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Associations of organochlorine pesticides and polychlorinated biphenyls with total, cardiovascular, and cancer mortality in elders with differing fat mass

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ABSTRACT

Background: We investigated if certain persistent organic pollutants (POPs), namely polychlorinated biphenyls (PCBs) and organochlorine (OC) pesticides, predicted total, cardiovascular disease (CVD), and cancer mortality among the elderly, with the hypothesis that associations differ by the amount of fat mass.

Methods: We studied serum concentrations of 11 PCBs in 633 elders (age ≥ 70 years) and of 5 OC pesticides in 675 elders within the National Health and Nutrition Examination Survey (NHANES) 1999–2004. Mean follow-up was 4.1-years.

Results: Neither PCBs nor OC pesticides were associated with total mortality when fat mass was not considered in analyses. However, associations of PCBs and OC pesticides with total mortality depended on fat mass ($P_{interaction} < 0.01$ and 0.06, respectively). PCBs associated inversely with total mortality for high fat mass, but not for lower fat mass. On the contrary, OC pesticides associated positively with total mortality for low fat mass and this association weakened at higher fat mass. The interaction was also observed with CVD mortality. In elders with low fat mass, higher PCBs associated with 2–3 fold higher risk of CVD mortality, while this association was absent in elders with more fat mass ($P_{interaction} = 0.03$). The positive association between OC pesticides and CVD mortality was also observed only among elderly with low fat mass ($P_{interaction} = 0.03$).

Conclusions: The possibility of interaction between POPs and the amount of fat mass on risk of mortality from chronic diseases is clinically important in modern societies with an obesity epidemic and requires confirmation in other studies with larger sample size.

1. Introduction

Background exposure to persistent organic pollutants (POPs) has recently been linked to a variety of chronic diseases. However, few studies have focused on associations between POPs and mortality in general populations. Exposure to a mixture of dioxin-like chemicals was associated with an increased total mortality risk among U.S. adults (Lin et al., 2012). POPs without dioxin activity, such as nondioxin-like polychlorinated biphenyls (PCBs) or organochlorine (OC) pesticides, have not been evaluated in relation to mortality in general populations yet.

On the other hand, mortality studies among workers who were exposed to high levels of PCBs or OC pesticides in occupational settings have reported lower total and cardiovascular diseases (CVD) mortality among workers compared to general populations and associations with site-specific cancer mortality differ across studies (Brown, 1992; Kimbrough and Krouskas, 2003; Kimbrough et al., 2014; Prince et al., 2006; Ruder et al., 2006; Swaen et al., 2002). The decreased risk of mortality among workers has commonly been interpreted as a bias due to healthy worker effect (Brown, 1992; Ruder et al., 2006).

Interestingly, one prospective study among the elderly reported that obesity was differently associated with total mortality depending on serum concentrations of POPs including nondioxin-like PCBs or OC pesticides (Hong et al., 2012). In that study, mortality was not analyzed and interpreted from the viewpoint of POPs because it was performed to evaluate if the obesity paradox,

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better survival among obese patients or elders than among lean persons, can be explained by POPs. Although obesity is commonly regarded as harmful to human health, from the viewpoint of lipophilic chemicals like POPs with very long half-lives, adipose tissue may provide a relatively safe harbor for POPs in humans, protecting other critical organs from POP insults (La Merrill et al., 2013; Lee et al., 2014). Experimental studies also suggested that adipose tissue can protect against harm from POPs. Coplanar polychlorinated biphenyls (PCBs) impaired glucose homeostasis in lean mice but not in obese mice and obese mice developed impaired glucose homeostasis after weight loss (Baker et al., 2013). In rats, diet-induced obesity also significantly increased survival time following exposure to a potentially lethal dose of dioxin (Tuomisto et al., 1999).

Therefore, this study was performed with two purposes. First, we evaluated associations of serum concentrations of PCBs, including both dioxin-like and nondioxin-like PCBs, and OC pesticides with total, CVD, and cancer mortality. Second, we further tested if POPs were differently associated with mortality by the amount of fat mass. As the findings were more clearly observed with aging, we focused on men and women aged 70 or over.

2. Methods

2.1. Study subjects

The continuous NHANES, conducted annually since 1999 by the Centers for Disease Control and Prevention (CDC), is an ongoing survey designed to measure the health and nutritional status of the civilian noninstitutionalized U.S. population. In the NHANES 1999–2002, all POPs were measured in the same subsample while in the NHANES 2003–2004, OC pesticides were measured in a different subsample from the subsample in which other POPs were measured. Thus, the final partially overlapping sample sizes were 633 for PCBs and 675 for OC pesticides, including subjects aged 70 years or older with information on fat mass and followed for mortality through the end of 2006. The study protocol was reviewed and approved by the institutional review board of Center for Disease Control in the U.S. Also, informed written consent was obtained from all subjects before they took part in the study.

2.2. Measurement

Detailed sample collection and laboratory analysis was reported in the NHANES Laboratory/Medical Technologists Procedures Manual (CDC, 1999–2000; CDC, 2001–2002; CDC, 2003–2004). Briefly, venous blood samples were collected and shipped weekly at −20 °C. PCBs and OC pesticides were all measured as individual chemicals by high-resolution gas chromatography/high-resolution mass spectrometry using isotope dilution for quantification. We selected 11 PCBs (PCB074, PCB099, PCB118, PCB126, PCB146, PCB153, PCB156, PCB169, PCB170, PCB180, and PCB187) and 5 OC pesticides (p,p'-DDE, trans-nonachlor, oxychlordane, heptachlor epoxide, and β-hexachlorocyclohexane) for which at least 80% of study subjects had concentrations more than the limit of detection. Fat mass was measured by dual X-ray absorptiometry (DEXA) using Hologic QDR 4500A fan-beam densitometers (Hologic, Bedford, MA, USA).

2.3. Mortality follow-up

Probabilistic matching was used to link NHANES participants with the National Death Index to ascertain vital status. Matching was based on 12 identifiers for each participant (eg, Social Security number, sex, and date of birth). The cause of death was determined using the underlying cause listed on death certificates, and was coded using the International Classification of Diseases, 10th Revision (ICD-10). Cause-specific mortality was ascertained for cardiovascular disease (codes: I00-I78), and cancer (codes: C00-C97). Persons who survived the entire follow-up period were censored on December 31, 2006. Follow-up time for each person was calculated as the difference between the NHANES examination date and the last known date alive or censored. More detailed information on the matching process and calibration study can be found elsewhere (CDC, 2014).

2.4. Statistical analysis

First, we checked if there were associations between serum concentrations of each of 11 PCBs and 5 OC pesticides (tertiles) and total, CVD, and cancer mortality using Cox proportional hazard models with linear continuous POP terms. Tertile cutpoints of individual POPs were presented in Supplementary Table 1. In addition to serum concentrations of each compound, we used summary measures of PCBs and of OC pesticides, again assessing *p*-values for continuous trends in proportion al hazards models. The summary measurements were estimated by summing the rank orders of the individual compounds belonging to PCBs or OC pesticides from rank 1 to 635 (PCBs) or 675 (OC pesticides). Concentrations lower than the LOD were assigned rank 1, and the remaining subjects were ranked according to increasing concentration. The ranks for individual compounds were summed, and the summed values were categorized into tertile groups. We did not use summary measurements formed by adding the absolute concentration of each compound because they were strongly influenced only by several compounds with high concentrations.

Second, we evaluated if there were statistically significant interactions of PCBs or OC pesticides (tertiles) with fat mass (quartiles) in predicting total, CVD, and cancer mortality. As most outcomes showed at least marginally statistically significant interactions with PCBs or OC pesticides, we presented results stratified by fat mass. For stratified analyses, we regrouped the quartiles of fat mass into <25th, 25th $\sim<75$th, and ≥ 75th percentile of fat mass for statistical stability of the middle category.

Adjusting covariates were age, gender, race-ethnicity, smoking status (current, ex, and never), physical activity (vigorous, moderate, and sedentary), and body mass index. Estimates of main results were calculated accounting for NHANES stratification and clustering (Korn and Graubard, 1991), adjusting for age, gender, race-ethnicity, smoking status, and physical activity instead of using sample weights; this adjustment has been regarded as a good compromise between efficiency and bias (Graubard and Korn, 1999; Korn and Graubard, 1991). As results were very similar with SAS 9.1 and SUDAAN 9.0, we present the results based on SAS 9.1.

3. Results

Among 633 elders with information on PCBs, 143 subjects (underlying causes: 50 cardiovascular, 34 cancer, 17 respiratory disease, and 42 others) died during the mean follow-up time of 4.1 years. Among 675 elders with information on OC pesticides, the numbers of all causes, CVD, and cancer deaths were 146, 56, and 32, respectively. Table 1 shows characteristics of study subjects. Among participants with information on PCBs, mean age was 77.6 years and proportions of men, white race, obesity, current smoker, and physically inactive were 52.6%, 69.5%, 23.9%, 6.5%, and 55.3%, respectively. Prevalence of physician-diagnosed heart diseases, cancer, diabetes, and hypertension were 24.5%, 23.4%, 15.6%, and 49.0%. Similar distributions were observed among 675