



저작자표시-비영리-변경금지 2.0 대한민국

이용자는 아래의 조건을 따르는 경우에 한하여 자유롭게

- 이 저작물을 복제, 배포, 전송, 전시, 공연 및 방송할 수 있습니다.

다음과 같은 조건을 따라야 합니다:



저작자표시. 귀하는 원저작자를 표시하여야 합니다.



비영리. 귀하는 이 저작물을 영리 목적으로 이용할 수 없습니다.



변경금지. 귀하는 이 저작물을 개작, 변형 또는 가공할 수 없습니다.

- 귀하는, 이 저작물의 재이용이나 배포의 경우, 이 저작물에 적용된 이용허락조건을 명확하게 나타내어야 합니다.
- 저작권자로부터 별도의 허가를 받으면 이러한 조건들은 적용되지 않습니다.

저작권법에 따른 이용자의 권리는 위의 내용에 의하여 영향을 받지 않습니다.

이것은 [이용허락규약\(Legal Code\)](#)을 이해하기 쉽게 요약한 것입니다.

[Disclaimer](#)

Serum persistent organic pollutants  
and prostate cancer risk

Jung-eun Lim

The Graduate School  
Yonsei University  
Department of Public Health

Serum persistent organic pollutants  
and prostate cancer risk

A Dissertation

Submitted to the Department of Public Health  
and the Graduate School of Yonsei University  
in partial fulfillment of the requirements for the degree of  
Doctor of Philosophy of Public Health

Jung-eun Lim

June 2016

This certifies that the dissertation of Jung-eun Lim is approved.

This certifies that the dissertation of Jung-eun Lim is approved.

Sun Ha Jee

Thesis Supervisor: Sun Ha Jee

Chungmo Nam

Chungmo Nam: Thesis Committee Member #1

Jiyeon Yang

Jiyeon Yang: Thesis Committee Member #2

Koon Ho Rha

Koon Ho Rha: Thesis Committee Member #3

KM Lim

Kyung-Min Lim: Thesis Committee Member #4

The Graduate School

Yonsei University

June 2016

# CONTENTS

|  |     |
|--|-----|
| TABLE INDEX .....                                    | iii |
| FIGURE INDEX .....                                   | v   |
| APPENDIX INDEX .....                                 | vi  |
| ABSTRACT .....                                       | vii |
| <br>   |     |
| <b>I. INTRODUCTION</b> .....                         | 1   |
| <br>   |     |
| <b>II. OBJECTIVES</b> .....                          | 3   |
| <br>   |     |
| <b>III. MATERIALS AND METHODS</b> .....              | 4   |
| A. Study population .....                            | 4   |
| B. Chemistry and anthropometric measurement .....    | 7   |
| C. Persistent organic pollutants analyses .....      | 7   |
| D. The definition of outcome .....                   | 8   |
| E. Statistical analysis .....                        | 9   |
| F. Toxicokinetic modeling .....                      | 10  |
| i. Basic model assumptions .....                     | 10  |
| ii. Toxicokinetic model structure .....              | 11  |
| <br>   |     |
| <b>IV. RESULTS</b> .....                             | 13  |
| A. General characteristics of study population ..... | 13  |
| B. Case-cohort study .....                           | 21  |
| C. Case-control study .....                          | 28  |
| D. Application of toxicokinetic modelling .....      | 32  |

|                             |    |
|-----------------------------|----|
| <b>V. DISCUSSION</b> .....  | 34 |
| <b>VI. CONCLUSION</b> ..... | 39 |
| REFERENCES .....            | 40 |
| APPENDIXES .....            | 47 |
| ABSTRACT IN KOREAN .....    | 53 |

## TABLE INDEX

|  |    |
|--|----|
| Table 1. Characteristics of the study population according to prostate cancer status .....   | 14 |
| Table 2. Previously suggested groupings of PCB congeners .....   | 15 |
| Table 3. Compound specific level in case and sub-cohort members who are included in case-cohort study .....  | 16 |
| Table 4. Spearman's rank correlation analysis of the relationship between concentrations of frequently detected (Detection rate $\geq 80$ % in total participants) pollutants in serum samples in participants without prostate cancer in sub-cohort (N=256) ..... | 19 |
| Table 5. Spearman's rank correlation analysis of the relationship between concentrations of frequently detected (Detection rate $\geq 80$ % in total participants) pollutants in serum samples in participants incidence case (N=110) .....                        | 20 |
| Table 6. HRs of prostate cancer in association with serum concentrations of individual organochlorine pesticides in weighted Cox regression model .....  | 22 |
| Table 7. HRs of prostate cancer in association with serum concentrations of individual polychlorinated biphenyl congeners in weighted Cox regression model .....   | 23 |
| Table 8. Summation effect of persistent organic pollutants on prostate cancer in weighted Cox regression model .....   | 25 |
| Table 9. Association between summarized polychlorinated biphenyls level and the risk for prostate cancer in weighted Cox regression model .....  | 27 |
| Table 10. Summation effect of persistent organic pollutants on prostate cancer in logistic regression analysis. (N=502) .....  | 29 |
| Table 11. Logistic analysis between summarized polychlorinated biphenyls level and the risk for prostate cancer .....  | 31 |

Table 12. Applying toxicokinetic model on the result of logistic regression of TEQ-based-dioxin-like PCBs and the risk for prostate cancer .....33



## FIGURE INDEX

|  |    |
|--|----|
| Figure 1. Participants eligibility and criteria for Cox proportional hazard model  | 5  |
| Figure 2. Participants eligibility and criteria for logistic regression model  | 6  |
| Figure 3. Individual organochlorine pesticides level with detection rate $\geq 80\%$ , in case-cohort study population (N=366) | 17 |
| Figure 4. Individual polychlorinated biphenyls level with detection rate $\geq 80\%$ , in case-cohort study population (N=366) | 18 |

## APPENDIX INDEX

|   |    |
|---|----|
| Table A1. The information of PCB congeners included in this study .....   | 47 |
| Figure A1. Persistent organic pollutants levels according to year at blood drawn to analysis in participants without prostate cancer in sub-cohort (N=256). The last category included 34 person whose blood was drawn in 2009, and one person whose blood was drawn in 2010. ....                | 49 |
| Figure A2. Persistent organic pollutants levels according to year at blood drawn to analysis in prostate cancer incidence case. The last category included four person whose blood were drawn in 2009, two person whose blood was drawn in 2011, and 1 person whose blood was drawn in 2013. .... | 50 |
| Appendix A.1. The process of calculating tolerable daily intake .....   | 51 |

# ABSTRACT

## Serum persistent organic pollutants and prostate cancer risk

Jung-eun Lim

Dept. of Public Health

The Graduate School

Yonsei University

### **Background:**

Until now, most of the human epidemiological studies examining health effects of persistent organic pollutants (POPs) on prostate cancer were conducted as a case-control study design with a small number of participants. Moreover, most of the health risk assessment results were based on animal studies. The present study was a prospective cohort analysis to evaluate the associations between serum concentrations of POPs and prostate cancer risk in Koreans. Using the toxicokinetic model, we estimated cancer hazard risk from exposure to POPs based on human bio-monitoring data.

### **Methods:**

A case-cohort study was performed based on the Korean Cancer Prevention Study-II. Within the cohort we identified 110 people diagnosed with prostate cancer based on the National Cancer Registry and randomly selected 256 sub-cohort participants without

prostate cancer. We measured concentrations of 32 polychlorinated biphenyl (PCB) congeners and 19 organochlorine pesticides (OCPs) in serum samples. The toxic equivalent (TEQ) was calculated based on the individual toxic equivalency factor (TEF) of each PCB congener released from the World Health Organization (WHO) in 2005. Associations between POPs and the risk of prostate cancer incidence were analyzed using the Cox proportional hazard model. We applied toxicokinetic model based on the crude logistic regression model of TEQ and prostate cancer risk to estimate cancer hazard for exposure to POPs.

**Results:**

The prostate cancer cases showed elevated serum POPs levels, except for two PCB congeners (PCB52 and PCB101). In a case-cohort study, the increased risk of prostate cancer incidence was observed in the upper tertile of the sum of dioxin-like PCBs (P for trend=0.0395), the sum of non- dioxin-like PCBs (P for trend=0.0019), and TEQ (P for trend=0.0063), compared with the lowest tertile of each POP. Individual POPs ( $\beta$ -HCH, PCB118, PCB167, PCB138, PCB153, and PCB180) showed positive associations with prostate cancer risk. Applying the one-compartment toxicokinetic model, regarding prostate cancer incidence risk we proposed a maximum daily exposure limit of 0.494 pg TEQ/kg bw/day to dioxin-like PCBs.

**Conclusion:**

The findings of this study suggested that the exposure to specific OCPs and PCBs is likely to be associated with the prostate cancer risk in the Korean population.

---

Keywords: prostate cancer, polychlorinated biphenyls, organochlorines, endocrine disruptors, persistent organic pollutants, cohort studies, tolerable daily intake

# I. INTRODUCTION

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 the health and environmental impact of POPs (WHO/UNEP 2012).

Not only diabetes but also cancer is suggested as a possible POPs-related disease (Wu et al. 2013; Lim et al. 2015). Biologic plausibility and experimental evidence support the hypothesis that endocrine disruptors could induce endocrine-related cancer including prostate cancer. However, studies on human health are limited.

In 2015, we conducted a meta-analysis of body POPs level and risk of prostate cancer (Lim et al. 2015). According to the meta-analysis, we confirmed only one prospective cohort study that estimates the effect of POPs on prostate cancer exists (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. One of the previous studies showed an inverted U-shape association between POPs and prostate cancer (Ritchie et al. 2003). Meanwhile, the study conducted in the United States suggested linear positive associations between PCBs and the risk of prostate cancer (Ritchie et al. 2005). Case-control studies are less costly and less time-consuming. However, those studies are placed low in the hierarchy of evidence, because it is difficult to establish the timeline of exposure to disease outcome in the setting of a case-control study. In 2016, a nested case-control study suggested a positive association between

plasma oxychlordan levels and metastatic prostate cancer risk in Norwegian (Koutros et al. 2015). In the nested case-control study, elevated but nonsignificant risk for prostate cancer was observed in the highest quartile compares with the lowest quartile of heptachlor epoxide, or hexachlorobenzene.

In Korea, although the POPs have been regulated since 2008, their long half-lives have resulted in the identification of residues in several foods and an ongoing presence in the human blood (Park et al. 2015; Moon et al. 2016 in press). Nevertheless, the association between POPs and prostate cancer in the general population is not clearly understood.

In 2003, the human tolerable daily intake (TDI) of PCBs, 20 ng per kg body weight per day (over the whole life), has been suggested based on animal (rhesus monkeys) experimental study using extremely high exposure dose of POPs, which is unmeasurable in humans (WHO, 2003). We need to estimate cancer hazard rates for exposure to POPs based on a real human bio-monitoring data.

## II. OBJECTIVES

In this study, using a prospective cohort data, we conducted a case-cohort study to evaluate the association between serum concentrations of POPs and the risk of prostate cancer incidence. Using the toxicokinetic model, we suggested a maximum daily exposure limit of POPs.

## III. MATERIALS AND METHODS

### A. Study population

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) (Jo et al. 2012; Jee et al. 2010; Lim and Jee 2015). Among the KCPS-II participants, 159,844 agreed to participate in this study.

We used a case-cohort design within the KCPS-II. A sub-cohort consisting of 1,879 subjects was randomly drawn from the full cohort. To investigate the association between POPs and prostate cancer, the followings were excluded in this study., 1) Women were excluded; 2) Participants who were younger than 20 years; 3) Persons who had insufficient availability of serum for POPs analysis; 4) Persons who were missing anthropometric measurements (i.e. weight, height, body mass index (BMI), systolic blood pressure, diastolic blood pressure, fasting blood sugar, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), or triglyceride); or 5) People whose self-report questionnaire information were missing.

As a result, 256 non-cases in sub-cohort and 110 incidence cases were included in final case-cohort analysis (Figure 1). In the logistic regression model for applying toxicokinetic model, similar exclusion criteria were applied (Figure 2). The Institutional Review Board of Yonsei University approved the study protocol.



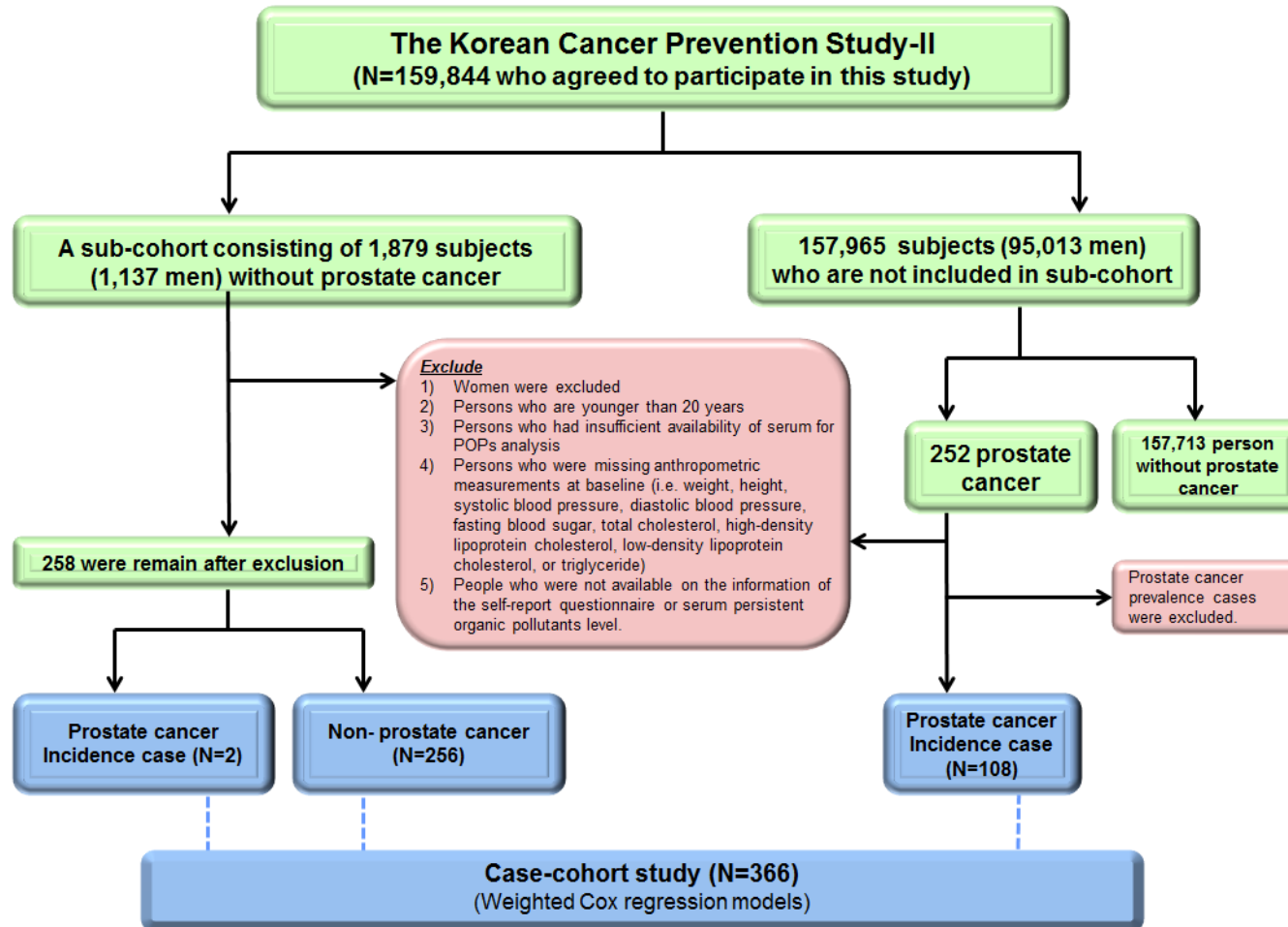


Figure 1. Participants eligibility and criteria for Cox proportional hazard model

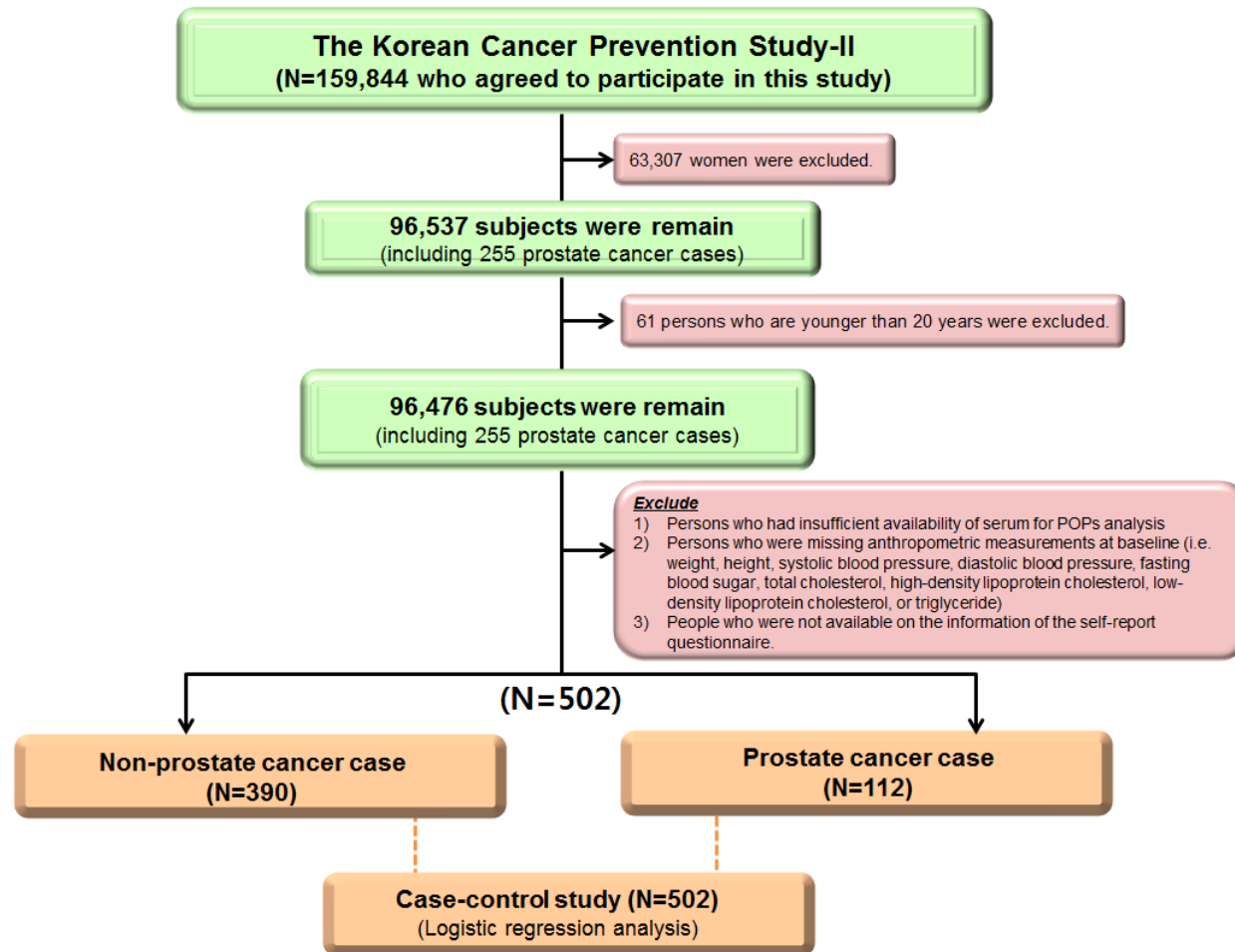


Figure 2. Participants eligibility and criteria for logistic regression model

## **B. Chemistry and anthropometric measurement.**

Weight and height of participants were measured while participants wore light clothes. BMI was calculated as weight (kg) divided by the square of their height in meters (m<sup>2</sup>). We measured the blood pressure of participants 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 (Jo et al. 2012; Jee et al. 2010; Lim and Jee 2015).

Serum, separated from peripheral venous blood, was obtained from each participant after 12 hours of fasting and then further stored at  $-70\text{ }^{\circ}\text{C}$  until it was further analyzed. Using the collected samples, we measured fasting blood glucose, total cholesterol, triglyceride, et al.

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

## **C. Persistent organic pollutants analyses**

The serum samples collected from the KCPS-II were used in laboratory analyses. In total, serum levels of 51 POPs including 32 PCBs (PCB 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) and 19 OCPs (oxychlordane, nonachlor (trans-, cis-), chlordane

(trans-, cis-), heptachlor, heptachlor epoxide (trans-, cis-), hexachlorobenzene (HCB), hexachlorocyclohexane (HCH) ( $\alpha$ -,  $\beta$ -,  $\gamma$ -,  $\delta$ -), p,p'-dichlorodiphenyltrichloroethane (p,p'-DDT), o,p'-dichlorodiphenyltrichloroethane (o,p'-DDT), p,p'-dichlorodiphenyl dichloroethane (p,p'-DDD), o,p'-dichlorodiphenyl dichloroethane (o,p'-DDD), p,p'-dichlorodiphenyldichloro ethylene (p,p'-DDE), and o,p'-dichlorodiphenyldichloro ethylene (o,p'-DDE)) were measured.

The detailed methodology of the persistent organic pollutants analyses was described in the previous study (Park et al. 2015; Moon et al. 2016 in press). Briefly, serum samples were spiked with isotopically labeled standards for OCPs (ES-5400, Cambridge Isotope Labs., USA) and PCBs (68C-LCS, Wellington Labs., Canada). A C<sub>18</sub> solid-phase extraction (SPE) was used. After evaporation, 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). Measurements were carried out by using a DB-5MS capillary column (60 m x 0.32 mm x 0.25  $\mu$ m, 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% - 120%. 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.

#### **D. The definition of outcome**

The principle outcome variable was prostate cancer incidence, based on National Cancer Registry. Since 1980, the Korean Ministry of Health and Welfare has provided a

nationwide, hospital-based cancer registry data that covers approximately 99% of new cases of cancer 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.

## **E. Statistical analysis.**

Descriptive analyses were conducted for variable baseline characteristics and both of serum OCPs and PCBs concentrations of the study population. We generated three groups based on chemical levels (0th–33th, 33th–66th, and  $\geq 66$ th percentiles). In a case-cohort study, the hazard ratio (HR) for prostate cancer was estimated using the weighted Cox regression model according to Self and Prentice method (Self and Prentice. 1988).

The odds ratio (OR) for prostate cancer was estimated using logistic regression analysis. We considered the following covariates for inclusion in the model: age, body mass index, smoking status, and physical activity, and age difference between enrollment age and age at blood draw. Analyses were conducted for individual POPs as well as the sum of POPs. Degree of chlorination and the definition that Wolff made was used to categorize PCBs (Wolff et al. 1997; Stalling et al. 1987; McFarland et al. 1989). According to the property of PCB congener, we defined the sum of dioxin-like PCBs (PCB118 + PCB156 + PCB167) and the sum of non-dioxin-like PCBs (PCB52 + PCB101 + PCB138 + PCB153 + PCB180). ‘Total PCBs’ was defined as the sum of ‘the sum of dioxin-like PCBs’ and ‘the sum of non-dioxin-like PCBs’. The toxic equivalency (TEQ) was calculated based on the individual toxic equivalency factor (TEF) of each PCB congener released from WHO in 2005.

As POPs are predominantly carried in the lipid component of the blood, lipid-adjusted concentrations (ng/g lipid) based on the formula proposed by Bernert et al. (2007) was used in this study (Bernert et al. 2007; Hardell et al. 2006; Sawada et al. 2010). Following previous studies, if the measurement of the POP levels was under the limit of detection (LOD), we substituted it for LOD/2 and included it in all analyses.

To calculate tolerable daily intake value, first, we obtained the probability ( $P_x$ ) for prostate cancer without POPs exposure. Then, we calculated POPs exposure level when the  $P_x$  was increased 1 % ( $P_{(01\%)}$ ). Applying the calculated POPs level to the one-compartment pharmacokinetic model, we obtained (a) external doses resulting in a 1% prostate cancer incidence risk effect above controls and (b) slope factor. Finally, we calculated the provisional tolerable daily intake. More detailed explanation is described in Appendix A.1.

All analyses were performed using SAS statistical software, version 9.2 (SAS Institute Inc., Cary, NC) and Stata version 10.0 software (StataCorp, College Station, TX). The null hypothesis of no difference was rejected if p-values were less than .05.

## **F. Toxicokinetic modeling**

### **i . Basic model assumptions**

The body burden of POPs (e.g. lipophilic PCBs) is expressed on a lipid weight basis (ng/g lipid) since they accumulate in lipids. Usually lipophilic compounds have a long elimination half-life, smoothing out short-term distribution processes including changes in

daily intake due to diet (Alcock et al. 2000; Verner et al. 2008; Kreuzer et al. 1997; Moser et al. 2001). Therefore, one-compartment pharmacokinetic models can be used to model lipid-soluble compounds with long-term concentrations in serum (Abass et al. 2013).

## ii. Toxicokinetic model structure

We used the population toxicokinetic model presented by Lim et al (Lim et al. 2004). The key components of the model are: population body weight, age-dependent body lipid mass, the lifetime average daily dose of POPs, the contact rate of media such as the daily inhalation rate, and the concentration of POPs in media.

The structure of the model is as follows:

$$\text{Dose} = [(\ln 2/t_{1/2}) * (V * CF1) * (C_{\text{tissue}}) * CF2] / (A)$$

$$\text{LADD} = \text{Dose} / \text{BW}_{\text{subject}}$$

Where

Dose (pg-TEQ/day) = the daily intake of dioxin

$t_{1/2}$ (yr) = the half-life of dioxin

V(g) = the volume of body fat

$C_{\text{tissue}}$ (ng-TEQ/kg fat or lipid) = the concentration of dioxin in tissues

CF1 = conversion factor (1,000 pg/ng)

CF2 = conversion factor (year/365 days)

A = the fraction of the dose that is absorbed

LADD(pg-TEQ/kg/day) = the lifetime average daily dose of dioxin

BW<sub>subject</sub>(kg) = the body weight of the subject (71.52kg)

As proposed by the US EPA in 2000, the half-life was assumed as 7.2 years and we used 0.9 as the absorbed rate (Lim et al. 2004; U.S. EPA, 2000). The normal range of body fat percentage in Korean men is 15~18% of body weight (Kwon et al. 2003). So, we substituted 11800g (16.5% of the mean body weight of the subjects). We applied toxicokinetic model based on the crude logistic regression model of TEQ and prostate cancer risk (Figure 2).



## IV. RESULTS

### A. General characteristics of study population

At baseline, cases were older than sub-cohort persons. Higher blood pressure and prostate-specific antigen value were observed in cases. 25.45% of cases and 48.05% of sub-cohort persons were current smokers (Table 1). We observed similar pattern of measured POPs level according to year at blood draw to analyze (Figure A1, Figure A2).

Table A1 showed the information of each PCB congener included in this study. According to previously suggested grouping methods of PCB congeners, we categorized PCBs (Table 2).

In Table 3, we presented the detection rate and the bio-monitored serum level of each analyte that was quantified in at least 80% of serum samples. The serum level of  $\beta$ -HCH, p,p'-DDE, p,p'-DDT, PCB138, PCB153, and PCB180 were quantified in all of the samples. Compared with sub-cohort persons, cases showed higher serum POPs level, except two PCB congeners (PCB52 and PCB101) (Table 3, Figure2, Figure3).

Spearman's rank correlation analysis showed the correlation between concentrations of frequently detected (Detection rate  $\geq$ 80 % in total participants) pollutants after adjusted for age. Compared with other compounds, p,p'-DDD, PCB52 and PCB101 were lowly correlated with others (Table 4, Table 5).

Table 1. Characteristics of the study population according to prostate cancer status

| Covariate                            | Non-case in sub-cohort (N=256) | Prostate cancer cases (N=110) | P-value |
|--------------------------------------|--------------------------------|-------------------------------|---------|
|                                      | Mean (SD)                      | Mean (SD)                     |         |
| Age at enrollment (years)            | 40.58 (8.77)                   | 59.22 (8.21)                  | <.0001  |
| Body mass index (kg/m <sup>2</sup> ) | 24.36 (2.71)                   | 24.23 (2.55)                  | 0.6492  |
| Systolic blood pressure (mmHg)       | 120.24 (14.26)                 | 128.80 (16.54)                | <.0001  |
| Diastolic blood pressure (mmHg)      | 75.96 (11.07)                  | 78.43 (9.95)                  | 0.0452  |
| Fasting blood sugar (mg/dL)          | 95.37 (27.67)                  | 100.56 (25.75)                | 0.0938  |
| Cholesterol (mg/dL)                  | 194.72 (31.40)                 | 191.55 (28.47)                | 0.3628  |
| Prostate-specific antigen (ng/mL)    | 0.90 (0.53)                    | 5.63 (6.71)                   | <.0001  |
| Age at diagnosis (years)             | -                              | 63.54 (7.70)                  |         |
|                                      | %                              | %                             |         |
| <b>Smoking status</b>                |                                |                               |         |
| Never                                | 30.47                          | 35.45                         | <.0001  |
| Former                               | 21.48                          | 39.09                         |         |
| Current                              | 48.05                          | 25.45                         |         |
| Alcohol consumption (Yes)            | 89.84                          | 76.36                         | 0.0013  |
| Exercise (Yes)                       | 66.54                          | 74.77                         | 0.1558  |
| Family history of cancer (Yes)       | 23.44                          | 34.55                         | 0.0383  |

Table 2. Previously suggested groupings of PCB congeners <sup>a</sup>

| Previously suggested groupings of PCB congeners | Included PCB congeners <sup>b</sup>  | Characteristics   |
|---|--|---|
| Low chlorinated                                 | PCBs 1, 3, 4, 15, 19, 28, 37, <b>52</b> , 54, 77, 81   | Monochlorobiphenyls, Dichlorobiphenyls, Trichlorobiphenyls, or Tetrachlorobiphenyls |
| Moderate chlorinated                            | PCBs <b>101</b> , 104, 105, 114, <b>118</b> , 123, 126, <b>138</b> , <b>153</b> , 155, <b>156</b> , 157, 167, 169, <b>180</b> , 188, 189 | Pentachlorobiphenyls, Hexachlorobiphenyls, or Heptachlorobiphenyls                  |
| Highly chlorinated                              | PCBs 202, 205, 206, 208  | Octachlorobiphenyls, Nonachlorobiphenyls, or Decachlorobiphenyls                    |
| Wolff 1A  | PCBs <b>52</b>   | Weak phenobarbital inducers, estrogenic, not persistent                             |
| Wolff 1B  | PCBs <b>101</b>  | Weak phenobarbital inducers, persistent   |
| Wolff 2A  | PCBs 105, <b>118</b> , <b>156</b> , <b>167</b>   | Non-ortho and mono-ortho substituted (moderately persistent)                        |
| Wolff 2B  | PCBs <b>138</b>  | Di-ortho substituted (limited dioxin activity, persistent)                          |
| Wolff 3   | PCBs <b>153</b> , <b>180</b>   | Phenobarbital, CYP1A and CYP2B inducers, biologically persistent                    |
| Dioxin-like PCBs                                | PCBs 77, 81, 105, 114, <b>118</b> , 123, 126, <b>156</b> , 157, <b>167</b> , 169, 189  | Dioxin-like   |
| Non-Dioxin-like PCBs                            | PCBs 1, 3, 4, 15, 19, 28, 37, <b>52</b> , 54, <b>101</b> , 104, <b>138</b> , <b>153</b> , 155, <b>180</b> , 188, 202, 205, 206, 208      | Non-Dioxin-like   |

<sup>a</sup>See McFarland et al. (1989) <sup>b</sup>The congeners with detection rate  $\geq 80\%$  were bolded.

Table 3. Compound specific level in case and sub-cohort members who are included in case-cohort study.

| Compound               | Detection rate (%) |                                      |                 | Non-case in sub-cohort<br>(N=256)            |  | Case<br>(N=110)                              |                                   |
|------------------------|--------------------|--------------------------------------|-----------------|--|--|--|-----------------------------------|
|                        | Total<br>(N=366)   | Non-case in<br>sub-cohort<br>(N=256) | Case<br>(N=110) | Median (25th–75th<br>percentile; ng/g lipid) | Percentage<br>contribution<br>(%) <sup>a</sup> | Median (25th–75th<br>percentile; ng/g lipid) | Percentage<br>contribution<br>(%) |
| <b>OCPs</b>            |                    |                                      |                 |  |  |  |                                   |
| β-HCH                  | 100                | 100                                  | 100             | 12.57 (8.44-18.89)                           | 6.76   | 21.74 (12.73-42.32)                          | 6.08                              |
| p,p'-DDE               | 100                | 100                                  | 100             | 95.99 (59.74-149.24)                         | 53.09  | 193.42 (114.87-329.70)                       | 56.54                             |
| cis-Heptachlor epoxide | 90                 | 88                                   | 93              | 1.89 (0.97-3.61)                             | 1.16   | 4.06 (2.29-7.11)                             | 1.09                              |
| trans-Nonachlor        | 98                 | 97                                   | 100             | 3.73 (2.18-6.17)                             | 2.06   | 9.01 (5.75-12.70)                            | 2.21                              |
| p,p'-DDD               | 87                 | 84                                   | 93              | 2.20 (0.94-3.84)                             | 1.14   | 3.47 (1.68-5.26)                             | 0.90                              |
| p,p'-DDT               | 100                | 100                                  | 100             | 10.27 (6.25-15.88)                           | 5.08   | 14.85 (9.84-21.76)                           | 3.64                              |
| <b>PCBs</b>            |                    |                                      |                 |  |  |  |                                   |
| PCB118                 | 100                | 100                                  | 99              | 2.63 (1.81-4.32)                             | 1.61   | 6.20 (3.64-9.22)                             | 1.56                              |
| PCB156                 | 96                 | 95                                   | 96              | 0.88 (0.59-1.46)                             | 0.52   | 2.36 (1.61-3.69)                             | 0.58                              |
| PCB167                 | 90                 | 88                                   | 95              | 0.50 (0.34-0.77)                             | 0.27   | 1.13 (0.75-1.63)                             | 0.28                              |
| PCB52                  | 96                 | 95                                   | 99              | 2.76 (1.75-4.23)                             | 1.41   | 1.86 (1.06-3.34)                             | 0.55                              |
| PCB101                 | 96                 | 96                                   | 97              | 1.28 (0.92-2.14)                             | 0.68   | 1.21 (0.78-1.95)                             | 0.34                              |
| PCB138                 | 100                | 100                                  | 100             | 5.28 (3.57-8.27)                             | 3.18   | 12.15 (6.84-17.73)                           | 2.96                              |
| PCB153                 | 100                | 100                                  | 100             | 10.63 (6.81-16.97)                           | 6.26   | 30.12 (19.08-45.10)                          | 7.29                              |
| PCB180                 | 100                | 100                                  | 100             | 6.87 (4.71-12.26)                            | 4.31   | 29.23 (17.21-46.56)                          | 6.86                              |

PCB, polychlorinated biphenyl; OCP, organochlorine pesticide

<sup>a</sup> the mean of the relevant compound percentage of 32 PCBs and 19 OCPs in serum

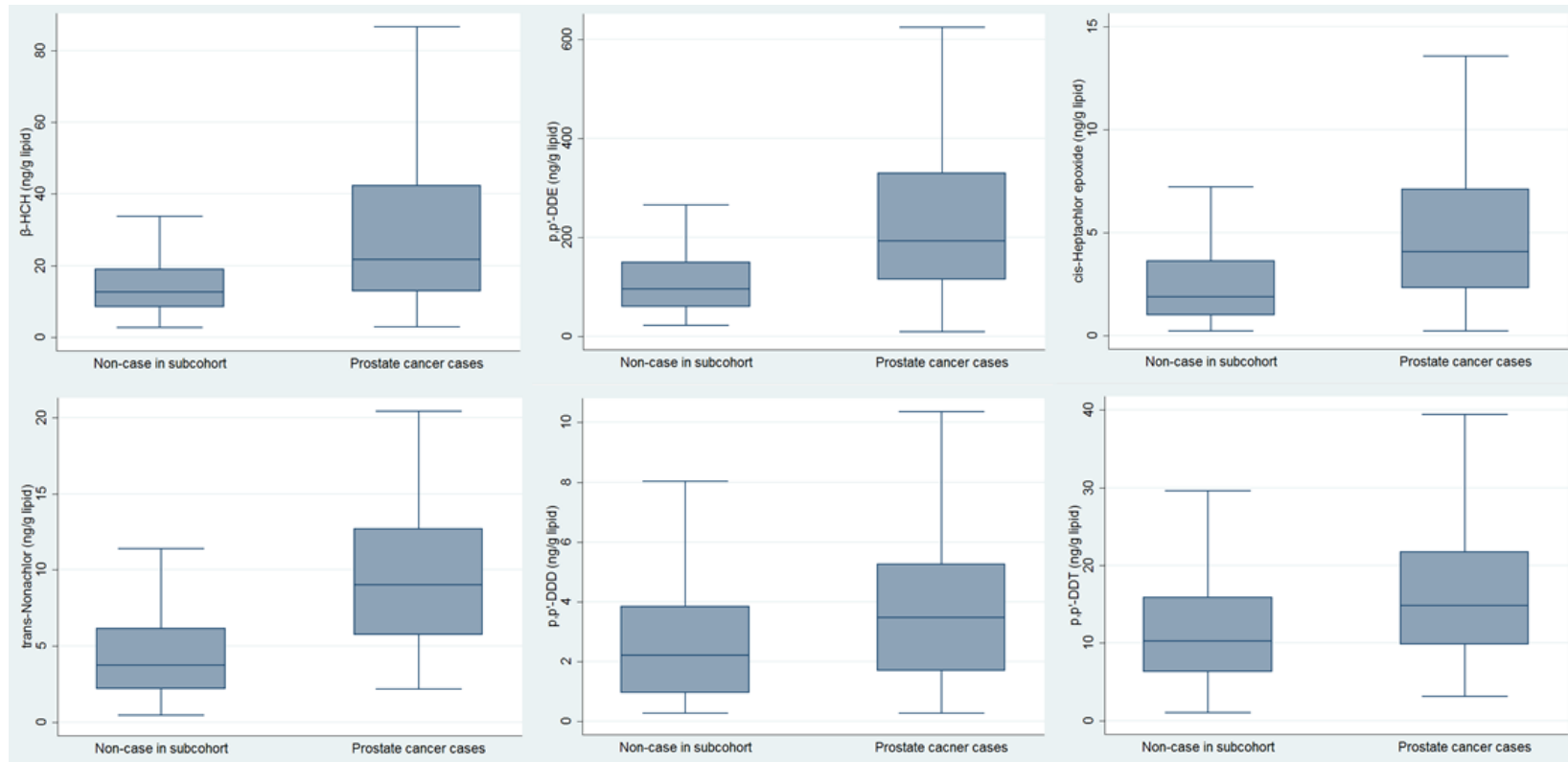


Figure 3. Individual organochlorine pesticides level with detection rate  $\geq 80\%$ , in case-cohort study population (N=366)

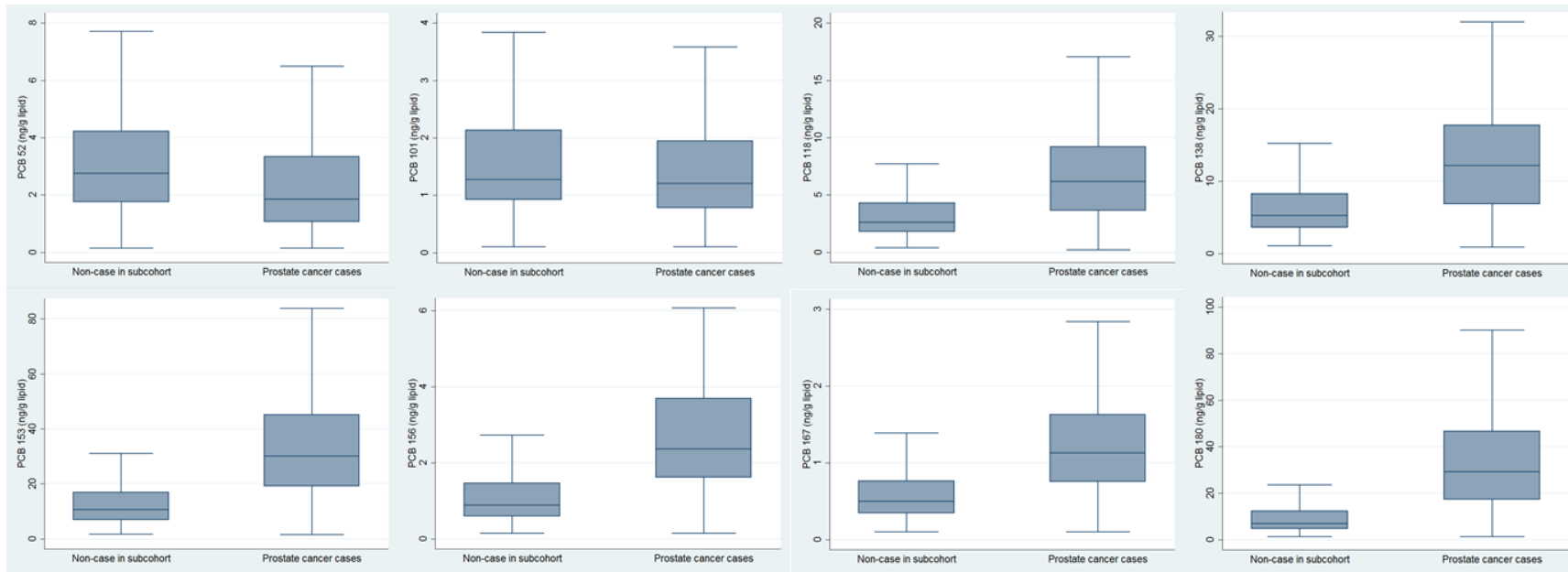


Figure 4. Individual polychlorinated biphenyls level with detection rate  $\geq 80\%$ , in case-cohort study population (N=366)

Table 4. Spearman's rank correlation analysis of the relationship between concentrations of frequently detected (Detection rate  $\geq 80$  % in total participants) pollutants in serum samples in participants without prostate cancer in sub-cohort (N=256)

|                        | p,p'-DDE              | cis-Heptachlor epoxide | trans-Nonachlor       | p,p'-DDD                | p,p'-DDT              | PCB118                  | PCB156                 | PCB167                 | PCB52                   | PCB101                  | PCB138                  | PCB153                 | PCB180                  |
|------------------------|-----------------------|------------------------|-----------------------|-------------------------|-----------------------|-------------------------|------------------------|------------------------|-------------------------|-------------------------|-------------------------|------------------------|-------------------------|
| $\beta$ -HCH           | r = 0.652<br>P<0.0001 | r = 0.513<br>P<0.0001  | r = 0.624<br>P<0.0001 | r = 0.239<br>P = 0.0001 | r = 0.448<br>P<0.0001 | r = 0.520<br>P<0.0001   | r = 0.511<br>P<0.0001  | r = 0.458<br>P<0.0001  | r = 0.116<br>P = 0.0637 | r = 0.116<br>P = 0.0633 | r = 0.433<br>P<0.0001   | r = 0.471<br>P<0.0001  | r = 0.480<br>P<0.0001   |
| p,p'-DDE               | -                     | r = 0.492<br>P<0.0001  | r = 0.684<br>P<0.0001 | r = 0.353<br>P<0.0001   | r = 0.662<br>P<0.0001 | r = 0.759<br>P<0.0001   | r = 0.683<br>P<0.0001  | r = 0.657<br>P<0.0001  | r = 0.175<br>P = 0.005  | r = 0.280<br>P<0.0001   | r = 0.723<br>P<0.0001   | r = 0.736<br>P<0.0001  | r = 0.673<br>P<0.0001   |
| cis-Heptachlor epoxide | -                     | -                      | r = 0.583<br>P<0.0001 | r = 0.149<br>P = 0.018  | r = 0.381<br>P<0.0001 | r = 0.427<br>P<0.0001   | r = 0.493<br>P<0.0001  | r = 0.338<br>P<0.0001  | r = 0.023<br>P = 0.713  | r = 0.145<br>P = 0.021  | r = 0.349<br>P<0.0001   | r = 0.400<br>P<0.0001  | r = 0.361<br>P<0.0001   |
| trans-Nonachlor        | -                     | -                      | -                     | r = 0.387<br>P = 0.0004 | r = 0.648<br>P<0.0001 | r = 0.641<br>P<0.0001   | r = 0.648<br>P<0.0001  | r = 0.607<br>P<0.0001  | r = 0.123<br>P = 0.050  | r = 0.227<br>P = 0.0003 | r = 0.586<br>P<0.0001   | r = 0.660<br>P<0.0001  | r = 0.635<br>P<0.0001   |
| p,p'-DDD               | -                     | -                      | -                     | -                       | r = 0.420<br>P<0.0001 | r = 0.215<br>P = 0.0005 | r = 0.101<br>P = 0.108 | r = 0.141<br>P = 0.025 | r = 0.040<br>P = 0.530  | r = 0.053<br>P = 0.404  | r = 0.226<br>P = 0.0003 | r = 0.150<br>P = 0.017 | r = 0.023<br>P = 0.051  |
| p,p'-DDT               | -                     | -                      | -                     | -                       | -                     | r = 0.617<br>P<0.0001   | r = 0.507<br>P<0.0001  | r = 0.575<br>P<0.0001  | r = 0.233<br>P = 0.0002 | r = 0.281<br>P<0.0001   | r = 0.484<br>P<0.0001   | r = 0.586<br>P<0.0001  | r = 0.546<br>P<0.0001   |
| PCB118                 | -                     | -                      | -                     | -                       | -                     | -                       | r = 0.783<br>P<0.0001  | r = 0.828<br>P<0.0001  | r = 0.223<br>P = 0.0003 | r = 0.457<br>P<0.0001   | r = 0.790<br>P<0.0001   | r = 0.869<br>P<0.0001  | r = 0.804<br>P<0.0001   |
| PCB156                 | -                     | -                      | -                     | -                       | -                     | -                       | -                      | r = 0.773<br>P<0.0001  | r = 0.179<br>P = 0.004  | r = 0.333<br>P<0.0001   | r = 0.758<br>P<0.0001   | r = 0.897<br>P<0.0001  | r = 0.876<br>P<0.0001   |
| PCB167                 | -                     | -                      | -                     | -                       | -                     | -                       | -                      | -                      | r = 0.223<br>P = 0.0003 | r = 0.327<br>P<0.0001   | r = 0.773<br>P<0.0001   | r = 0.855<br>P<0.0001  | r = 0.809<br>P<0.0001   |
| PCB52                  | -                     | -                      | -                     | -                       | -                     | -                       | -                      | -                      | -                       | r = 0.521<br>P<0.0001   | r = 0.141<br>P = 0.024  | r = 0.205<br>P = 0.001 | r = 0.210<br>P = 0.0007 |
| PCB101                 | -                     | -                      | -                     | -                       | -                     | -                       | -                      | -                      | -                       | -                       | r = 0.251<br>P<0.0001   | r = 0.381<br>P<0.0001  | r = 0.384<br>P<0.0001   |
| PCB138                 | -                     | -                      | -                     | -                       | -                     | -                       | -                      | -                      | -                       | -                       | -                       | r = 0.837<br>P<0.0001  | r = 0.760<br>P<0.0001   |
| PCB153                 | -                     | -                      | -                     | -                       | -                     | -                       | -                      | -                      | -                       | -                       | -                       | -                      | r = 0.945<br>P<0.0001   |

Adjusted for age.

Table 5. Spearman's rank correlation analysis of the relationship between concentrations of frequently detected (Detection rate  $\geq 80\%$  in total participants) pollutants in serum samples in participants incidence case (N=110)

|                        | p,p'-DDE              | cis-Heptachlor epoxide | trans-Nonachlor       | p,p'-DDD              | p,p'-DDT              | PCB118                | PCB156                | PCB167                | PCB52                  | PCB101                  | PCB138                 | PCB153                 | PCB180                  |
|------------------------|-----------------------|------------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|------------------------|-------------------------|------------------------|------------------------|-------------------------|
| $\beta$ -HCH           | r = 0.584<br>P<0.0001 | r = 0.593<br>P<0.0001  | r = 0.622<br>P<0.0001 | r = 0.374<br>P<0.0001 | r = 0.514<br>P<0.0001 | r = 0.634<br>P<0.0001 | r = 0.605<br>P<0.0001 | r = 0.609<br>P<0.0001 | r = 0.237<br>P = 0.013 | r = 0.380<br>P<0.0001   | r = 0.627<br>P<0.0001  | r = 0.458<br>P<0.0001  | r = 0.361<br>P = 0.0001 |
| p,p'-DDE               | -                     | r = 0.527<br>P<0.0001  | r = 0.680<br>P<0.0001 | r = 0.626<br>P<0.0001 | r = 0.717<br>P<0.0001 | r = 0.726<br>P<0.0001 | r = 0.634<br>P<0.0001 | r = 0.697<br>P<0.0001 | r = 0.195<br>P = 0.042 | r = 0.382<br>P<0.0001   | r = 0.745<br>P<0.0001  | r = 0.582<br>P<0.0001  | r = 0.465<br>P<0.0001   |
| cis-Heptachlor epoxide | -                     | -                      | r = 0.715<br>P<0.0001 | r = 0.410<br>P<0.0001 | r = 0.510<br>P<0.0001 | r = 0.546<br>P<0.0001 | r = 0.461<br>P<0.0001 | r = 0.518<br>P<0.0001 | r = 0.309<br>P = 0.001 | r = 0.360<br>P = 0.0001 | r = 0.468<br>P<0.0001  | r = 0.391<br>P<0.0001  | r = 0.263<br>P = 0.006  |
| trans-Nonachlor        | -                     | -                      | -                     | r = 0.583<br>P<0.0001 | r = 0.693<br>P<0.0001 | r = 0.674<br>P<0.0001 | r = 0.737<br>P<0.0001 | r = 0.727<br>P<0.0001 | r = 0.311<br>P = 0.001 | r = 0.407<br>P<0.0001   | r = 0.719<br>P<0.0001  | r = 0.605<br>P<0.0001  | r = 0.499<br>P<0.0001   |
| p,p'-DDD               | -                     | -                      | -                     | -                     | r = 0.744<br>P<0.0001 | r = 0.526<br>P<0.0001 | r = 0.471<br>P<0.0001 | r = 0.575<br>P<0.0001 | r = 0.255<br>P = 0.008 | r = 0.331<br>P = 0.0004 | r = 0.558<br>P<0.0001  | r = 0.462<br>P<0.0001  | r = 0.336<br>P = 0.0003 |
| p,p'-DDT               | -                     | -                      | -                     | -                     | -                     | r = 0.664<br>P<0.0001 | r = 0.601<br>P<0.0001 | r = 0.678<br>P<0.0001 | r = 0.252<br>P = 0.008 | r = 0.375<br>P<0.0001   | r = 0.646<br>P<0.0001  | r = 0.550<br>P<0.0001  | r = 0.439<br>P<0.0001   |
| PCB118                 | -                     | -                      | -                     | -                     | -                     | -                     | r = 0.780<br>P<0.0001 | r = 0.917<br>P<0.0001 | r = 0.243<br>P = 0.011 | r = 0.528<br>P<0.0001   | r = 0.864<br>P<0.0001  | r = 0.644<br>P<0.0001  | r = 0.540<br>P<0.0001   |
| PCB156                 | -                     | -                      | -                     | -                     | -                     | -                     | -                     | r = 0.872<br>P<0.0001 | r = 0.310<br>P = 0.001 | r = 0.515<br>P<0.0001   | r = 0.840<br>P<0.0001  | r = 0.673<br>P<0.0001  | r = 0.607<br>P<0.0001   |
| PCB167                 | -                     | -                      | -                     | -                     | -                     | -                     | -                     | -                     | r = 0.280<br>P = 0.003 | r = 0.531<br>P<0.0001   | r = 0.869<br>P<0.0001  | r = 0.685<br>P<0.0001  | r = 0.596<br>P<0.0001   |
| PCB52                  | -                     | -                      | -                     | -                     | -                     | -                     | -                     | -                     | -                      | r = 0.614<br>P<0.0001   | r = 0.308<br>P = 0.001 | r = 0.079<br>P = 0.414 | r = -0.061<br>P = 0.527 |
| PCB101                 | -                     | -                      | -                     | -                     | -                     | -                     | -                     | -                     | -                      | -                       | r = 0.522<br>P<0.0001  | r = 0.211<br>P = 0.028 | r = 0.138<br>P = 0.152  |
| PCB138                 | -                     | -                      | -                     | -                     | -                     | -                     | -                     | -                     | -                      | -                       | -                      | r = 0.610<br>P<0.0001  | r = 0.482<br>P<0.0001   |
| PCB153                 | -                     | -                      | -                     | -                     | -                     | -                     | -                     | -                     | -                      | -                       | -                      | -                      | r = 0.822<br>P<0.0001   |

Adjusted for age.



## B. Case-cohort study

After adjusting for potential confounding factors, compared with the lowest tertile of each POP the increased risk of prostate cancer incidence was observed in the upper tertile in relation with  $\beta$ -HCH, cis-Heptachlor epoxide, PCB118, PCB153, PCB180. (Table 6, Table 7). However, several POPs (PCB167, PCB52, PCB101, PCB138) showed U-shape or inverse associations with the risk of prostate cancer (Table 7).

When we performed the similar analysis according to categorized POPs, increased risks of prostate cancer incidence were observed in the upper tertile of moderate chlorinated PCBs, Group 3, the sum of dioxin-like PCBs, the sum of non-dioxin-like PCBs, and TEQ compared with the lowest tertile (Table 8). Low chlorinated PCBs, Group 1, and Group 2 PCBs showed U-shape or inverse association with the risk of prostate cancer (Table 8).

Table 9 showed association between log-transformed PCBs group and the risk for prostate cancer in weighted Cox regression model. Consistently positive associations between PCBs and prostate cancer were observed.

Table 6. HRs of prostate cancer in association with serum concentrations of individual organochlorine pesticides in weighted Cox regression model

| Compound<br>concentration (ng/g<br>lipid) <sup>a</sup> | N(cases/sub-<br>cohort) | HR (95% CI)      |                 |                  |
|--|-------------------------|------------------|-----------------|------------------|
|  |                         | Model 1          | Model 2         | Model 3          |
| <b>β-HCH</b>   |                         |                  |                 |                  |
| < 11.04  | 18/103                  | 1.00             | 1.00            | 1.00             |
| 11.04-19.42  | 27/95                   | 5.22(2.34-11.63) | 3.54(1.53-8.23) | 4.71(1.82-12.14) |
| 19.42≤   | 65/58                   | 5.85(2.94-11.66) | 3.64(1.60-8.26) | 5.01(1.97-12.69) |
| P for trend  |                         | <.0001           | 0.0048          | 0.0018           |
| <b>p,p'-DDE</b>  |                         |                  |                 |                  |
| < 81.49  | 14/107                  | 1.00             | 1.00            | 1.00             |
| 81.49-155.62   | 32/90                   | 0.56(0.27-1.17)  | 0.83(0.39-1.76) | 0.68(0.31-1.52)  |
| 155.62≤  | 64/59                   | 1.18(0.62-2.24)  | 0.82(0.41-1.66) | 0.75(0.37-1.52)  |
| P for trend  |                         | 0.0765           | 0.6255          | 0.5471           |
| <b>cis-Heptachlor<br/>epoxide</b>                      |                         |                  |                 |                  |
| < 1.53   | 17/104                  | 1.00             | 1.00            | 1.00             |
| 1.53-3.66  | 31/90                   | 1.96(1.06-3.60)  | 1.98(1.07-3.66) | 2.13(1.14-3.96)  |
| 3.66≤  | 62/62                   | 0.80(0.44-1.47)  | 0.71(0.39-1.28) | 0.68(0.37-1.24)  |
| P for trend  |                         | 0.2659           | 0.1124          | 0.0907           |
| <b>trans-Nonachlor</b>                                 |                         |                  |                 |                  |
| < 3.25   | 8/114                   | 1.00             | 1.00            | 1.00             |
| 3.25-6.99  | 30/92                   | 1.83(0.82-4.08)  | 1.71(0.76-3.87) | 1.99(0.86-4.61)  |
| 6.99≤  | 72/50                   | 1.56(0.67-3.64)  | 1.33(0.57-3.06) | 1.36(0.59-3.15)  |
| P for trend  |                         | 0.5344           | 0.8304          | 0.8917           |
| <b>p,p'-DDD</b>  |                         |                  |                 |                  |
| < 1.63   | 25/94                   | 1.00             | 1.00            | 1.00             |
| 1.63-3.7   | 34/90                   | 0.97(0.56-1.68)  | 0.81(0.44-1.49) | 0.71(0.38-1.32)  |
| 3.7≤   | 51/72                   | 0.58(0.33-1.02)  | 0.73(0.41-1.29) | 0.60(0.33-1.09)  |
| P for trend  |                         | 0.0366           | 0.2916          | 0.1044           |
| <b>p,p'-DDT</b>  |                         |                  |                 |                  |
| < 8.45   | 25/100                  | 1.00             | 1.00            | 1.00             |
| 8.45-15.48   | 36/86                   | 0.71(0.39-1.31)  | 1.03(0.56-1.90) | 0.97(0.52-1.81)  |
| 15.48≤   | 53/70                   | 1.27(0.75-2.14)  | 1.39(0.78-2.47) | 1.33(0.74-2.38)  |
| P for trend  |                         | 0.1679           | 0.2319          | 0.2847           |

<sup>a</sup>The cutoffs between the exposure groups were the 25th, 50th, and 75th percentiles.

Model 1: Adjusted for age. Model2: Adjusted for age, BMI, smoking status, and physical activity.

Model3: Adjusted for age, BMI, smoking status, physical activity, and age difference between enrollment age and age at blood draw

Table 7. HRs of prostate cancer in association with serum concentrations of individual polychlorinated biphenyl congeners in weighted Cox regression model

| Compound concentration (ng/g lipid) <sup>a</sup> | N(cases/sub-cohort) | HR (95% CI)      |                  |                   |
|--|---------------------|------------------|------------------|-------------------|
|  |                     | Model 1          | Model 2          | Model 3           |
| <b>PCB118</b>                                    |                     |                  |                  |                   |
| < 2.36   | 14/108              | 1.00             | 1.00             | 1.00              |
| 2.36- 4.63                                       | 27/95               | 6.36(2.66-15.23) | 5.48(2.05-14.68) | 8.54(2.72-26.84)  |
| 4.63≤  | 69/53               | 8.89(4.19-18.87) | 6.96(2.74-17.64) | 10.70(3.54-32.34) |
| P for trend                                      |                     | <.0001           | <.0001           | <.0001            |
| <b>PCB156</b>                                    |                     |                  |                  |                   |
| <0.8   | 7/115               | 1.00             | 1.00             | 1.00              |
| 0.8-1.68   | 26/97               | 1.53(0.65-3.61)  | 1.18(0.49-2.85)  | 1.12(0.46-2.72)   |
| 1.68≤  | 77/44               | 2.36(0.97-5.77)  | 1.83(0.75-4.47)  | 1.68(0.68-4.13)   |
| P for trend                                      |                     | 0.0308           | 0.0803           | 0.1235            |
| <b>PCB167</b>                                    |                     |                  |                  |                   |
| < 0.44   | 11/110              | 1.00             | 1.00             | 1.00              |
| 0.44-0.85  | 26/97               | 0.26(0.11-0.62)  | 0.36(0.14-0.90)  | 0.23(0.08-0.64)   |
| 0.85≤  | 73/49               | 1.51(0.73-3.13)  | 1.75(0.76-4.04)  | 1.37(0.58-3.24)   |
| P for trend                                      |                     | <.0001           | 0.0002           | 0.0002            |
| <b>PCB52</b>                                     |                     |                  |                  |                   |
| < 1.814  | 52/70               | 1.00             | 1.00             | 1.00              |
| 1.814-3.4  | 31/91               | 0.38(0.23-0.62)  | 0.30(0.18-0.51)  | 0.31(0.18-0.52)   |
| 3.4≤   | 27/95               | 0.24(0.14-0.41)  | 0.36(0.20-0.64)  | 0.29(0.16-0.55)   |
| P for trend                                      |                     | <.0001           | 0.0001           | <.0001            |
| <b>PCB101</b>                                    |                     |                  |                  |                   |
| < 1.01   | 43/79               | 1.00             | 1.00             | 1.00              |
| 1.01-1.75  | 34/88               | 0.19(0.11-0.32)  | 0.26(0.14-0.47)  | 0.22(0.12-0.42)   |
| 1.75≤  | 33/89               | 0.43(0.27-0.68)  | 0.37(0.22-0.62)  | 0.29(0.16-0.50)   |
| P for trend                                      |                     | 0.0013           | 0.0004           | <.0001            |
| <b>PCB138</b>                                    |                     |                  |                  |                   |
| < 4.79   | 14/108              | 1.00             | 1.00             | 1.00              |
| 4.79-9.33  | 26/96               | 0.29(0.13-0.65)  | 0.25(0.11-0.58)  | 0.15(0.06-0.39)   |
| 9.33≤  | 70/52               | 1.80(0.97-3.33)  | 1.39(0.73-2.64)  | 1.12(0.58-2.16)   |
| P for trend                                      |                     | <.0001           | 0.0010           | 0.0014            |
| <b>PCB153</b>                                    |                     |                  |                  |                   |
| < 9.46   | 7/115               | 1.00             | 1.00             | 1.00              |
| 9.46-21.50                                       | 25/97               | 0.91(0.36-2.29)  | 0.98(0.39-2.51)  | 0.67(0.24-1.87)   |
| 21.50≤   | 78/44               | 3.98(1.74-9.12)  | 3.44(1.44-8.20)  | 3.04(1.27-7.27)   |
| P for trend                                      |                     | <.0001           | 0.0001           | 0.0002            |
| <b>PCB180</b>                                    |                     |                  |                  |                   |
| <6.44  | 3/119               | 1.00             | 1.00             | 1.00              |
| 6.44-16.67                                       | 24/98               | 3.80(1.12-12.82) | 3.46(1.02-11.73) | 3.16(0.92-10.78)  |
| 16.67≤   | 83/39               | 7.08(2.01-24.94) | 5.69(1.59-20.39) | 5.21(1.45-18.78)  |
| P for trend                                      |                     | 0.0007           | 0.0044           | 0.0068            |

PCB, polychlorinated biphenyl

Model 1: Adjusted for age.

Model 2: Adjusted for age, BMI, smoking status, and physical activity.

Model 3: Adjusted for age, BMI, smoking status, physical activity, and age difference between enrollment age and age at blood draw

Table 8. Summation effect of persistent organic pollutants on prostate cancer in weighted Cox regression model

| Compound concentration<br>(ng/g lipid) <sup>a</sup> | N(cases/su<br>b-cohort) | HR (95% CI)      |                  |                  |
|---|-------------------------|------------------|------------------|------------------|
|   |                         | Model1           | Model2           | Model3           |
| $\Sigma$ OCPs                                       |                         |                  |                  |                  |
| <115.70   | 13/109                  | 1.00             | 1.00             | 1.00             |
| 115.70-208.57                                       | 30/91                   | 0.58(0.27-1.23)  | 0.81(0.37-1.75)  | 0.63(0.27-1.46)  |
| 208.57 $\leq$                                       | 67/56                   | 1.45(0.75-2.79)  | 1.15(0.56-2.36)  | 1.06(0.52-2.16)  |
| P for trend   |                         | 0.0108           | 0.5406           | 0.6036           |
| $\Sigma$ PCBs                                       |                         |                  |                  |                  |
| <29.86  | 6/116                   | 1.00             | 1.00             | 1.00             |
| 29.86-62.69   | 25/96                   | 2.54(1.03-6.25)  | 2.94(1.10-7.87)  | 2.66(0.98-7.20)  |
| 62.69 $\leq$  | 79/44                   | 3.22(1.27-8.21)  | 2.82(1.02-7.80)  | 2.51(0.89-7.04)  |
| P for trend   |                         | 0.0164           | 0.0857           | 0.1487           |
| Degree of chlorination <sup>b</sup>                 |                         |                  |                  |                  |
| Low   |                         |                  |                  |                  |
| <1.83   | 53/70                   | 1.00             | 1.00             | 1.00             |
| 1.83-3.41   | 30/91                   | 0.36(0.22-0.58)  | 0.28(0.16-0.48)  | 0.28(0.17-0.48)  |
| 3.41 $\leq$   | 27/95                   | 0.23(0.13-0.40)  | 0.35(0.19-0.62)  | 0.28(0.15-0.53)  |
| P for trend   |                         | <.0001           | <.0001           | <.0001           |
| Moderate  |                         |                  |                  |                  |
| < 26.46   | 5/117                   | 1.00             | 1.00             | 1.00             |
| 26.46-57.14   | 26/96                   | 3.25(1.24-8.53)  | 3.00(1.13-7.98)  | 2.74(1.02-7.35)  |
| 57.14 $\leq$  | 79/43                   | 4.00(1.47-10.88) | 2.89(1.04-8.00)  | 2.58(0.92-7.24)  |
| P for trend   |                         | 0.0083           | 0.0748           | 0.1316           |
| Wolff group <sup>c</sup>                            |                         |                  |                  |                  |
| Group 1   |                         |                  |                  |                  |
| <3.00   | 51/71                   | 1.00             | 1.00             | 1.00             |
| 3.00-4.89   | 29/91                   | 0.35(0.22-0.56)  | 0.35(0.21-0.57)  | 0.32(0.20-0.53)  |
| 4.89 $\leq$   | 30/94                   | 0.22(0.13-0.38)  | 0.32(0.18-0.59)  | 0.24(0.13-0.46)  |
| P for trend   |                         | <.0001           | <.0001           | <.0001           |
| Group 2   |                         |                  |                  |                  |
| <8.52   | 12/110                  | 1.00             | 1.00             | 1.00             |
| 8.52-17.28  | 28/95                   | 0.50(0.22-1.09)  | 0.54(0.23-1.27)  | 0.37(0.15-0.96)  |
| 17.28 $\leq$  | 70/51                   | 1.85(0.95-3.60)  | 1.57(0.77-3.21)  | 1.35(0.66-2.78)  |
| P for trend   |                         | <.0001           | 0.0212           | 0.0268           |
| Group 3   |                         |                  |                  |                  |
| < 16.79   | 4/118                   | 1.00             | 1.00             | 1.00             |
| 16.79-39.26   | 25/97                   | 3.46(1.19-10.04) | 3.16(1.08-9.24)  | 2.90(0.98-8.56)  |
| 39.26 $\leq$  | 81/41                   | 5.01(1.67-15.10) | 3.67(1.20-11.28) | 3.30(1.07-10.21) |
| P for trend   |                         | 0.0033           | 0.0337           | 0.0587           |
| $\Sigma$ Dioxin-like PCBs <sup>d</sup>              |                         |                  |                  |                  |
| <3.64   | 11/113                  | 1.00             | 1.00             | 1.00             |
| 3.64-7.51   | 27/93                   | 0.57(0.25-1.26)  | 0.73(0.31-1.70)  | 0.52(0.21-1.32)  |
| 7.51 $\leq$   | 72/50                   | 2.05(1.02-4.12)  | 1.81(0.85-3.84)  | 1.62(0.76-3.43)  |
| P for trend   |                         | <.0001           | 0.0341           | 0.0395           |
| $\Sigma$ Non-dioxin-like PCBs <sup>e</sup>          |                         |                  |                  |                  |

|                     |        |                  |                  |                 |
|---------------------|--------|------------------|------------------|-----------------|
| < 26.14             | 5/117  | 1.00             | 1.00             | 1.00            |
| 26.14-53.98         | 25/97  | 2.58(0.97-6.85)  | 2.03(0.75-5.52)  | 1.84(0.67-5.05) |
| 53.98≤              | 80/42  | 4.92(1.84-13.13) | 3.91(1.46-10.49) | 3.50(1.29-9.51) |
| P for trend         |        | 0.0003           | 0.0009           | 0.0019          |
| <b>TEQ</b>          |        |                  |                  |                 |
| < 0.0132064         | 11/111 | 1.00             | 1.00             | 1.00            |
| 0.0132064-0.0133675 | 28/94  | 0.53(0.24-1.18)  | 0.64(0.28-1.46)  | 0.46(0.19-1.13) |
| 0.0133675≤          | 71/51  | 2.26(1.13-4.53)  | 2.02(0.95-4.32)  | 1.72(0.80-3.69) |
| P for trend         |        | <.0001           | 0.0049           | 0.0063          |

<sup>a</sup>The cutoffs between the exposure groups were the 25th, 50th, and 75th percentiles.

<sup>b</sup>Low: PCB 52; moderate: PCBs 101, 118, 138, 153, 156, 180.

<sup>c</sup>Group1: PCBs 52, 101; Group2: PCBs 118, 138, 156, 167; Group3: PCBs 153, 180.

<sup>d</sup>PCBs 118, 156, 167.

<sup>e</sup>PCBs 52, 101, 138, 153, 180.

Model 1: Adjusted for age.

Model 2: Adjusted for age, BMI, smoking status, and physical activity.

Model 3: Adjusted for age, BMI, smoking status, physical activity, and age difference between enrollment age and age at blood drawn

TEQ, toxic equivalence quotient; PCB, polychlorinated biphenyl; OCP, organochlorine pesticide

Table 9. Association between summarized polychlorinated biphenyls level and the risk for prostate cancer in weighted Cox regression model

| Compound concentration<br>(ng/g lipid)          | HR (95% CI)     |                 |                 |                 |
|---|-----------------|-----------------|-----------------|-----------------|
|   | Crude           | Model1          | Model2          | Model3          |
| ln ( $\sum$ PCBs)                               | 4.28(3.34-5.49) | 2.19(1.63-2.95) | 1.88(1.36-2.61) | 1.80(1.28-2.55) |
| ln ( $\sum$ Dioxin-like PCBs <sup>a</sup> )     | 2.81(2.21-3.56) | 1.79(1.37-2.35) | 1.45(1.06-1.99) | 1.36(0.97-1.90) |
| ln ( $\sum$ Non dioxin-like PCBs <sup>b</sup> ) | 4.44(3.46-5.70) | 2.21(1.64-2.98) | 1.91(1.38-2.65) | 1.84(1.30-2.59) |
| ln (TEQ)  | 1.91(1.36-2.37) | 2.13(1.51-3.00) | 2.94(1.96-4.41) | 3.14(2.10-4.71) |

<sup>a</sup>PCBs 118, 156, 167.

<sup>b</sup>PCBs 52, 101, 138, 153, 180.

TEQ, toxic equivalence quotient; PCB, polychlorinated biphenyl

Model 1: Adjusted for age.

Model 2: Adjusted for age, BMI, smoking status, and physical activity.

Model 3: Adjusted for age, BMI, smoking status, physical activity, and age difference between enrollment age and age at blood drawn

### C. Case-control study

We performed multiple logistic regression analysis to apply toxicokinetic modeling (Table 10). After adjusting for age, BMI, smoking status, physical activity, and age difference between enrollment age and age at blood drawn, the sum of PCBs, moderate chlorinated PCBs, Group 3, the sum of non-dioxin-like PCBs, and TEQ were positively associated with the risk of prostate cancer in the multiple logistic regression analysis (Table 10). When we treated summarized polychlorinated biphenyls levels as continuous variables, log-transformed sum of PCBs, log-transformed sum of dioxin-like PCBs (P-value= 0521), log-transformed sum of non-dioxin-like PCBs, and log transformed TEQ showed linear positive associations with the prostate cancer risk (Table 11).



Table 10. Summation effect of persistent organic pollutants on prostate cancer in logistic regression analysis. (N=502)

| Compound concentration (ng/g lipid) <sup>a</sup> | N (cases/control) | OR (95% CI)     |                 |                 |
|--|-------------------|-----------------|-----------------|-----------------|
|  |                   | Model1          | Model2          | Model3          |
| $\Sigma$ OCPs                                    |                   |                 |                 |                 |
| <122.22  | 20/146            | 1.00            | 1.00            | 1.00            |
| 122.22-226.43                                    | 31/138            | 1.22(0.62-2.41) | 1.07(0.53-2.16) | 1.05(0.52-2.13) |
| 226.43 $\leq$                                    | 61/106            | 1.62(0.85-3.10) | 1.57(0.80-3.08) | 1.50(0.76-2.96) |
| P for trend                                      |                   | 0.1271          | 0.1567          | 0.2034          |
| $\Sigma$ PCBs                                    |                   |                 |                 |                 |
| <34.654  | 11/157            | 1.00            | 1.00            | 1.00            |
| 34.654-70.699                                    | 30/136            | 1.77(0.81-3.86) | 1.81(0.81-4.05) | 1.84(0.82-4.11) |
| 70.699 $\leq$                                    | 71/97             | 3.51(1.65-7.49) | 3.39(1.53-7.53) | 3.34(1.50-7.44) |
| P for trend                                      |                   | 0.0004          | 0.0012          | 0.0016          |
| Degree of chlorination <sup>b</sup>              |                   |                 |                 |                 |
| Low  |                   |                 |                 |                 |
| <1.794   | 55/112            | 1.00            | 1.00            | 1.00            |
| 1.794-3.306                                      | 29/138            | 0.34(0.18-0.61) | 0.34(0.18-0.64) | 0.33(0.18-0.62) |
| 3.306 $\leq$                                     | 28/140            | 0.36(0.20-0.65) | 0.34(0.18-0.64) | 0.33(0.18-0.62) |
| P for trend                                      |                   | 0.0004          | 0.0004          | 0.0003          |
| Moderate   |                   |                 |                 |                 |
| < 30.75  | 11/156            | 1.00            | 1.00            | 1.00            |
| 30.75-65.937                                     | 30/137            | 1.64(0.75-3.59) | 1.66(0.74-3.74) | 1.70(0.75-3.82) |
| 65.937 $\leq$                                    | 71/97             | 3.41(1.60-7.31) | 3.27(1.47-7.29) | 3.21(1.44-7.16) |
| P for trend                                      |                   | 0.0004          | 0.0014          | 0.0020          |
| Wolff group <sup>c</sup>                         |                   |                 |                 |                 |
| Group 1  |                   |                 |                 |                 |
| <2.968   | 54/113            | 1.00            | 1.00            | 1.00            |
| 2.968-4.89                                       | 28/136            | 0.37(0.20-0.68) | 0.37(0.20-0.69) | 0.36(0.19-0.67) |
| 4.89 $\leq$                                      | 30/141            | 0.37(0.20-0.67) | 0.35(0.19-0.65) | 0.34(0.18-0.64) |
| P for trend                                      |                   | 0.0007          | 0.0006          | 0.0005          |
| Group 2  |                   |                 |                 |                 |
| < 9.39   | 17/150            | 1.00            | 1.00            | 1.00            |
| 9.39-18.17                                       | 32/135            | 1.39(0.69-2.80) | 1.37(0.66-2.83) | 1.38(0.66-2.85) |
| 18.17 $\leq$                                     | 63/105            | 1.88(0.96-3.69) | 1.86(0.91-3.80) | 1.80(0.88-3.68) |
| P for trend                                      |                   | 0.0604          | 0.0788          | 0.1049          |
| Group 3  |                   |                 |                 |                 |
| <19.28   | 9/158             | 1.00            | 1.00            | 1.00            |
| 19.28-45.12                                      | 29/138            | 1.73(0.75-4.00) | 1.60(0.69-3.72) | 1.62(0.70-3.78) |
| 45.12 $\leq$                                     | 74/94             | 4.15(1.83-9.40) | 3.75(1.62-8.67) | 3.68(1.59-8.52) |
| P for trend                                      |                   | <.0001          | 0.0003          | 0.0005          |
| $\Sigma$ Dioxin-like PCBs <sup>d</sup>           |                   |                 |                 |                 |
| <4.1   | 16/151            | 1.00            | 1.00            | 1.00            |
| 4.1- 8.095                                       | 32/135            | 1.20(0.59-2.45) | 1.19(0.57-2.52) | 1.21(0.57-2.55) |
| 8.095 $\leq$                                     | 64/104            | 1.83(0.91-3.65) | 1.79(0.85-3.75) | 1.75(0.83-3.67) |

|                                     |        |                 |                 |                 |
|-------------------------------------|--------|-----------------|-----------------|-----------------|
| P for trend                         |        | 0.0616          | 0.0888          | 0.1087          |
| Σ Non-dioxin-like PCBs <sup>e</sup> |        |                 |                 |                 |
| < 29.88                             | 11/156 | 1.00            | 1.00            | 1.00            |
| 29.88- 61.24                        | 30/137 | 1.59(0.72-3.47) | 1.62(0.72-3.65) | 1.65(0.73-3.72) |
| 61.24≤                              | 71/97  | 3.28(1.53-7.04) | 3.16(1.41-7.07) | 3.13(1.40-7.02) |
| P for trend                         |        | 0.0006          | 0.0019          | 0.0024          |
| <hr/>                               |        |                 |                 |                 |
| TEQ                                 |        |                 |                 |                 |
| < 0.01322623                        | 14/153 | 1.00            | 1.00            | 1.00            |
| 0.01322623- 0.01338808              | 32/135 | 1.38(0.66-2.86) | 1.41(0.65-3.06) | 1.44(0.66-3.11) |
| 0.01338808≤                         | 66/102 | 2.42(1.19-4.92) | 2.49(1.16-5.33) | 2.44(1.14-5.24) |
| P for trend                         |        | 0.0077          | 0.0102          | 0.0134          |

<sup>a</sup> The cutoffs between the exposure groups were the 25th, 50th, and 75th percentiles.

<sup>b</sup> Low: PCB 52; moderate: PCBs 101, 118, 138, 153, 156, 180.

<sup>c</sup> Group1: PCBs 52, 101; Group2: PCBs 118, 138, 156, 167; Group3: PCBs 153, 180.

<sup>d</sup> PCBs 118, 156, 167.

<sup>e</sup> PCBs 52, 101, 138, 153, 180.

Model 1: Adjusted for age.

Model 2: Adjusted for age, BMI, smoking status, and physical activity.

Model 3: Adjusted for age, BMI, smoking status, physical activity, and age difference between enrollment age and age at blood drawn

TEQ, toxic equivalence quotient; PCB, polychlorinated biphenyl; OCP, organochlorine pesticide

Table 11. Logistic analysis between summarized polychlorinated biphenyls level and the risk for prostate cancer

| Compound concentration<br>(ng/g lipid)          | OR (95% CI)      |                  |                  |                 |
|---|------------------|------------------|------------------|-----------------|
|   | Crude            | Model1           | Model2           | Model3          |
| ln ( $\sum$ PCBs)                               | 3.41 (2.44-4.77) | 1.88 (1.29-2.73) | 1.84 (1.24-2.72) | 1.81(1.22-2.68) |
| ln ( $\sum$ Dioxin-like PCBs <sup>a</sup> )     | 2.51 (1.86-3.38) | 1.45 (1.04-2.04) | 1.47 (1.03-2.10) | 1.43(1.00-2.06) |
| ln ( $\sum$ Non dioxin-like PCBs <sup>b</sup> ) | 3.43 (2.46-4.79) | 1.89 (1.30-2.75) | 1.85 (1.25-2.73) | 1.82(1.23-2.69) |
| ln (TEQ)  | 1.58 (1.03-2.42) | 2.02 (1.22-3.34) | 2.06 (1.25-3.39) | 2.03(1.23-3.35) |

<sup>a</sup> PCBs 118, 156, 167.

<sup>b</sup> PCBs 52, 101, 138, 153, 180.

TEQ, toxic equivalence quotient; PCB, polychlorinated biphenyl

Model 1: Adjusted for age.

Model 2: Adjusted for age, BMI, smoking status, and physical activity.

Model 3: Adjusted for age, BMI, smoking status, physical activity, and age difference between enrollment age and age at blood drawn

#### **D. Application of toxicokinetic modelling**

From the result of logistic regression analysis, we obtained the external dose resulting in a 1% prostate cancer incidence risk effect above controls as 0.0494 ng/kg bw/day after applying the one-compartment toxicokinetic model. We suggested a maximum daily exposure limit of 0.494 pg TEQ/kg bw/day for dioxin-like PCBs (1% additional risk per 10,000 people) (Table 12).

Table 12. Applying toxicokinetic model on the result of logistic regression of TEQ-based–dioxin-like PCBs and the risk for prostate cancer.

| TEQ-based–dioxin-like PCBs                               |                            |  |
|--|----------------------------|--|
| External dose for 1% risk <sup>a</sup> increase (95% CI) | Slop factor                | The provisional tolerable daily intake (95% CI) <sup>b</sup> |
| 0.049 (0.001-2.636) ng-TEQ/kg bw/day                     | 0.202 per (ng-PCBs/kg-day) | 0.494 (0.009-26.364) pg TEQ /kg bw/day                       |

<sup>a</sup> 1% prostate cancer incidence risk effect above controls

<sup>b</sup> For 1% additional prostate cancer incidence risk effect per 10,000 people  
CI; confidence interval.

The mean age of participants was 49.71 years.

The mean weight of participants was 71.52kg

## V. DISCUSSION

In this study, we observed significant positive associations between prostate cancer risk and serum concentrations of several POPs. This study's results were consistent with the recent meta-analysis of POPs and prostate cancer. In the meta-analysis, the pooled ORs of prostate cancer for the sum of PCBs was 1.49 (95% CI: 1.07, 2.06).

In this study, some inverse or U-shape associations between several POPs and prostate cancer risk were also observed. Although these are unexpected results that PCBs might be inversely associated with prostate cancer risk, some previous studies supported these findings. A case-control study in Guadelope showed inverse associations between PCB153 and prostate cancer (OR = 0.30; 95% CI: 0.19, 0.47 for the highest vs. lowest quintile of exposure values;  $p$  trend < 0.001, Emeville et al. 2015). In that study, after grouping prostate cancer by Gleason score and clinical stage, the significance of the inverse associations disappeared for a high-grade or advanced prostate cancer risk. In Japanese nested case-control study using a mean follow-up period of 12.8 years, no statistically significant associations with total, advanced, or localized prostate cancer were observed for any plasma organochlorines (Sawada et al. 2010). Meanwhile, a recent nested case-control study in the Norwegian Janus Serum Bank Cohort suggested a significant inverse association between PCB44 and risk of metastatic prostate cancer (Koutros et al. 2015). Another study has also reported inverse associations between specific PCB congeners and prostate cancer (Aronson et al. 2010). Both PCB52 and PCB101, which showed inverse associations with prostate cancer risk in our study, are defined as Group 2 according to the definition by Wolff (Wolff et al. 1997). These

compounds are known as potentially estrogenic and less persistent chemicals. It is possible that the observed inverse associations could be reflective of the chemical specific differences in the mechanisms of action as endocrine disruptors. However, since humans are exposed to large number of exposures, studying the effect of multicomponent mixture rather than of each compound on prostate cancer will be more meaningful (Lee et al. 2013; Lim et al. 2015). A consistent positive association of sum of PCBs on prostate cancer was observed in our study (table 9, table 11). Our findings need to be replicated in other populations, and caution is required in interpretation of inverse associations.

The WHO expert group's proposed tolerable daily intake (TDI) for human could be found in the range of 1-4 pg TEQ /kg bw/day (WHO 1998). This range was established for dioxins and dioxin-like compounds by applying an uncertainty factor of 10 to the range of the Lowest Observed Adverse Effect Levels (LOAELs), 14-37 pg TCDD/kg bw/day from experimental animal study. In 2012 using human epidemiologic data, the US EPA set 0.7 pg TEQ/kg bw/day as exposure guidance values for total exposure of polychlorinated dibenzodioxins (PCDD) / polychlorinated dibenzofurans (PCDF) and dioxin-like PCBs (U.S. EPA 2012a,b; St-Amand et al. 2014).

In our study, TDI was calculated for the dioxin-like PCBs exposure because we did not measure PCDD/PCDF level. Considering that the percent contribution of dioxin-like PCBs among the whole TEF available chemicals is about 30% - 65% (La Rocca et al. 2008), 0.494 pg TEQ/kg bw/day looks like a relatively high reference value as TDI for human dioxin-like PCB exposure. However, we need to consider several points to compare the TDI value of our study with previously suggested reference values. In our study, we suggested the TDI value for the prostate cancer incidence risk in men. The exposure guidance value from the US EPA was based on the occupational exposure data for all cancer risk mortality. Compared with the occupational exposure group, the general

population is more likely to be exposed to low doses of POPs. The long survival rate and the pathological characteristic of prostate cancer, as follows, also could have an effect on the suggested TDI value. Most of the time, prostate cancer grows slowly. Moreover, as prostate cancer does not show any symptoms in early stage, early diagnosis of prostate cancer is very difficult. Most prostate cancers are usually found during screening with a prostate-specific antigen (PSA) blood test, alone or in combination with a digital rectal exam, followed by a diagnostic biopsy and potentially imaging if there is suspicion of cancer spread. Once the diagnosis of prostate cancer is confirmed, PSA levels are used to define tumor stages and to track cancer progression. However, only around 25% of men with an elevated PSA level, defined as  $> 4.0$  ng/mL, are diagnosed with prostate cancer at biopsy; conversely, false-negatives results are also common (Kelly et al. 2016). In our study, these prostate cancer specific characteristics would be reflected in the suggested TDI value.

This study has several limitations. First, limited number of participants was available to analyze serum PCBs concentration. So, tertile analyses resulted in the modest numbers of cases in some categories, limiting the power to detect associations if they existed. Limited number of participants could also lead to a broad 95% confidence interval range for the suggested TDI. Second, unknown and unmeasured co-exposures may influence the risk of prostate cancer, because humans are exposed to complex mixtures of toxic substances every day. Third, we drew TDI from the OR in logistic regression using KCPS-II. To generalize the usefulness of suggested TDI, further evidence from large-scale population-based cohort studies are needed. Fourth, the significant difference of age between case and control existed in the case-control study (data not shown). However, the age difference will not change the main results due to POPs' accumulative and long elimination half-life. Fifth, because of low detection rates of low chlorinated PCBs, and as PCBs were defined



as Group 2 by Wolff definition, the effect sizes of these PCBs group for prostate cancer only reflected the effect of PCB52 or PCB101. Sixth, we could not ignore the measurement errors in POPs analysis. However, with measurement error, effect estimates are usually biased toward the null (Armstrong et al. 1990; Thomas et al. 1993). So, it is possible that the true association between POPs and prostate cancer risk could be much stronger than the result of this study. Lastly, Gleason score or clinical stage information was not available in this study.

To the best of our knowledge, this is the first study that observed the body burden of serum POPs on prostate cancer risk in Korea. Until now, the most of previous studies of POPs and prostate cancer were based on the results of case-control studies. In this study, we directly measured the serum level of POPs and conducted case-cohort study using a prospective cohort data. Moreover, we estimated associations of prostate cancer risk not only with each individual compound but also with mixtures of individual compounds that have similar properties. Since humans are exposed to complex mixtures of toxic substances at the same time, analyzing the association between PCB groupings and prostate cancer risk will improve the significance of the interpretation. In this study, matching the cohort data with both National Cancer Registry and death certificate data from the Korean National Statistical Office allowed an exact definition of prostate cancer as well as identification of all subjects' vital status without loss during follow-up period. Lastly, as one of the interdisciplinary convergence researches, we attempted to combine toxicokinetics with epidemiological study.

The mechanism by which POPs can play as a potential risk factor for prostate cancer is unclear. However, a possible mechanism for POPs and prostate cancer was suggested in our previous study (Lim et al. 2015). Prostate carcinogenesis involves androgen receptor-mediated mechanisms that enhance the carcinogenic activity of genotoxins, including

estrogen, prostatitis-generated reactive oxygen species and possible environmental carcinogens such as POPs. The results of an experimental study showed that dioxin-like coplanar PCBs could interfere with androgenic properties in the androgen-sensitive human prostate cancer cell line LNCaP in vitro (Pflieger-Bruss et al. 2006). The significant inhibitory effects on testosterone-stimulated cell proliferation were also observed in PCB concentrations at low levels as those measured in human blood (Kimbrough et al. 1995). Mainly on the basis of animal experiments, the International Agency for Research on Cancer (IARC) currently classifies DDT as “possibly carcinogenic to humans” and PCBs as “probably carcinogenic to humans” (IARC 1991). Chemical carcinogenic properties, as well as postulated estrogenic or antiandrogenic activities (Diamanti-Kandarakis et al. 2009), could play a role in prostate carcinogenesis (Emeville et al. 2015).

## VI. CONCLUSIONS

This study suggests that exposure to specific OCPs or PCBs may be associated with prostate cancer risk in the Korean population. Observed chemical-specific associations with prostate cancer may have different biological roles or multiple modes of hormonal action of each POP. However, humans are exposed to a complex mixture of toxic substances. Thus, analyzing the associations between ‘POPs’ that have similar properties and prostate cancer risk, as done in this study, will be very significant. The increased risk of prostate cancer was observed in the upper tertile of TEQ and the sum of PCBs.

After applying the one-compartment toxicokinetic model, we suggested a maximum daily exposure limit of 0.494 pg I-TEQ/kg bw/day for dioxin-like PCBs (for 1% prostate cancer incidence risk effect per 10,000 people) (Table 12). As an interdisciplinary convergence research, this study combined toxicokinetic models and epidemiologic data. Confirmatory evidence through replication studies in other populations and mechanistic studies are needed.

## REFERENCES

Abass K, Huusko A, Nieminen P, et al. Estimation of health risk by using toxicokinetic modelling: a case study of polychlorinated biphenyl PCB153. *J Hazard Mater.* 2013; 261:1-10.

Alcock RE, Sweetman AJ, Juan CY, et al. A generic model of human lifetime exposure to persistent organic contaminants: development and application to PCB-101, *Environ Pollut.* 2000;110(2):253-65.

Armstrong BG. The effects of measurement errors on relative risk regressions. *Am J Epidemiol* 1990;132(6): 1176–84.

Bernert JT, Turner WE, Patterson DG Jr, et al. Calculation of serum "total lipid" concentrations for the adjustment of persistent organohalogen toxicant measurements in human samples. *Chemosphere* 2007; 68(5):824-31.

Bocio A, Llobet JM, Domingo JL, et al. Polybrominated diphenyl ethers (PBDEs) in foodstuffs: human exposure through the diet. *J Agric Food Chem* 2003; 51(10):3191-5.

Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, et al. 2009. Endocrine- disrupting chemicals: an Endocrine Society scientific statement. *Endocr Rev* 30(4):293-342.

Emeville E, Giusti A, Coumoul X, et al. Associations of plasma concentrations of dichlorodiphenyldichloroethylene and polychlorinated biphenyls with prostate cancer: a case-control study in Guadeloupe (French West Indies). *Environ Health Perspect* 2015;123(4):317-23.

Falcó G, Bocio A, Llobet JM, et al. Health risks of dietary intake of environmental pollutants by elite sportsmen and sportswomen. *Food Chem Toxicol* 2005; 43(12):1713-21.

Hardell L, Andersson SO, Carlberg M, et al. Adipose tissue concentrations of persistent organic pollutants and the risk of prostate cancer. *J Occup Environ Med* 2006; 48(7):700-7.

IARC (International Agency for Research on Cancer). Occupational exposures in insecticide application, and some pesticides. *IARC Monogr Eval Carcinog Risk Hum* 1991;53:5-586.

Jee SH, Sull JW, Lee JE, et al. Adiponectin concentrations: a genome-wide association study. *Am J Hum Genet* 2010; 87(4):545-52.

Jo J, Nam CM, Sull JW, et al. Prediction of Colorectal Cancer Risk Using a Genetic Risk Score: The Korean Cancer Prevention Study-II (KCPS-II). *Genomics Inform* 2012; 10(3):175-83

Kelly RS, Vander Heiden MG, Giovannucci E, et al. Metabolomic Biomarkers of Prostate Cancer: Prediction, Diagnosis, Progression, Prognosis, and Recurrence. *Cancer Epidemiol Biomarkers Prev.* 2016;25(6):887-906.

Kimbrough RD. Polychlorinated biphenyls (PCBs) and human health: an update. *Crit Rev Toxicol.* 1995; 25(2):133-63.

Koutros S, Langseth H, Grimsrud TK, et al. Prediagnostic Serum Organochlorine Concentrations and Metastatic Prostate Cancer: A Nested Case-Control Study in the Norwegian Janus Serum Bank Cohort. *Environ Health Perspect* 2015;123(9):867-72.

Kreuzer PE, Csanády GA, Baur C, et al. 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and congeners in infants. A toxicokinetic model of human lifetime body burden by TCDD with special emphasis on its uptake by nutrition, *Arch Toxicol* 1997;71(6):383-400.

Kwon W, Kin J, Chae J, et al. The Relationship between adiposity and risk factors for cardiovascular disease at normal body weight male. *Yeungnam Univ. J. of Med* 2003;20(1):62-70.

Lee YM, Bae SG, Lee SH, et al. Persistent organic pollutants and hyperuricemia in the U.S. general population. *Atherosclerosis* 2013;230(1):1-5.

Lim JE, Jee SH. Association between serum levels of adiponectin and polychlorinated biphenyls in Korean men and women. *Endocrine* 2015; 48(1):211-7.

Lim JE, Park SH, Jee SH, et al. Body concentrations of persistent organic pollutants and prostate cancer: a meta-analysis. *Environ Sci Pollut Res Int* 2015; 22(15):11275-84.

Lim Y, Yang J, Kim Y, et al. Assessment of human health risk of dioxin in Korea. *Environ Monit Assess*. 2004;92(1-3):211-28.

Martorell I, Perelló G, Martí-Cid R, et al. Polycyclic aromatic hydrocarbons (PAH) in foods and estimated PAH intake by the population of Catalonia, Spain: Temporal trend. *Environ Int* 2010; 36(5):424-32.

McFarland VA, Clarke JU. Environmental occurrence, abundance, and potential toxicity of polychlorinated biphenyl congeners: considerations for a congener-specific analysis. *Environ Health Perspect*. 1989; 81:225-39.

Moser GA, McLachlan MS. The influence of dietary concentration on the absorption and excretion of persistent lipophilic organic pollutants in the human intestinal tract, *Chemosphere*. 2001 Oct; 45(2):201-11.

Park SH, Hong YS, Ha EH, et al. Serum concentrations of PCBs and OCPs among prepubertal Korean children. *Environ Sci Pollut Res Int*. 2015; 23(4):3536-47.

Pflieger-Bruss S, Hagemann S, Körner W, et al. Effects of single non-ortho, mono-ortho, and di-ortho chlorinated biphenyls on human sperm functions in vitro. *Reprod Toxicol* 2006; 21(3):280-4.

Ritchie JM, Vial SL, Fuortes LJ, et al. Organochlorines and risk of prostate cancer. *J Occup Environ Med* 2003; 45(7):692-702.

Ritchie JM, Vial SL, Fuortes LJ, et al. Comparison of proposed frameworks for grouping polychlorinated biphenyl congener data applied to a case-control pilot study of prostate cancer. *Environ Re* 2005;98(1):104-13.

Sawada N, Iwasaki M, Inoue M, et al. Plasma organochlorines and subsequent risk of prostate cancer in Japanese men: a nested case-control study. *Environ Health Perspect* 2010; 118(5):659-65.

Self SG, Prentice RL. Asymptotic distribution theory and efficiency results for case-cohort studies. *Ann Statist* 1988;16(1):64-81.

Shin HR, Won YJ, Jung KW, et al. Nationwide cancer incidence in Korea, 1999,2001; first result using the national cancer incidence database. *Cancer Res Treat* 2005;37(6):325-31.



Stalling DL, Schwartz TR, Dunn WJ 3rd, et al. Classification of polychlorinated biphenyl residues: Isomers vs. homologue concentrations in modeling Aroclors and polychlorinated biphenyl residues. *Anal. Chem* 1987; 59(14):1853-9.

St-Amand A, Werry K, Aylward LL, et al. Screening of population level biomonitoring data from the Canadian Health Measures Survey in a risk-based context. *Toxicol Lett* 2014; 231(2):126-34.

Thomas D, Stram D, Dwyer J. Exposure measurement error: influence on exposure-disease relationships and methods of correction. *Ann Rev Public Health* 1993;14:69-93.

WHO/UNEP. Polychlorinated biphenyls : Human health aspects. Concise international chemical assessment document 55. 2003. Available: <http://www.greenfacts.org/en/pcbs/> (accessed 06.14.16.)

WHO European Centre for Environment and Health International Programme. Assessment of the health risk of dioxins: re-evaluation of the Tolerable Daily Intake (TDI). WHO Consultation May 25-29 1998, Geneva, Switzerland.

WHO/UNEP. State of the science of endocrine disrupting chemicals – 2012: An assessment of the state of the science of endocrine disruptors prepared by a group of experts for the United Nations Environment Programme (UNEP) and WHO. 2013. ISBN: 978 92 4 150503 1

U.S. EPA (U.S. Environmental Protection Agency). 2012. EPA's reanalysis of key issues related to dioxin toxicity and response to NAS comments, vol. 1, (CAS No. 1746-01-6). EPA/600/R-10/038F. Washington, DC: U.S. EPA. Available: <http://www.epa.gov/iris/supdocs/dioxinv1sup.pdf> (accessed 04.13.16.)

U.S. EPA. (U.S. Environmental Protection Agency). 2012. Integrated Risk Information System (IRIS): 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Available: <http://www.epa.gov/iris/subst/1024htm> (accessed 04.13.16)

U.S. EPA. (U.S. Environmental Protection Agency). 2000. Exposure and Human Health Reassessment of 2,3,7,8-TCDD and Related Compounds, Part I, Vol. 3. EPA/600/p-00/001Bc, Washington DC, US EPA.

Verner MA, Charbonneau M, López-Carrillo L, et al. Physiologically based pharmacokinetic modeling of persistent organic pollutants for lifetime exposure assessment: a new tool in breast cancer epidemiologic studies. *Environ Health Perspect* 2008;116(7):886-92.

Wolff MS, Camann D, Gammon M, et al. Proposed PCB congener groupings for epidemiological studies. *Environ Health Perspect* 1997; 105(1):13-4.

Wu H, Bertrand KA, Choi AL, et al. Persistent organic pollutants and type 2 diabetes: a prospective analysis in the nurses' health study and meta-analysis. *Environ Health Perspect* 2013; 121(2):153-61.

## APPENDIXES

Table A1. The information of PCB congeners included in this study

| IUPAC no. | Isomer group <sup>a</sup> | Structure <sup>b</sup> | Inducer type <sup>c</sup> |
|-----------|---------------------------|------------------------|---------------------------|
| 1         | 1                         | 2                      |                           |
| 3         | 1                         | 4                      |                           |
| 4         | 2                         | 2,2'                   |                           |
| 15        | 2                         | 4,4'                   | Wk PB                     |
| 19        | 3                         | 2,2',6                 |                           |
| 28        | 3                         | 2,4,4'                 |                           |
| 37        | 3                         | 3,4,4'                 | Mixed                     |
| 52        | 4                         | 2,2',5,5'              | Wk PB                     |
| 54        | 4                         | 2,2',6,6'              | Wk PB                     |
| 77        | 4                         | 3,3',4,4'              | 3-MC                      |
| 81        | 4                         | 3,4,4',5               | Mixed                     |
| 101       | 5                         | 2,2',4,5,5'            | PB                        |
| 104       | 5                         | 2,2',4,6,6'            |                           |
| 105       | 5                         | 2,3,3',4,4'            | Mixed                     |
| 114       | 5                         | 2,3,4,4',5             | Mixed                     |
| 118       | 5                         | 2,3',4,4',5            | Mixed                     |
| 123       | 5                         | 2',3,4,4',5            | Mixed                     |
| 126       | 5                         | 3,3',4,4',5            | 3-MC                      |
| 138       | 6                         | 2,2',3,4,4',5'         | Mixed                     |
| 153       | 6                         | 2,2',4,4',5,5'         | PB                        |
| 155       | 6                         | 2,2',4,4',6,6'         | Wk PB                     |
| 156       | 6                         | 2,3,3',4,4',5          | Mixed                     |
| 157       | 6                         | 2,3,3',4,4',5'         | Mixed                     |
| 167       | 6                         | 2,3',4,4',5,5'         | Mixed                     |
| 169       | 6                         | 3,3',4,4',5,5'         | 3-MC                      |
| 180       | 7                         | 2,2',3,4,4',5,5'       | PB                        |

|     |   |                       |       |
|-----|---|-----------------------|-------|
| 188 | 7 | 2,2',3,4',5,6,6'      |       |
| 189 | 7 | 2,3,3',4,4',5,5'      | Mixed |
| 202 | 8 | 2,2',3,3',5,5',6,6'   |       |
| 205 | 8 | 2,3,3',4,4',5,5',6    | PB    |
| 206 | 9 | 2,2',3,3',4,4',5,5',6 | PB*   |
| 208 | 9 | 2,2',3,3',4,5,5',6,6' |       |

<sup>a</sup>Isomer groups are defined by the number of chlorine atoms in the molecule.

<sup>b</sup>See McFarland et al. (1989), Stalling et al. (1987).

<sup>c</sup>PB, phenobarbital-type; wk BP, weak phenobarbital-type or inactive; PB\*, theoretical phenobarbital-type according to structure-activity rules; 3-MC, 3-methylcholanthrene-type; mixed, mixed phenobarbital- and 3-methylcholanthrene-type microsomal enzyme inducers.

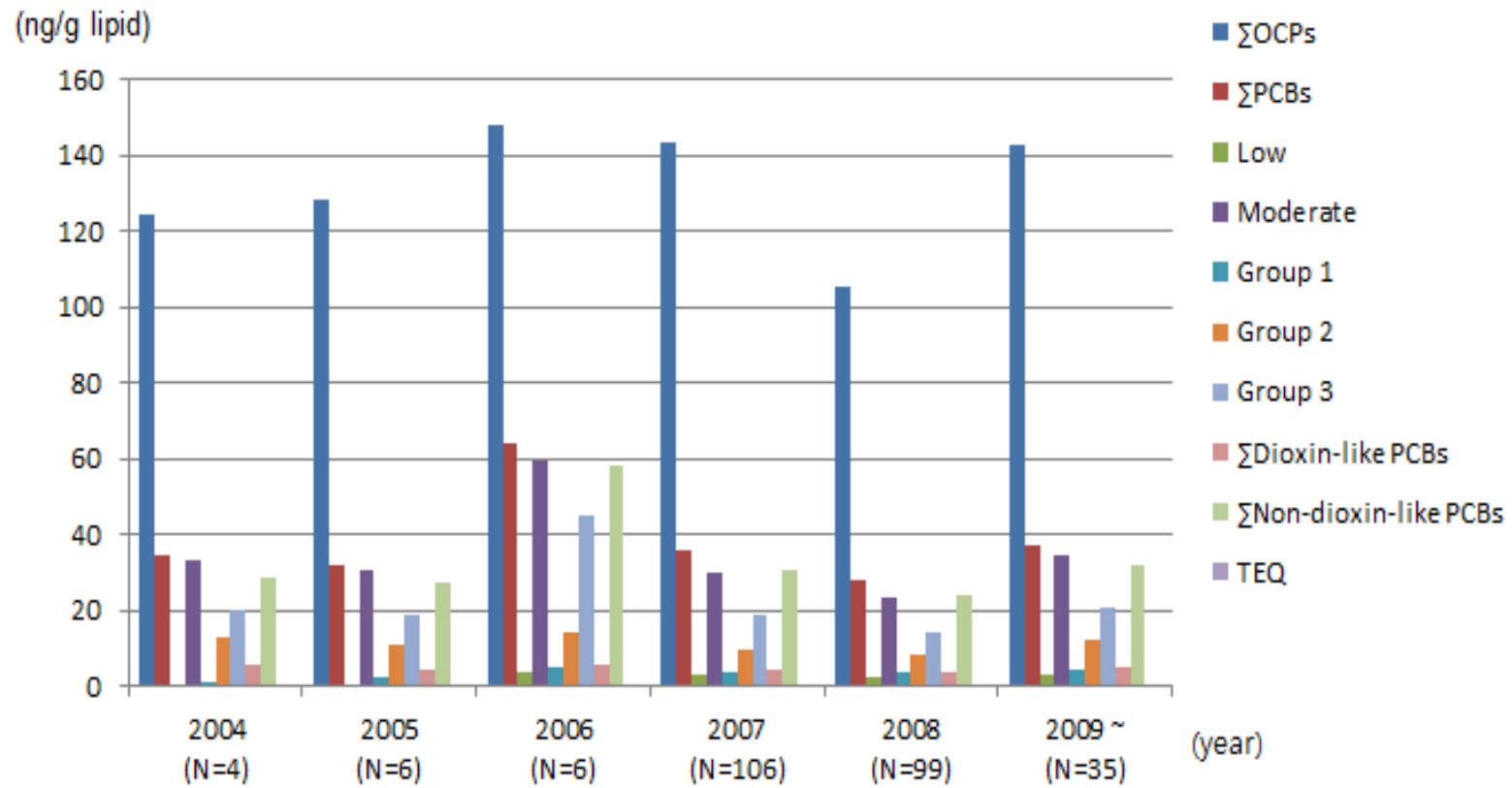


Figure A1. Persistent organic pollutants levels according to year at blood drawn to analysis in participants without prostate cancer in sub-cohort (N=256). The last category included 34 person whose blood was drawn in 2009, and one person whose blood was drawn in 2010.

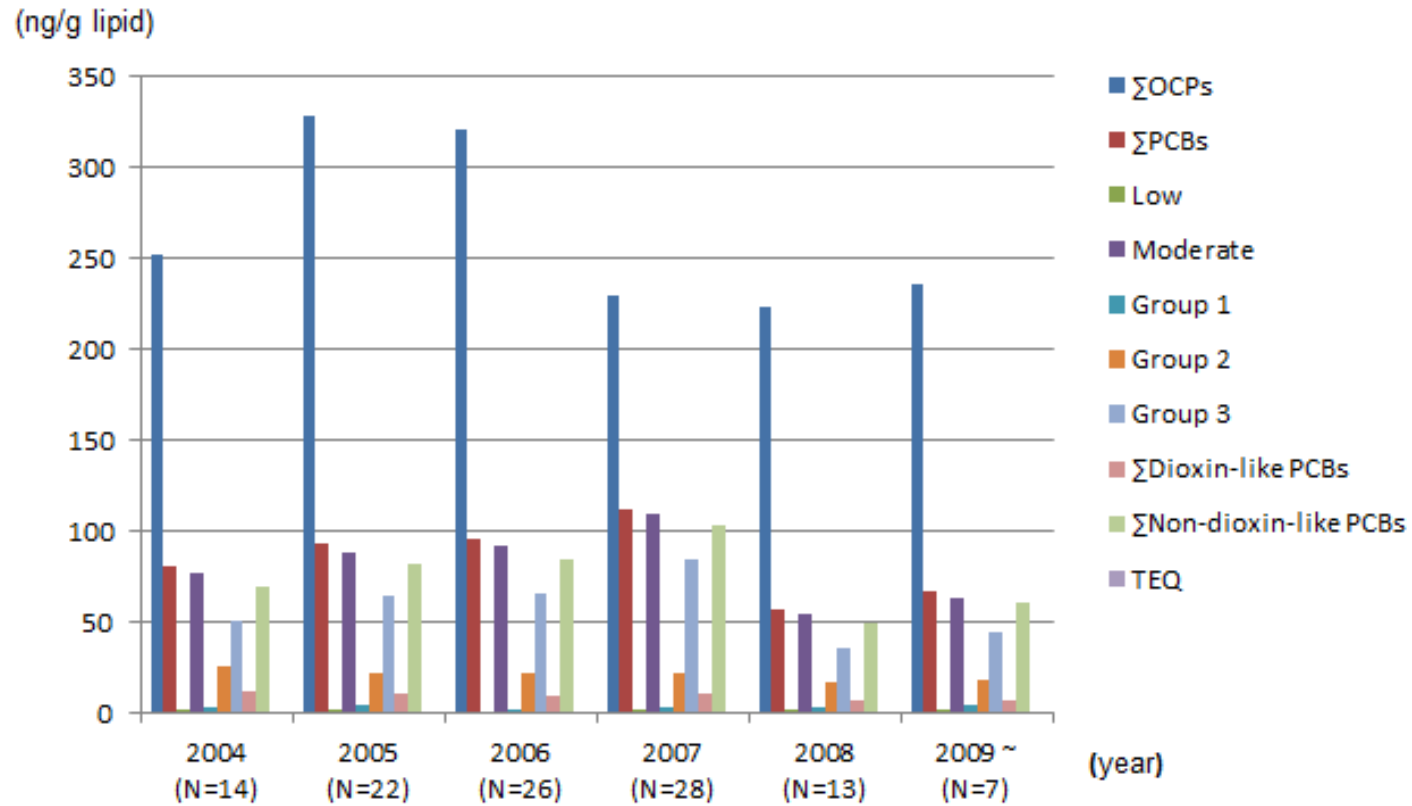


Figure A2. Persistent organic pollutants levels according to year at blood drawn to analysis in prostate cancer incidence case. The last category included four person whose blood were drawn in 2009, two person whose blood was drawn in 2011, and 1 person whose blood was drawn in 2013.

## Appendix A.1. The process of calculating tolerable daily intake

### Step 1)

#### a) Find the predicted probability of prostate cancer, $\hat{p}$ , when $x = 0$

To find  $\hat{p}_{x=0}$ , we should know the intercept of the model.

In case-control study, we can get the intercept after applying sampling fraction (Agresti et al. 1996<sup>i</sup>).

The incidence rate for prostate cancer is 11.4 per 100,000 persons in 2013 (National Cancer Information Center, 2013).

Among the men ( $\geq 20$  years),

the number of prostate incidence case =  $(19,828,321 \times 11.4) / 100,000 = 2,260$  (person)

the number of non-prostate incidence case =  $19,828,321 - 2,260 = 19,826,061$  (person)

from the Korean Statistical Information Service data (2013.06).

Sampling fraction of case =  $\rho_1 = 112 / 2,260 = 4.96 \times 10^{-2}$

Sampling fraction of control =  $\rho_0 = 390 / 19,826,061 = 1.97 \times 10^{-5}$

When  $\alpha^*$  means the intercept of logistic regression model,

the modified intercept,  $\hat{\alpha} = \alpha^* - \ln(\rho_1 / \rho_0) = 0.6701 - \ln(4.96 \times 10^{-2} / 1.97 \times 10^{-5}) = -7.16$

As a result, the modified logistic function is as follows;

$$\hat{p} = e^{(-7.16164 + 0.4550x)} / (1 + e^{(-7.16164 + 0.4550x)}).$$

So, we can obtain  $\hat{p}_{x=0}$  as  $7.75 \times 10^{-4}$

#### b) Find the 95% confidence interval of $\hat{p}_{x=0}$

---

<sup>i</sup> Agresti, A. 1996. An introduction to categorical data analysis. New York: Wiley.

95% confidence interval of  $\hat{p}_{x=0}$  can be expressed as follows;

$$(e^{L_1}/(1+e^{L_1}), e^{L_2}/(1+e^{L_2}))$$

When,  $L_1 = \hat{\alpha} - 1.96\sqrt{\text{Var}(\hat{\alpha})}$ ,  $L_2 = \hat{\alpha} + 1.96\sqrt{\text{Var}(\hat{\alpha})}$

In the step a), we found  $\hat{\alpha}$  as -7.16,  $\text{Var}(\hat{\alpha}) = 0.85223$ .

As a result, 95% confidence interval of  $\hat{p}_{x=0}$  is  $(1.27 \times 10^{-4}, 4.72 \times 10^{-3})$

### Step 2) Find TEQ when $P_x$ was increased 1% ( $P_x'$ )

$$P_x' = (7.75 \times 10^{-4}) * 1.01 = 7.83 \times 10^{-4}$$

From the modified logistic function in Step1,

$$P_x' = 7.83 \times 10^{-4} = e^{(-7.16164 + 0.4550x)} / (1 + e^{(-7.16164 + 0.4550x)})$$

$$x = \ln(\text{TEQ}) = 2.19 \times 10^{-2}, \text{TEQ} = 1.02 \text{ ng-TEQ/g lipid}$$

### Step 3) Apply toxicokinetic model to obtain LADD

$$\text{LADD} = \{(\ln 2) / 7.2 * (11800 * 1000 * 1.02 \text{ ng-TEQ/g lipid} / 365) / 0.9\} / 71.52$$

$$= 49.4 \text{ pg-TEQ/kg bw/day} = 4.94 \times 10^{-2} \text{ ng-TEQ/kg bw/day}$$

### Step 4) Slope factor

$$\text{Slope} = P(01\%) / \text{LED}(01) = 0.01 / 4.94 \times 10^{-2} = 0.202 \text{ per (ng-TEQ/kg bw/day)}$$

### Step 5) Calculate the provisional tolerable daily intake (Risk per 10,000 people)

$$10^{-4} / \text{Slope factor}$$

$$= 10^{-4} / 0.2023325 = 4.94 \times 10^{-4} \text{ ng TEQ/kg bw/day} = 0.494 \text{ pg TEQ/kg bw/day}$$

By similar method (Step2~ Step5), 95% confidence interval of the provisional tolerable daily intake was calculated as  $(9.22 \times 10^{-3}, 26.3) \text{ pg TEQ/kg bw/day}$



## ABSTRACT IN KOREAN

### 혈청 잔류성유기오염물질 농도와 전립선암 위험

연세대학교 대학원 보건학과

임정은

#### 배경 및 목적

세계보건기구 (the World Health Organization, WHO)와 유엔환경계획 (the United Nations Environment Programme, UNEP) 에서는 잔류성유기오염물질에 대한 노출이 전립선암을 포함한 여러 만성질환의 위험을 증가시킬 수 있음을 제안하고 있다. 하지만 현재까지 진행된 역학연구는 대부분 소규모 연구대상자를 대상으로 한 환자-대조군 연구에 그친다. 뿐만 아니라, 그 동안 제안된 폴리염화비페닐류 (polychlorinated biphenyls, PCBs)의 일일섭취한계량 (tolerable daily intake, TDI)은 대부분 동물 실험 연구 자료에 기반하고 있다. 이에 본 연구에서는 전향적 코호트 자료를 이용하여 한국인 남자에서 혈청 잔류성유기오염물질 농도와 전립선암 위험의 관련성을 분석하고, human bio-monitoring data 에 기반하여 일일섭취한계량을 제안하고자 하였다.

#### 연구 방법

본 연구에는 1994 년부터 2013 년까지 전국 11 개 건강검진센터에 방문한 대상자를 대상으로 구축된 한국인 암 예방 연구-II (Korean Cancer Prevention Study-II) 자료를 이용하였다. 110 명의 전립선암 발생 대상자와 서브코호트 내 전립선암이 없는 256 명을 대상으로 case-cohort study 를

수행하였다. 혈청에서 32 종의 PCB congener 와 19 종의 유기염소계살충제 (organochlorine pesticides, OCPs)를 고분해능 기체크로마토그래피 질량분석분석기 (gas chromatography / high-resolution mass spectrometry, GC/HRMS) 를 이용하여 측정하였다. 2005 년에 WHO 에서 제안한 독성등가계수(toxic equivalency factor, TEF)를 이용하여 독성등가량 (toxic equivalent, TEQ)를 계산하였다. 전립선암 발생에 대한 위험비 (hazard ratio, HR)는 Cox proportional hazard model 을 이용하여 도출하였으며, one-compartment toxicokinetic model 을 이용하여 일일섭취한계량을 제안하였다.

## 연구 결과

혈청 중 다이옥신 유사 PCBs 의 총량 (P for trend=0.0395), 비다이옥신 유사 PCBs 의 총량 (P for trend=0.0019), 독성등가량 (P for trend=0.0063)이 증가할 수록 전립선암 발생에 대한 위험이 증가하는 경향성을 보였다. 각각의 물질별로 분석 하였을 때에는 혈청 중  $\beta$ -HCH, PCB118, PCB167, PCB138, PCB153, PCB180 농도가 전립선암 발생 위험과 양의 관련성을 보였다. 본 연구 자료에 one-compartment model 을 적용한 결과, 다이옥신 유사 PCBs 에 대해 0.494 pg TEQ/kg bw/day 가 한국인 남자에서 비노출군에 비해 1 만명당 1 명의 추가적인 전립선암 발생 위험을 높이는 일일섭취한계량으로 계산되었다.

## 결론

본 연구는 한국인 전향적 코호트 역학자료를 이용하여 잔류성 유기오염물질 노출이 전립선암 위험 증가와 양의 관련성이 있음을 제안하였다. 또한 학제간 융합연구의 일환으로, 역학연구에 독성역학모델을 접목하여 일일섭취한계량을 도출하였다는 것에 의의가 있다.

○ 본 연구는 2013 년도 식품의약품안전처 용역연구개발과제의 연구개발비 지원(13162 유해연 891)과, 2015 년도 식품의약품안전처 용역연구개발과제의 연구개발비 지원(15162 호르몬 631)에 의해 수행되었으며 이에 감사드립니다.

---

핵심어: 전립선암, 코호트연구, 내분비교란물질, 잔류성유기오염물질,  
폴리염화비페닐류, 유기염소계살충제, 일일섭취한계량