), n (%)	30 (25.4)	44 (17.5)
Borderline high (150–199 mg/dL), n (%)	20 (17.0)	48 (19.1)
Optimal (< 150 mg/dL), n (%)	68 (57.6)	160 (63.5)
Lifetime pesticide use, n (%)		
No	18 (15.3)	88 (34.9)
Yes	100 (84.8)	164 (65.1)

SD, standard deviation; BMI, body mass index.
[a] excluding non-smokers.

All statistical tests were two-sided with a significance level of $P < 0.05$. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for data analysis.

Table 2
Serum concentrations of persistent organic pollutants stratified by lung cancer cases and controls.

	Lung cancer cases						Controls						
	GM (95% CI)	Distribution					GM (95% CI)	Distribution					*P*
		Min	25th	Median	75th	Max		Min	25th	Median	75th	Max	
ΣOCs	2320.8 (2023.7–2661.5)	441.1	1255.9	2140.1	4013.8	34378.9	1830.9 (1670.9–2006.3)	197.3	1087.8	1800.3	2821.6	21110.2	0.004
ΣDDTs[a]	1706.0 (1466.8–1984.2)	228.3	876.9	1582.4	3260.8	33077.3	1365.8 (1239.1–1505.4)	107.3	836.3	1329.8	2135.8	20699.9	0.013
ΣChlordanes[b]	124.0 (109.2–140.7)	28.9	72.9	129.2	204.2	954.2	80.4 (73.0–88.5)	12.8	46.8	74.5	125.6	786.0	< 0.001
β-HCH	141.1 (123.2–161.6)	11.6	87.9	134.0	224.7	1443.1	151.6 (136.8–168.0)	1.0	89.2	149.8	251.1	1511.1	0.423
p,p′-DDE	1546.7 (1323.1–1808.0)	200.8	774.6	1483.2	3031.3	32776.8	1210.8 (1094.3–1339.7)	96.1	717.5	1207.2	1940.5	20303.0	0.008
cis-heptachlor epoxide	29.7 (24.0–36.8)	1.8	15.7	34.1	62.8	330.9	21.1 (17.6–25.2)	1.8	9.9	26.8	55.8	407.2	0.016
trans-nonachlor	87.1 (77.8–97.5)	19.6	58.1	92.4	137.7	411.5	55.2 (50.0–61.0)	3.5	35.4	55.5	88.1	627.9	< 0.001
p,p′-DDD	23.3 (20.2–26.8)	2.1	13.8	22.7	40.2	112.5	22.2 (20.1–24.4)	2.1	12.9	21.5	36.3	169.6	0.568
p,p′-DDT	65.1 (50.3–84.3)	2.0	56.5	89.9	156.3	572.6	79.4 (70.5–89.5)	2.0	57.3	82.1	133.4	866.7	0.170
ΣPCBs	611.8 (549.5–681.1)	147.8	419.5	594.4	888.1	6353.5	418.5 (386.4–453.4)	77.3	264.8	384.3	660.8	5785.5	< 0.001
Mono/dichlorobiphenyls[c]	11.7 (10.1–13.7)	4.8	4.8	9.6	23.1	77.4	9.0 (8.1–9.9)	4.8	4.8	4.8	16.6	101.0	0.003
Tri/tetrachlorobiphenyls[d]	40.6 (36.7–45.0)	14.1	26.5	38.5	57.9	163.1	32.0 (29.9–34.3)	12.6	21.3	30.9	44.5	585.9	< 0.001
Penta/hexachlorobiphenyls[e]	366.5 (328.4–408.9)	98.4	261.9	356.3	529.3	2857.5	263.0 (241.9–285.9)	33.0	169.8	249.6	407.8	2791.3	< 0.001
Hepta/octa/nona/deca-chlorobiphenyls[f]	171.1 (149.6–195.7)	20.4	116.3	169.8	282.6	3348.9	96.0 (86.8–106.1)	18.2	56.5	86.6	169.0	2963.6	< 0.001
Non–/mono-*ortho* PCBs[g]	112.8 (102.0–124.8)	32.4	75.4	107.8	179.9	390.3	86.8 (80.8–93.2)	19.7	57.2	81.6	128.3	718.8	< 0.001
Dioxin-like PCBs[h]	80.9 (72.8–89.8)	22.7	52.4	78.7	116.4	293.0	64.4 (59.7–69.4)	12.1	41.7	62.4	94.7	332.6	< 0.001
Dioxin-like PCB TEQs ($\times 10^{-5}$) [i]	8604.7 (8323.6–8895.4)	8243.5	8332.7	8411.5	8531.8	60484.5	8550.5 (8385.3–8719.0)	8211.7	8300.6	8362.8	8462.9	39164.2	0.732
Non-dioxin-like non–/mono-*ortho* PCBs[j]	25.3 (21.9–29.3)	7.7	14.0	22.8	42.5	146.2	17.5 (15.9–19.2)	7.7	8.7	16.8	29.0	467.4	< 0.001
Di-ortho PCBs[k]	470.0 (419.7–526.4)	91.4	333.1	460.1	693.7	5516.1	312.2 (286.6–340.2)	47.8	192.0	293.9	510.7	5129.2	< 0.001
Tri-/tetra-*ortho* PCBs[l]	7.6 (6.7–8.8)	3.3	3.3	8.2	12.4	213.4	4.7 (4.4–5.1)	3.3	3.3	3.3	6.7	122.2	< 0.001
PCB-52	18.5 (17.0–20.0)	6.4	13.0	18.1	24.8	58.2	17.2 (16.1–18.3)	5.0	11.9	16.2	24.3	166.6	0.161
PCB-101	9.6 (8.5–10.9)	0.9	7.7	10.1	13.8	33.2	7.3 (6.7–8.1)	0.9	5.2	8.1	12.5	57.2	< 0.001
PCB-105	7.5 (6.5–8.6)	1.7	4.3	8.6	13.6	32.2	6.4 (5.8–7.1)	1.7	4.0	7.0	11.0	41.2	0.091
PCB-118	36.5 (32.4–41.1)	8.4	21.3	35.7	59.1	136.4	32.6 (29.9–35.5)	1.4	20.8	32.4	48.5	171.3	0.131
PCB-138	87.2 (77.4–98.4)	15.4	56.5	91.9	139.1	603.8	65.5 (59.7–71.9)	0.8	40.7	63.5	106.4	594.6	< 0.001
PCB-153	186.1 (165.4–209.4)	29.0	127.8	188.3	269.0	1985.2	119.8 (108.3–132.5)	0.5	74.7	115.8	203.3	2022.6	< 0.001
PCB-156	15.7 (13.9–17.7)	1.1	11.5	16.0	25.3	59.7	8.9 (7.9–10.0)	1.1	6.0	9.7	16.8	66.5	< 0.001
PCB-180	150.9 (131.5–173.1)	13.8	103.1	150.0	250.1	2883.5	84.1 (75.7–93.6)	11.6	49.1	78.6	155.6	2485.3	< 0.001

Abbreviations: GM, geometric mean; CI, confidence interval; Min, minimum; 25th, 25th percentile; 75th, 75th percentile; Max, maximum; LOD, limit of detection; OCs, organochlorine pesticides; HCH, hexachlorocyclohexane; DDE, dichlorodiphenyldichloroethylene; DDD, dichlorodiphenyldichloroethane; DDT, dichlorodiphenyltrichloroethane; PCBs, polychlorinated biphenyls; TEQs, total dioxin equivalents.

[a] DDTs: o,p′-DDT, p,p′-DDT, o,p′-DDE, p,p′-DDE, o,p′-DDD, and p,p′-DDD.

[b] Chlordanes: *cis*-chlordane, *trans*-chlordane, oxychlordane, *cis*-nonachlor, *trans*-nonachlor.

[c] Mono- and di-chloro biphenyls: IUPAC# 1, 3, 4, 15.

[d] Tri- and tetra-chloro biphenyls: 19, 28, 37, 52, 54, 77, 81.

[e] Penta- and *hexa*-chloro biphenyls: 101, 104, 105, 114, 118, 123, 126, 138, 153, 155, 156, 157, 167, 169.

[f] Hepta-, octa-, nona-, and deca-chloro biphenyls: 180, 188, 189, 202, 205, 206, 208.

[g] Non– and mono-*ortho* biphenyls: 1, 3, 15, 28, 37, 77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, 189.

[h] Dioxin-like PCBs: 77, 81, 126, 169, 105, 114, 118, 123, 156, 157, 167, 189.

[i] Dioxin-like PCB TEQs: 77, 81, 126, 169, 105, 114, 118, 123, 156, 157, 167, 189.

[j] Non-dioxin-like non– and mono-*ortho* biphenyls: 105, 114, 118, 123, 156, 157, 167, 189.

[k] Di-ortho biphenyls: 4, 52, 101, 138, 153, 180.

[l] Tri- and tetra-ortho biphenyls: 19, 123, 206.

3. Results

Baseline characteristics of the 118 participants with lung cancer and 252 control participants are shown in Table 1. The median follow-up periods for lung cancer cases and controls were 6.5 years (interquartile range [IQR], 3.7–8.7) and 10.1 years (IQR, 8.5–12.1), respectively. Participants with lung cancer were older and less educated, and had a higher proportion of men, cigarette smokers and pesticide users, whereas the control participants were more obese and had a higher total lipid concentrations.

Serum concentrations of total OCs, total PCBs, subgrouped OCs, subgrouped PCBs, and individual POP analytes with a detection rate > 80% are presented in Table 2. Serum concentrations of most OCs and PCBs were significantly higher in lung cancer cases than in control cases. The geometric means of β-HCH and *p,p′*-DDT were higher in controls than in lung cancer cases, but these differences did not reach significance. There were no obvious temporal trends in serum POP concentrations between 2001 and 2010 (Table S4). Concentrations of the 19 OC and 32 PCB analytes are presented in Table S1. Spearman correlations among different POPs were generally moderate or strong (Tables S5 and S6).

4. Serum POP concentrations and risk of lung cancer

Fig. 1 and Table S7 show associations between serum POP concentrations and risk of lung cancer. The risk of lung cancer increased per unit increase in the sum of chlordane congeners, total PCBs, and all PCBs subgrouped by the number of chlorines or *ortho*- substituted chlorines on the molecules, except for tri/tetrachlorobiphenyls, in all models. In addition, among individual POP analytes with a detection rate > 80%, the risk of lung cancer increased per unit increase in the natural log-transformed concentration of *cis*-heptachlor epoxide, *trans*-nonachlor, PCB-101, PCB-138, PCB-153, PCB-156, and PCB-180. However, after strict Bonferroni adjustment, which lowered the significance level to P < 0.004, only *trans*-nonachlor was associated with lung cancer risk.

Similar results were found in sensitivity analyses excluding lung cancer cases diagnosed within 3 and 5 years of cohort entry (Tables S8 and S9).

Results of Cox proportional-hazards models with POP quartiles showed positive dose-response relationships with risk of lung cancer, similar to those with continuous POP variables. Associations between risk of lung cancer and serum concentrations of total and subgrouped OCs by quartiles are shown in Table 3. There were no associations between total OC or sum of DDT quartiles and risk of lung cancer. However, there was an association between risk of lung cancer and the

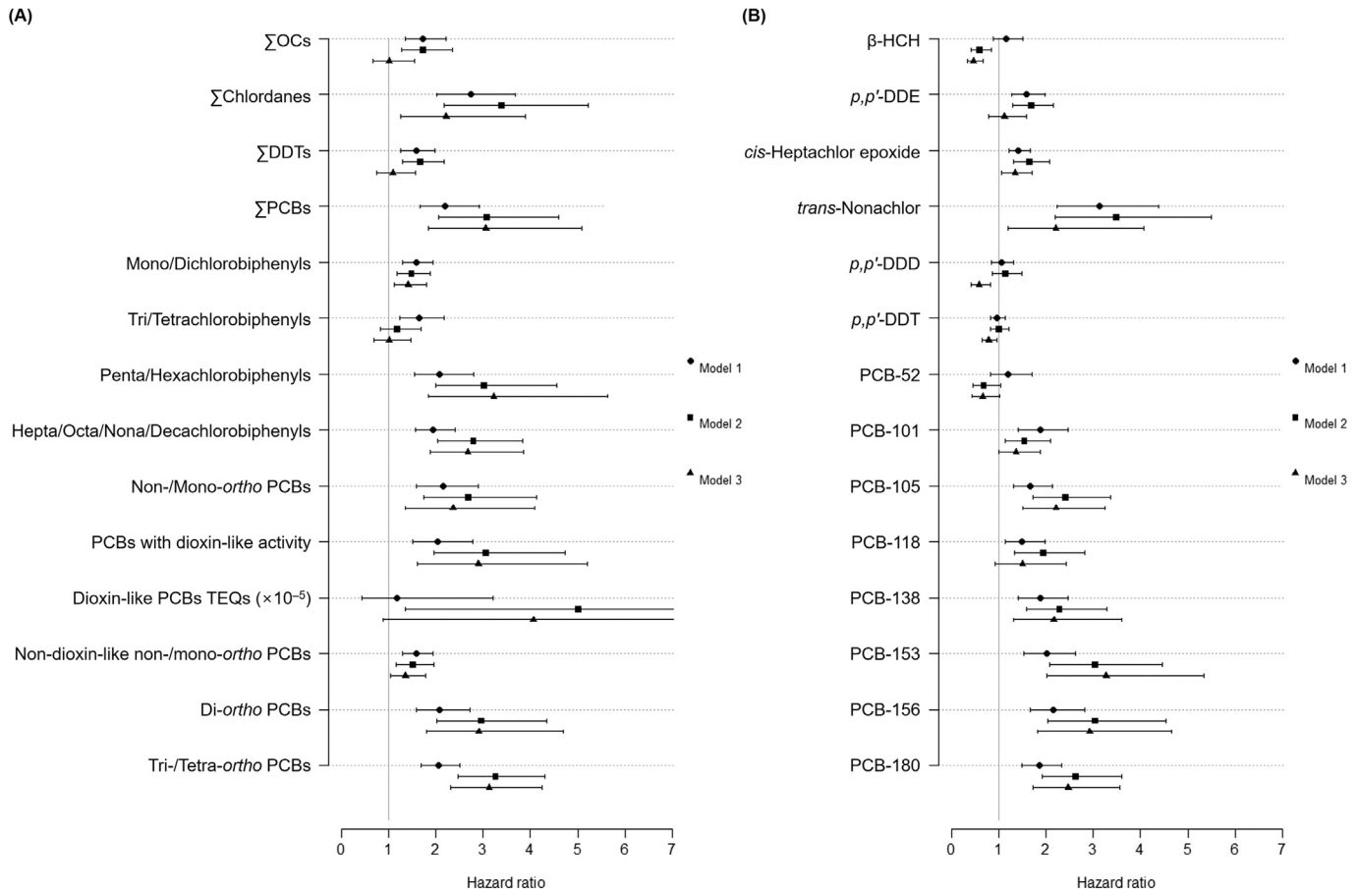

Fig. 1. Associations between wet-weight concentrations of persistent organic pollutants (POPs) and risk of lung cancer in linear Cox proportional-hazards models. Hazard ratios (HRs) are given per unit increase in natural log-transformed serum POP values obtained from Cox proportional-hazards models. **(A)** HRs of lung cancer risk per unit increase in organochlorine pesticide (OC) subgroups metabolites and polychlorinated biphenyl (PCB) congeners subgrouped by the number of chlorines or *ortho*- substituted chlorines on the molecules. **(B)** HRs of lung cancer risk per unit increase in individual analytes with a detection rate > 80%. Model 1: adjusted for age, gender, and total lipids; Model 2: further adjusted for year of entry into the cohort, region, education, cigarette smoking (pack-years), alcohol consumption status, body mass index, and pesticide use; Model 3: further adjusted for total PCBs (in models for OCs) or total OCs (in models for PCBs). Abbreviations: HCH, hexachlorocyclohexane; DDE, dichlorodiphenyldichloroethylene; DDD, dichlorodiphenyldichloroethane; DDT, dichlorodiphenyltrichloroethane.

Table 3
Associations between risk of lung cancer and serum concentrations of total organochlorine pesticides (OCs), sum of dichlorodiphenyltrichloroethanes (DDT), and sum of chlordanes by quartiles.

			Model 1			Model 2			Model 3		
	Level (pg/mL)	Ca/Co	HR (95% CI)	*P*	*P* for trend	HR (95% CI)	*P*	*P* for trend	HR (95% CI)	*P*	*P* for trend
ΣOCs											
1st quartile	< 1133.3	19/63	1		< 0.001	1		0.010	1		0.257
2nd quartile	1133.3–1933.3	25/63	1.70 (0.93–3.12)	0.087		1.34 (0.64–2.82)	0.437		0.85 (0.39–1.86)	0.689	
3rd quartile	1933.4–3070.6	31/63	1.87 (1.05–3.33)	0.034		1.47 (0.72–2.98)	0.286		0.54 (0.24–1.21)	0.134	
4th quartile	≥3070.7	43/63	3.32 (1.84–5.98)	< 0.001		2.34 (1.17–4.68)	0.016		0.61 (0.26–1.47)	0.273	
ΣDDTs											
1st quartile	< 836.3	25/63	1		0.002	1		0.073	1		0.055
2nd quartile	836.3–1329.7	23/63	0.92 (0.52–1.62)	0.760		0.56 (0.28–1.12)	0.100		0.31 (0.15–0.65)	0.002	
3rd quartile	1329.8–2135.7	26/63	1.16 (0.67–2.04)	0.595		0.69 (0.35–1.34)	0.273		0.25 (0.12–0.52)	< 0.001	
4th quartile	≥2135.8	43/63	2.27 (1.32–3.90)	0.003		1.41 (0.75–2.64)	0.286		0.35 (0.16–0.79)	0.012	
ΣChlordanes											
1st quartile	< 46.8	10/63	1		< 0.001	1		< 0.001	1		< 0.001
2nd quartile	46.8–74.4	20/63	1.76 (0.82–3.80)	0.150		2.57 (1.07–6.17)	0.035		2.12 (0.87–5.13)	0.097	
3rd quartile	74.5–125.5	28/63	2.55 (1.22–5.33)	0.013		2.62 (1.09–6.28)	0.031		1.62 (0.61–4.33)	0.336	
4th quartile	≥125.6	59/63	7.34 (3.54–15.23)	< 0.001		17.03 (6.46–44.88)	< 0.001		8.79 (2.77–27.97)	< 0.001	

Abbreviations: HR, hazard ratio; CI, confidence interval. Model 1: adjusted for age, gender, and total lipids; Model 2: further adjusted for year of entry into the cohort, region, education, cigarette smoking (pack-years), alcohol consumption status, body mass index, and pesticide use; Model 3: further adjusted for total polychlorinated biphenyls.

4th quartile of the sum of chlordanes (HR [95% confidence interval (CI)]: 8.79 [2.77–27.97]), with a significant dose-response relationship (*P* for trend < 0.001).

Table 4 shows associations between risk of lung cancer and quartiles of serum concentrations of total PCBs and PCBs subgrouped by the number of chlorines on the molecules. There was an association between risk of lung cancer and concentrations of mono- and dichloro-biphenyls > 4.8 pg/mL (HR [95% CI]: 4.03 [2.53–6.43]). There was no association between risk of lung cancer and tri- and tetrachloro-biphenyl quartiles. For both mid-chlorinated PCBs (i.e., penta- and hexachloro-biphenyls) and high-chlorinated PCBs (i.e., hepta-, octa-, nona-, and decachloro-biphenyls), there were associations between risk of lung cancer and 3rd and 4th quartiles (mid-chlorinated PCBs: 3rd quartile [HR (95% CI): 3.51 (1.43–8.62)], 4th quartile [HR (95% CI): 5.13 (1.71–15.41)]; high-chlorinated PCBs: 3rd quartile [HR (95% CI): 4.39 (1.68–11.46)], 4th quartile [HR (95% CI): 5.10 (1.73–15.08)]), with significant dose-response relationships (mid-chlorinated PCBs: *P* for trend = 0.004, high-chlorinated PCBs: *P* for trend < 0.001).

Serum concentrations of all PCBs subgrouped by the number of *ortho*-substituted chlorines were associated with risk of lung cancer in Cox proportional-hazards models (Table 5). For non- and mono-*ortho* PCBs, risk of lung cancer increased from the 2nd quartile (HR [95% CI]: 4.51 [1.98–10.29]), with a significant dose-response relationship (*P* for trend = 0.031). When we evaluated whether these associations were due to dioxin-like or non-dioxin-like PCBs, we found that increased serum concentrations of dioxin-like PCBs increased the risk of lung cancer across quartiles (2nd quartile [HR (95% CI): 2.99 (1.42–6.30)]; 3rd quartile [HR (95% CI): 2.23 (0.93–5.34)]; 4th quartile [HR (95% CI): 4.03 (1.58–10.29)]), with a significant dose-response relationship (*P* for trend = 0.011), and dioxin TEQs showed a similar association. For non-dioxin-like PCBs, there was an association between risk of lung cancer and the 3rd quartile (HR [95% CI]: 2.82 [1.33–5.99]) but not the 4th quartile (HR [95% CI]: 1.97 [0.96–4.04]). For di-*ortho* PCBs, there were associations between risk of lung cancer and the 3rd (HR [95% CI]: 3.54 [1.43–8.75]) and 4th (HR [95% CI]: 4.63 [1.59–13.52]) quartiles, with a significant dose-response relationship (*P* for trend = 0.003). In addition, risk of lung cancer was associated with concentrations of tri- and tetra-*ortho* PCBs higher than the median (HR [95% CI]: 6.97 [4.15–11.71]).

Table 6 shows associations between risk of lung cancer and serum concentrations of individual POP analytes with a detection rate > 80% by quartiles to evaluate the carcinogenic impact of specific OCs and PCBs. The association between risk of lung cancer and *cis*-heptachlor epoxide was not significant at all quartiles. By contrast, risk of lung cancer was associated with *trans*-nonachlor at the 4th quartile (HR [95% CI]: 4.88 [1.79–13.32]), with a significant dose-response relationship (*P* for trend < 0.001). Associations between risk of lung cancer and β-HCH or DDT congener (e.g., *p,p′*-DDE, *p,p′*-DDD and *p,p′*-DDT) quartiles were inconsistent and mostly non-significant.

Certain PCB congeners were significantly associated with risk of lung cancer. PCB-101 and PCB-105 showed associations from the 2nd quartile, with a significant dose-response relationship (PCB-101: 2nd quartile [HR (95% CI): 4.00 (1.76–9.20)], 3rd quartile [HR (95% CI): 5.80 (2.50–13.46)], 4th quartile [HR (95% CI): 3.70 (1.53–8.96)], *P* for trend = 0.022; PCB-105: 2nd quartile [HR (95% CI): 5.09 (2.56–10.14)], 3rd quartile [HR (95% CI): 2.37 (1.11–5.08)], 4th quartile [HR (95% CI): 5.52 (2.32–13.19)], *P* for trend = 0.001). PCB-138 showed an association at the 4th quartile (HR [95% CI]: 2.46 [1.04–5.83]), not showing a significant dose-response relationship (*P* for trend = 0.056). PCB-153, PCB-156, and PCB-180 showed associations from the 3rd quartile, with significant dose-response relationships (PCB-153: 3rd quartile [HR (95% CI): 3.91 (1.50–10.20)], 4th quartile [HR (95% CI): 5.95 (1.87–18.87)], *P* for trend < 0.001; PCB-156: 3rd quartile [HR (95% CI): 4.59 (1.75–12.00)], 4th quartile [HR (95% CI): 6.28 (2.22–17.78)], *P* for trend < 0.001; PCB-180: 3rd quartile [HR (95% CI): 4.76 (1.83–12.38)], 4th quartile [HR (95% CI): 4.61 (1.56–13.63)], *P* for trend = 0.001). Similar results were found in sensitivity analyses excluding lung cancer cases diagnosed within 3 and 5 years of cohort entry (Tables S8 and S9).

5. Discussion

To the best of our knowledge, this study is the first prospective evaluation of associations between pre-diagnostic serum concentrations of POPs and risk of lung cancer in the general population, in which the body burden of these chemicals is low due to the decades-long ban on their production and usage. Our results suggest that low-dose environmental exposure to POPs increases the risk of lung cancer, with consistent associations between lung cancer risk and chlordane and PCBs across all models. Moreover, the present study included large numbers of chlorinated pesticides and PCB congeners as individual analytes and POPs subgrouped by different mechanisms of action,

Table 4
Associations between risk of lung cancer and quantiles of serum concentrations of total polychlorinated biphenyls (PCBs) and PCBs by the number of chlorines on the molecules.

			Model 1			Model 2			Model 3		
	Levels (pg/mL)	Ca/Co	HR (95% CI)	*P*	*P* for trend	HR (95% CI)	*P*	*P* for trend	HR (95% CI)	*P*	*P* for trend
ΣPCBs											
1st quartile	< 287.3	12/63	1		< 0.001	1		< 0.001	1		0.002
2nd quartile	287.3–463.3	13/63	1.21 (0.55–2.66)	0.643		2.39 (1.00–5.70)	0.050		2.23 (0.92–5.42)	0.076	
3rd quartile	463.4–724.1	39/63	2.83 (1.46–5.48)	0.002		4.32 (1.99–9.41)	< 0.001		3.78 (1.62–8.83)	0.002	
4th quartile	≥724.2	54/63	4.02 (2.09–7.73)	< 0.001		6.16 (2.74–13.84)	< 0.001		4.88 (1.80–13.23)	0.002	
Mono/dichlorobiphenyls											
< 50th	< 4.8	34/134	1		NA	1		NA	1		NA
≥ 50th	≥ 4.8	84/118	4.46 (2.92–6.82)	< 0.001		4.25 (2.66–6.80)	< 0.001		4.03 (2.53–6.43)	< 0.001	
Tri/tetrachlorobiphenyls											
1st quartile	< 21.3	15/63	1		0.007	1		0.750	1		0.616
2nd quartile	21.3–30.8	26/63	1.62 (0.85–3.08)	0.143		1.52 (0.76–3.05)	0.237		1.52 (0.76–3.01)	0.235	
3rd quartile	30.9–44.4	32/63	1.70 (0.90–3.19)	0.102		1.12 (0.55–2.25)	0.757		0.99 (0.49–1.99)	0.969	
4th quartile	≥44.5	45/63	2.30 (1.26–4.21)	0.007		1.26 (0.64–2.49)	0.504		0.99 (0.49–2.00)	0.980	
Penta/hexachlorobiphenyls											
1st quartile	< 169.8	14/63	1		< 0.001	1		< 0.001	1		0.004
2nd quartile	169.8–249.5	13/63	1.00 (0.47–2.13)	0.990		2.30 (0.96–5.51)	0.063		2.20 (0.87–5.55)	0.094	
3rd quartile	249.6–407.7	38/63	2.45 (1.31–4.58)	0.005		3.74 (1.72–8.12)	0.001		3.51 (1.43–8.62)	0.006	
4th quartile	≥407.8	52/63	3.27 (1.76–6.08)	< 0.001		5.69 (2.54–12.78)	< 0.001		5.13 (1.71–15.41)	0.004	
Hepta/octa/nona/decachlorobiphenyls											
1st quartile	< 56.5	9/63	1		< 0.001	1		< 0.001	1		< 0.001
2nd quartile	56.5–86.5	12/63	0.84 (0.35–2.02)	0.694		1.10 (0.41–2.97)	0.849		1.06 (0.39–2.88)	0.908	
3rd quartile	86.6–168.9	38/63	2.76 (1.30–5.86)	0.008		4.96 (1.99–12.36)	0.001		4.39 (1.68–11.46)	0.003	
4th quartile	≥169.0	58/63	3.52 (1.65–7.54)	0.001		6.35 (2.42–16.71)	< 0.001		5.10 (1.73–15.08)	0.003	

Abbreviations: HR, hazard ratio; CI, confidence interval. Model 1: adjusted for age, gender, and total lipids; Model 2: further adjusted for year of entry into the cohort, region, education, cigarette smoking (pack-years), alcohol consumption status, body mass index, and pesticide use; Model 3: further adjusted for total organochlorine pesticides.

Table 5
Associations between risk of lung cancer and quartiles of serum concentrations of polychlorinated biphenyls (PCBs) subgrouped by the number of *ortho*-substituted chlorines on the molecules.

			Model 1			Model 2			Model 3		
	Levels (pg/mL)	Ca/Co	HR (95% CI)	*P*	*P* for trend	HR (95% CI)	*P*	*P* for trend	HR (95% CI)	*P*	*P* for trend
Non-/mono-*ortho* PCBs											
1st quartile	< 57.2	13/63	1		< 0.001	1		< 0.001	1		0.031
2nd quartile	57.2–81.5	21/63	2.73 (1.34–5.56)	0.006		5.03 (2.26–11.20)	< 0.001		4.51 (1.98–10.29)	< 0.001	
3rd quartile	81.6–128.2	41/63	3.93 (2.07–7.47)	< 0.001		5.95 (2.76–12.85)	< 0.001		4.74 (2.01–11.20)	< 0.001	
4th quartile	≥128.3	43/63	4.01 (2.09–7.69)	< 0.001		5.84 (2.60–13.10)	< 0.001		4.31 (1.66–11.16)	0.003	
PCBs with dioxin-like activity											
1st quartile	< 41.7	16/63	1		< 0.001	1		< 0.001	1		0.011
2nd quartile	41.7–62.3	25/63	2.21 (1.16–4.18)	0.015		3.36 (1.63–6.92)	0.001		2.99 (1.42–6.30)	0.004	
3rd quartile	62.4–94.6	30/63	2.51 (1.34–4.69)	0.004		2.89 (1.33–6.32)	0.008		2.23 (0.93–5.34)	0.071	
4th quartile	≥94.7	47/63	3.40 (1.87–6.19)	< 0.001		5.66 (2.61–12.28)	< 0.001		4.03 (1.58–10.29)	0.004	
Dioxin-like PCB TEQs ($\times 10^{-5}$)											
1st quartile	< 8300.6	16/63	1		< 0.001	1			1		0.033
2nd quartile	8300.6–8362.7	25/63	2.23 (1.18–4.23)	0.014		3.43 (1.66–7.07)	0.001	< 0.001	3.03 (1.43–6.42)	0.004	
3rd quartile	8362.8–8462.8	28/63	2.24 (1.19–4.20)	0.012		3.00 (1.37–6.57)	0.006		2.35 (0.98–5.60)	0.055	
4th quartile	≥8462.9	48/63	3.71 (2.04–6.75)	< 0.001		4.98 (2.32–10.69)	< 0.001		3.49 (1.35–9.01)	0.010	
Non-dioxin-like non–/mono-*ortho* PCBs											
1st quartile	< 8.7	12/63	1		< 0.001	1		0.009	1		0.060
2nd quartile	8.7–16.7	30/63	2.09 (1.06–4.11)	0.033		1.28 (0.61–2.68)	0.513		1.34 (0.64–2.77)	0.439	
3rd quartile	16.8–28.9	32/63	3.53 (1.79–6.95)	< 0.001		3.21 (1.53–6.75)	0.002		2.82 (1.33–5.99)	0.007	
4th quartile	≥29.0	44/63	2.97 (1.54–5.71)	0.001		2.30 (1.14–4.64)	0.020		1.97 (0.96–4.04)	0.064	
Di-*ortho* PCBs											
1st quartile	< 192.0	11/63	1		< 0.001	1		< 0.001	1		0.003
2nd quartile	192.0–293.8	13/63	0.99 (0.44–2.21)	0.971		1.68 (0.67–4.17)	0.267		1.57 (0.62–3.99)	0.344	
3rd quartile	293.9–510.6	43/63	2.78 (1.41–5.46)	0.003		4.03 (1.77–9.16)	0.001		3.54 (1.43–8.75)	0.006	
4th quartile	≥510.7	50/63	3.56 (1.80–7.05)	< 0.001		5.77 (2.44–13.62)	< 0.001		4.63 (1.59–13.52)	0.005	
Tri-/tetra-*ortho* PCBs											
< 50th	< 3.3	39/168	1		NA	1		NA	1		NA
≥50th	≥3.3	78/84	4.84 (3.25–7.22)	< 0.001		7.47 (4.53–12.31)	< 0.001		6.97 (4.15–11.71)	< 0.001	

Abbreviations: HR, hazard ratio; CI, confidence interval; TEQs, total dioxin equivalents. Model 1: adjusted for age, gender, and total lipids; Model 2: further adjusted for year of entry into the cohort, region, education, cigarette smoking (pack-years), alcohol consumption status, body mass index, and pesticide use; Model 3: further adjusted for total organochlorine pesticides.

Table 6
Associations between risk of lung cancer and serum concentrations of individual persistent organic pollutants analytes with a detection rate > 80% by quartiles.

			Model 1			Model 2			Model 3		
	Levels (pg/mL)	Ca/Co	HR (95% CI)	*P*	*P* for trend	HR (95% CI)	*P*	*P* for trend	HR (95% CI)	*P*	*P* for trend
OCs											
β-HCH											
1st quartile	< 88.5	31/63	1		0.191	1		0.007	1		0.002
2nd quartile	88.5–143.3	34/63	1.63 (0.98–2.69)	0.059		1.19 (0.68–2.08)	0.554		1.23 (0.69–2.19)	0.487	
3rd quartile	143.4–244.3	28/63	1.64 (0.93–2.88)	0.087		0.78 (0.37–1.63)	0.507		0.76 (0.36–1.63)	0.484	
4th quartile	≥244.4	25/63	1.50 (0.81–2.80)	0.202		0.26 (0.11–0.64)	0.003		0.18 (0.07–0.48)	0.001	
p,p′-DDE											
1st quartile	< 747.5	21/63	1		< 0.001	1		0.044	1		0.089
2nd quartile	747.5–1301.6	28/63	1.36 (0.77–2.41)	0.294		0.87 (0.43–1.75)	0.690		0.50 (0.24–1.06)	0.070	
3rd quartile	1301.7–2150.5	27/63	1.68 (0.94–3.02)	0.083		1.23 (0.61–2.46)	0.561		0.45 (0.21–0.98)	0.044	
4th quartile	≥2150.6	42/63	2.58 (1.46–4.56)	0.001		1.63 (0.84–3.17)	0.153		0.41 (0.18–0.96)	0.040	
cis-heptachlor epoxide											
1st quartile	< 12.4	17/63	1		< 0.001	1		< 0.001	1		0.093
2nd quartile	12.4–28.5	31/63	2.10 (1.16–3.79)	0.014		2.46 (1.23–4.92)	0.011		1.91 (0.96–3.81)	0.065	
3rd quartile	28.6–56.7	36/63	3.06 (1.71–5.51)	< 0.001		3.23 (1.48–7.05)	0.003		2.18 (1.00–4.76)	0.050	
4th quartile	≥56.8	34/63	3.66 (1.94–6.88)	< 0.001		4.66 (2.06–10.55)	< 0.001		2.29 (0.97–5.40)	0.060	
trans-nonachlor											
1st quartile	< 38.9	11/63	1		< 0.001	1		< 0.001	1		< 0.001
2nd quartile	38.9–65.4	15/63	1.03 (0.47–2.26)	0.940		1.38 (0.57–3.37)	0.477		1.24 (0.51–3.01)	0.630	
3rd quartile	65.5–109.4	30/63	2.30 (1.15–4.62)	0.019		2.36 (1.03–5.45)	0.044		1.42 (0.57–3.57)	0.453	
4th quartile	≥109.5	62/63	6.38 (3.24–12.59)	< 0.001		9.24 (3.87–22.08)	< 0.001		4.88 (1.79–13.32)	0.002	
p,p′-DDD											
1st quartile	< 13.4	25/63	1		0.878	1		0.919			
	1		< 0.001								
2nd quartile	13.4–21.4	34/63	1.77 (1.04–3.01)	0.036		2.94 (1.51–5.69)	0.001		1.65 (0.84–3.24)	0.146	
3rd quartile	21.5–37.9	20/63	0.89 (0.49–1.62)	0.695		0.87 (0.40–1.87)	0.714		0.36 (0.16–0.83)	0.017	
4th quartile	≥38.0	39/63	1.30 (0.75–2.25)	0.354		1.60 (0.82–3.10)	0.169		0.41 (0.18–0.90)	0.025	
p,p′-DDT											
1st quartile	< 56.9	32/63	1		0.821	1		0.343	1		0.030
2nd quartile	56.9–83.7	22/63	0.90 (0.52–1.58)	0.721		0.74 (0.39–1.39)	0.342		0.49 (0.26–0.93)	0.029	
3rd quartile	83.8–140.5	28/63	0.80 (0.48–1.33)	0.383		0.66 (0.35–1.23)	0.186		0.41 (0.21–0.78)	0.007	
4th quartile	≥140.6	36/63	1.13 (0.67–1.90)	0.651		1.40 (0.76–2.58)	0.287		0.45 (0.21–0.94)	0.035	
PCBs											
PCB-52											
1st quartile	< 12.4	19/63	1		0.318	1		0.241	1		0.277
2nd quartile	12.4–16.9	29/63	1.77 (0.98–3.17)	0.057		1.73 (0.89–3.38)	0.108		1.54 (0.77–3.06)	0.222	
3rd quartile	17.0–24.5	36/63	1.46 (0.82–2.57)	0.195		0.97 (0.51–1.86)	0.929		0.91 (0.48–1.74)	0.784	
4th quartile	≥24.6	34/63	1.51 (0.85–2.67)	0.158		0.91 (0.47–1.76)	0.770		0.90 (0.46–1.76)	0.755	
PCB-101											
1st quartile	< 6.0	9/63	1		< 0.001	1		< 0.001	1		0.022
2nd quartile	6.0–8.7	27/63	3.33 (1.56–7.11)	0.002		3.97 (1.70–9.27)	0.002		4.00 (1.74–9.20)	0.001	
3rd quartile	8.8–13.0	41/63	5.88 (2.81–12.29)	< 0.001		7.49 (3.30–16.98)	< 0.001		5.80 (2.50–13.46)	< 0.001	
4th quartile	≥13.1	41/63	5.54 (2.63–11.67)	< 0.001		5.07 (2.18–11.82)	< 0.001		3.70 (1.53–8.96)	0.004	
PCB-105											
1st quartile	< 4.2	23/63	1		< 0.001	1		< 0.001	1		0.001
2nd quartile	4.2–7.1	29/63	3.00 (1.69–5.33)	< 0.001		5.50 (2.78–10.88)	< 0.001		5.09 (2.56–10.14)	< 0.001	
3rd quartile	7.2–11.9	26/63	1.81 (1.02–3.22)	0.044		2.95 (1.44–6.05)	0.003		2.37 (1.11–5.08)	0.026	
4th quartile	≥12.0	40/63	3.63 (2.02–6.55)	< 0.001		7.76 (3.59–16.79)	< 0.001		5.52 (2.31–13.19)	< 0.001	
PCB-118											
1st quartile	< 21.1	27/63	1		0.049	1		0.106	1		0.768
2nd quartile	21.1–33.1	25/63	1.33 (0.76–2.32)	0.317		1.41 (0.72–2.74)	0.313		1.04 (0.52–2.08)	0.904	
3rd quartile	33.2–53.6	27/63	1.27 (0.74–2.20)	0.387		0.94 (0.47–1.86)	0.857		0.63 (0.31–1.30)	0.212	
4th quartile	≥53.7	39/63	1.79 (1.05–3.07)	0.034		2.05 (1.01–4.17)	0.048		1.05 (0.46–2.41)	0.905	
PCB-138											
1st quartile	< 45.3	17/63	1		< 0.001	1		< 0.001	1		0.056
2nd quartile	45.3–70.9	19/63	1.30 (0.67–2.52)	0.445		1.92 (0.90–4.11)	0.092		1.72 (0.79–3.74)	0.170	
3rd quartile	71.0–114.3	34/63	2.07 (1.14–3.76)	0.017		2.74 (1.34–5.60)	0.006		2.12 (0.96–4.68)	0.063	
4th quartile	≥114.4	48/63	3.05 (1.70–5.49)	< 0.001		3.62 (1.78–7.35)	< 0.001		2.46 (1.04–5.83)	0.041	
PCB-153											
1st quartile	< 85.2	12/63	1		< 0.001	1		< 0.001	1		< 0.001

(*continued on next page*)

Table 6 (*continued*)

			Model 1			Model 2			Model 3		
	Levels (pg/mL)	Ca/Co	HR (95% CI)	*P*	*P* for trend	HR (95% CI)	*P*	*P* for trend	HR (95% CI)	*P*	*P* for trend
2nd quartile	85.2–145.6	13/63	0.95 (0.43–2.09)	0.896		1.67 (0.66–4.20)	0.276		1.61 (0.61–4.28)	0.336	
3rd quartile	145.7–230.9	39/63	2.36 (1.22–4.56)	0.011		4.11 (1.79–9.46)	0.001		3.91 (1.50–10.20)	0.005	
4th quartile	≥231.0	54/63	3.42 (1.77–6.61)	< 0.001		6.45 (2.69–15.46)	< 0.001		5.95 (1.87–18.87)	0.003	
PCB-156											
1st quartile	< 7.3	8/63	1		< 0.001	1		< 0.001	1		< 0.001
2nd quartile	7.3–11.6	13/63	1.82 (0.74–4.43)	0.190		2.49 (0.93–6.68)	0.069		2.36 (0.88–6.35)	0.088	
3rd quartile	11.7–18.9	41/63	4.56 (2.11–9.87)	< 0.001		5.47 (2.15–13.90)	< 0.001		4.59 (1.75–12.00)	0.002	
4th quartile	≥19.0	56/63	5.55 (2.57–11.99)	< 0.001		8.49 (3.23–22.32)	< 0.001		6.28 (2.22–17.78)	0.001	
PCB-180											
1st quartile	< 56.1	9/63	1		< 0.001	1		< 0.001	1		0.001
2nd quartile	56.1–103.9	11/63	0.82 (0.34–2.01)	0.668		1.06 (0.39–2.91)	0.911		1.02 (0.37–2.82)	0.968	
3rd quartile	104.0–179.4	41/63	3.12 (1.48–6.56)	0.003		5.56 (2.24–13.79)	< 0.001		4.76 (1.83–12.38)	0.001	
4th quartile	≥179.5	57/63	3.53 (1.66–7.51)	0.001		6.10 (2.31–16.11)	< 0.001		4.61 (1.56–13.63)	0.006	

Abbreviations: HR, hazard ratio; CI, confidence interval; HCH, hexachlorocyclohexane; DDE, dichlorodiphenyldichloroethylene; DDD, dichlorodiphenyldichloroethane; DDT, dichlorodiphenyltrichloroethane; OCs, organochlorine pesticides; PCBs, polychlorinated biphenyls. Model 1: adjusted for age, gender, and total lipids; Model 2: further adjusted for year of entry into the cohort, region, education, cigarette smoking (pack-years), alcohol consumption status, body mass index, and pesticide use; Model 3: further adjusted for total PCBs (in models for OCs) or total OCs (in models for PCBs).

which were not investigated in previous studies. These meaningful findings were strengthened by comprehensive adjustment for several potential confounders including smoking, alcohol consumption, obesity, and exposure to other POPs.

Despite the comprehensive findings, the associations between environmental exposure to POPs and lung cancer risk may be underestimated. We presented the findings based on a model further adjusted for serum concentrations of total OCs or total PCBs like previous study (Aminov et al., 2016). However, these approaches may lead to attenuate strength of the associations, due to over-adjustment because serum concentrations of POPs are highly correlated. In particular, exposure to POPs in general populations need to be considered as lipophilic chemical mixtures rather than individual chemical or specific groups of chemicals, and thus their adverse health outcomes may be results of the mixture (Goodson et al., 2015; Lee et al., 2017a). In the current study, all significant associations found in this study had lower HRs in the model with adjustment for other POPs than in model without. Adjustment of PCBs even changed the direction of association of OCs from positive in model 1 and 2 to inverse in model 3, which may be due to stronger association of PCBs with lung cancer than that of OCs in this study. Thus, the findings from statistical model without further adjustment for exposure to other POPs, may be closer to real relationships between exposure to POPs and lung cancer risk. Furthermore, associations between pre-diagnostic serum concentrations of POPs and lung cancer risk in this study may reflect carcinogenic effects on POPs mixtures stored in adipose tissue, because background serum concentrations of POPs are determined by the physiological release of POPs from adipose tissue into the circulation, except the cases of increased lipolysis such as weight loss (Lee et al., 2017a). This is supported with sensitivity analyses excluding lung cancer cases diagnosed within 3 or 5 years of entry into the cohort to determine whether serum concentrations of lipids and POPs were influenced by weight loss which could be caused by undiagnosed or preclinical lung cancer. Therefore, these findings may have important implications for the effect of POPs bioaccumulated and persisted in human body on risk of lung cancer.

The International Agency for Research on Cancer (IARC) evaluated chlordane and heptachlor in 2000 and classified these compounds as possible human carcinogens (Group 2B) due to inadequate evidence from humans and sufficient evidence of carcinogenicity from experimental animals (IARC, 2001). However, recent well-designed prospective cohort studies suggest that pre-diagnostic serum levels of chlordane and heptachlor metabolites are associated with the development of liver cancer, non-Hodgkin's lymphoma, and acute myeloid leukemia (Bassig et al., 2019b; Engel et al., 2019) and then the present study also shows that serum levels of *trans*-nonachlor (i.e., chlordane metabolite) was associated with lung cancer risk, even after strict Bonferroni adjustment.

In 2013, the IARC classified PCBs as carcinogenic to humans (i.e., group 1) due to sufficient evidence of carcinogenicity from both humans and experimental animals, and dioxin-like PCBs were classified as group 1, based on several lines of evidence that aryl hydrocarbon receptor (AhR)-mediated carcinogenesis is identical to that of 2,3,7,8-tetrachlorodibenzo-*para*-dioxin. Relationships between malignant melanoma and PCBs are consistently detected in occupational cohort studies. PCBs are also associated with the risk of developing non-Hodgkin's lymphoma and breast cancer, but these associations are inconsistent, providing limited evidence. In addition, available data on other cancers are scanty (IARC, 2016).

The present study shows that low-dose exposure to PCBs could be strongly carcinogenic in humans regardless of their degree of chlorination, substitution pattern, or binding affinity to receptors (e.g., strong affinity for AhRs). All PCBs have multiple modes of action, including formation of reactive oxygen species, genotoxic effects, immune suppression and inflammatory response, and interaction with numerous receptors through a variety of pathways (IARC, 2016; Kumar et al., 2014a; Kumar et al., 2014b). Low-chlorinated PCBs are rapidly metabolized into highly reactive oxygen species by CYP-dependent monooxygenases, which produce DNA adducts and cause direct genotoxic and mutagenic effects. By contrast, highly chlorinated PCBs are poorly metabolized and thus very persistent. They act on enzymes involved in the metabolism of xenobiotics via binding to AhRs as well as CYP-dependent mono-oxygenases, microsomal epoxide hydrolase, glutathione transferases, and UDP-glucuronosyl transferases, thereby producing reactive oxygen species, lipid peroxidation, and alkylating DNA adducts (IARC, 2016) and exerting carcinogenic effects. PCBs also bind to many different receptors, including AhRs, constitutive androstane, pregnane xenobiotic, and steroid nuclear receptors such as androgen and estrogen receptors. AhR activation is a key mechanism of

carcinogenesis mediated by dioxin-like PCBs, which induce deregulation of cell cycle control and cell proliferation, inhibition of apoptosis, and suppression of cell-to-cell communication and adhesion (Guerrina et al., 2018; IARC, 2016). Recent studies provide mounting evidence of an association between AhR overexpression and lung cancer. The overexpression of AhRs promotes tumor growth, and carcinogenicity related to AhR overexpression in the context of lung cancer might be a consequence of AhR-dependent acceleration of cell proliferation and cell cycle progression and increased cell survival (Tsay et al., 2013). Non-dioxin-like PCBs induce activation of constitutive androstane and pregnane xenobiotic receptors, inhibiting cell-to cell communication and cell adhesion (IARC, 2016; Kumar et al., 2014a; Kumar et al., 2014b). Thus, low-dose environmental exposure to a mixture of PCBs may have more than additive effects. On the other hand, unlike the extensive mechanistic evidence supporting the carcinogenicity of PCBs, available mechanistic data on the carcinogenicity of chlordane and heptachlor are limited. Several studies report that exposure to chlordane and heptachlor is associated with global DNA methylation, including DNA hypermethylation and nonmonotonic relationships, and T-cell immunosenescence (Alexander et al., 2017; Lee et al., 2017b; Ryu et al., 2018).

This study has several limitations. First, serum samples were collected at baseline when participants entered the cohort, and POP concentrations were only measured once. However, due to the long half-life of POPs and their bioaccumulation in the human body, a single measurement of POPs is generally accepted as an appropriate proxy for chronic exposure levels. Second, we could not consider lifestyle changes, including smoking history (e.g., intensity of cigarette smoking, types of smoked tobacco, change of preferred tobacco products), diet, physical activity, and weight loss etc., which could increase (or reduce) the external exposure, or could elevate the elimination from body, or could cause release of POPs from adipose tissue into the circulation. However, it might not distort the association between POPs exposure and lung cancer risk in the current study, as these were not accounted both in cases and controls and additional analyses excluding lung cancer cases diagnosed within 3 and 5 years after cohort entry produced consistent findings. Third, the effect of multiple exposures to OCs and/or PCBs on lung cancer risk was not considered, although we evaluated relationships between total and subgroup serum concentrations of OCs and PCBs and lung cancer risk. Regarding the fact that POPs are present as chemical mixtures in the environment and are known to be inter-correlated, further studies to measure carcinogenic effects of POPs as chemical mixtures may be needed (Goodson et al., 2015; Lee et al., 2017a). Fourth, as with most observational studies, our study involves several potentially confounding factors. To overcome this limitation, we adjusted for age, gender, region, education, smoking history, alcohol consumption, obesity, and history of pesticide use. However, our results may still be influenced by bias related to other confounders (e.g., demographic characteristics, behavioral habits, past medical history) due to self-reporting and the possibility of unobserved or excluded confounders (e.g., family history of cancer, occurrence of stressful events). Fifth, the KNCCC cohort is not representative of the general population of Korea, as it was derived from only a few counties and cities. However, prospective cohort studies are greatly needed to determine causal associations between exposure and disease and may not require representativeness (Rothman et al., 2013). Moreover, despite our efforts to ensure randomness and reduce the possibility of selection bias, the potential for such biases remain. Finally, we had limited statistical power due to a relatively small sample size, which led to risk estimates with wide confidence intervals in sensitivity analyses and made it impossible to conduct effect modification analysis to investigate interaction with known risk factors such as cigarette smoke. Thus, studies with larger sample sizes are needed to validate our findings.

In the Republic of Korea, the production and use of chlordane and heptachlor were banned in 1977 and 1979, respectively (Cha et al., 2014). Also, the use of PCBs in electrical equipment has been banned since 1979, but contamination by PCBs continues due to the recycling of contaminated insulating oil and dissolution from equipment (Kim and Lee, 2010). The present study shows that POPs are still detected in serum samples collected 20–30 years after their ban and could induce lung cancer. However, the serum concentrations of POPs observed in the present study are lower than previously reported values. For example, the control participants in this study (mean age: 61.1 years, 2001–2010) had lower concentrations of *p,p′*-DDE (164.8 ng/g lipid) and PCB-180 (11.1 ng/g lipid) than those in a US population (age: ≥20 years, 2003–2004; *p,p′*-DDE: 233 ng/g lipid; PCB-180: 21.5 ng/g lipid) or Asian populations (mean age: 57 years, Shanghai Women's Health Study (1996–2000), Shanghai Cohort Study (1986–1989), and Singapore Chinese Health Study (2000–2004); *p,p′*-DDE: 8,070 ng/g lipid; PCB-180: 15.5 ng/g lipid) (Bassig et al., 2019a; Centers for Disease Control and Prevention, 2019).

Our findings indicate that the current ubiquitous exposure to POPs in the environment worldwide could lead to lung cancer. However, the serum concentrations of POPs associated with risk of lung cancer in the present study were lower than those in the general US population (e.g., 75th percentile, PCB-156: 2.1 ng/g lipid in this study vs. 7.81 ng/g lipid in US adults) (Centers for Disease Control and Prevention, 2019), which has important implications for reducing the incidence of lung cancer.

6. Conclusions

In conclusion, serum concentrations of chlordane and PCBs are associated with risk of lung cancer in the general population, even decades after the ban on their production and use. These results suggest that public health actions should be taken to limit exposure to POPs, especially PCBs, and to provide information on the adverse effects of POPs to the public.

CRediT authorship contribution statement

Eun Young Park: Conceptualization, Funding acquisition, Methodology, Validation, Writing - original draft & editing. **Eunjung Park:** Data curation, Formal analysis, Validation. **Jinsun Kim:** Formal analysis, Visualization. **Jinkyoung Oh:** Investigation, Writing - review & editing. **Byungmi Kim:** Data Interpretation, Writing - review & editing. **Yun-Chul Hong:** Data Interpretation, Writing - review & editing. **Min Kyung Lim:** Supervision, Funding acquisition, Resources, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We appreciate our collaborators at the public health centers of Haman-gun, Changwon-si, Chungju-si, Chuncheon-si, and the Health Center and County Hospital of Sancheong-gun for their support with implementation of the field surveys, clinical laboratory examinations, and data collection, retrieval, and analyses.

Funding

This work was supported by the National Cancer Center, Republic of Korea (No. 1710240-3) and a National Research Foundation of Korea (NRF), Republic of Korea (No. 2017R1A2B4009663). The funders had no role in the design or conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, review,

or approval of the manuscript; or the decision to submit the manuscript for publication.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105925.

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