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Plasma polychlorinated biphenyl concentrations and immune function in postmenopausal women ☆

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ABSTRACT

Background: Polychlorinated biphenyl (PCB) exposure has been associated with non-Hodgkin lymphoma in several studies, and the immune system is a potential mediator.
Objectives: We analyzed associations of plasma PCBs with immune function measures. We hypothesized that higher plasma PCB concentrations are associated with lower immune function cross-sectionally, and that increases in PCB concentrations over a one year period are associated with decreases in immune function.
Methods: Plasma PCB concentrations and immune function [natural killer (NK) cell cytotoxicity and PHA-induced T-lymphocyte proliferation (PHA-TLP)] were measured at baseline and one year in 109 postmenopausal overweight women participating in an exercise intervention study in the Seattle, Washington (USA) area. Mixed models, with adjustment for body mass index and other potential confounders, were used to estimate associations of PCBs with immune function cross-sectionally and longitudinally.
Results: Associations of PCBs with immune function measures differed across groups of PCBs (*e.g.*, medium- and high-chlorinated and dioxin-like [mono-*ortho*-substituted]) and by the time frame for the comparison (cross-sectional *vs.* longitudinal). Higher concentrations of medium- and high-chlorinated PCBs were associated with higher PHA-TLP cross-sectionally but not longitudinally. The mean decrease in 0.5 μg/mL PHA-TLP/50.0 pmol/g-lipid increase in dioxin-like PCBs over one year was 51.6 (95% confidence interval 2.7, 100.5; $P=0.039$). There was no association between plasma PCBs and NK cytotoxicity.
Conclusions: These results do not provide strong evidence of impaired cellular immunity from PCB exposure. Larger longitudinal studies with greater variability in PCB exposures are needed to further examine temporal associations of PCBs with immune function.
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Abbreviations: CDC, Centers for Disease Control and Prevention; Con A, Concanavalin A; CV, coefficient of variation; FHCRC, Fred Hutchinson Cancer Research Center; IMEX, Immune Function and Exercise; LOD, limit of detection; LP, lymphocyte proliferation; NK, natural killer; NHL, non-Hodgkin lymphoma; PBMCs, peripheral blood mononuclear cells; PCB, polychlorinated biphenyl; PHA, phytohemagglutinin; PHA-TLP, PHA-induced T-lymphocyte proliferation; UW, University of Washington

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1. Introduction

Polychlorinated biphenyls (PCBs) continue to be found in human tissues despite the introduction of manufacturing bans in the United States and other countries decades ago (CDC, 2009; Dallaire et al., 2002). Organochlorine pollutants, which include PCBs and organochlorine pesticides/pesticide metabolites, are lipid soluble compounds that do not break down easily in the environment or in humans. The main route of human exposure to organochlorines is through the diet, and these compounds concentrate as they move up the food chain. Circulating blood organochlorine concentrations are regulated by homeostasis between adipose tissue storage and blood lipid levels (Brown and Lawton, 1984).

Exposure to organochlorines has been implicated as a risk factor for non-Hodgkin lymphoma (NHL) (Ballschmiter and Zell, 1980; Hardell et al., 1996; Rothman et al., 1997; Colt et al., 2005, 2009; DeRoos et al., 2005; Engel et al., 2007; Spinelli et al., 2007; Bertrand et al., 2010; Ng et al., 2010), and immune suppression is among the proposed mechanisms for this increased risk. An association between organochlorines and immunosuppressive effects, including decreases in natural killer (NK) cell cytotoxicity and T-lymphocyte proliferation (TLP), has been observed *in vitro* (Daniel et al., 2001; Hammond et al., 2005), in animal studies (Exon et al., 1985; Talcott et al., 1985; Ross et al., 1996; Beckman et al., 2003; Beineke et al., 2005; Mori et al., 2006; Sormo et al., 2009), and in human studies (Lü and Wu 1985; Svensson et al., 1994; Leijs et al., 2009), although associations are not entirely consistent. Toxic effects and potential mechanisms of action of PCBs and related organochlorine pesticides/pesticide by-products appear to vary by structural characteristics. PCB congeners with mono-*ortho*-substituted (dioxin-like) structures exert toxicity through binding to the aryl hydrocarbon receptor, while different mechanisms may exist for other organochlorines (CDC, 2009; Duffy and Zelikoff, 2006; Lyche et al., 2006; Ng et al., 2010). Several studies of NHL found the strongest associations with PCB 180, a moderately chlorinated PCB, compared to other PCB congeners (Bertrand et al., 2010; DeRoos et al., 2005; Spinelli et al., 2007), indicating possible differences in biologic effects between individual, non-dioxin-like congeners that may vary by degree of chlorination. Few studies have examined the association of organochlorines with immune effects in humans (Lü and Wu, 1985; Svensson et al., 1994; Leijs et al., 2009), and no study that we are aware of has reported on the effect of within-person changes in organochlorines with within-person changes in immune function.

We investigated the association between plasma PCB concentrations and immune function in a study of postmenopausal, overweight and obese women living in the Seattle, Washington metropolitan area. We focused on three summed measures of plasma PCBs: dioxin-like (mono-ortho substituted), high-chlorinated (8 or more chlorines), and medium-chlorinated (5–8 chlorines) PCBs (CDC, 2009; Ng et al., 2010). Cellular immune function was evaluated by TLP (lower levels are believed to reflect less effective immune responses) and NK cell cytotoxicity (lower levels may predict risk of future adverse health events) (Levy et al., 1991; Mizutani et al., 1996; Vedhara et al., 1999; Imai et al., 2000; Albers et al., 2005). We hypothesized that (1) higher plasma PCB concentrations are associated with lower baseline immune function cross-sectionally; and (2) increases in PCB concentrations over time are associated with decreases in immune parameters. We based our hypotheses that higher-chlorinated and dioxin-like PCBs, in particular, have immune effects on existing studies of the relationship between PCBs and immune measures (Daniel et al., 2001; Leijs et al., 2009) and between PCBs and NHL (Bertrand et al., 2010; DeRoos et al., 2005; Spinelli et al., 2007).

2. Materials and Methods

2.1. Study population

The study included participants in a previously conducted exercise intervention trial and ancillary study of immune function in sedentary and overweight/obese postmenopausal women. The Physical Activity for Total Health study, conducted at the Fred Hutchinson Cancer Research Center (FHCRC), was a randomized controlled trial comparing the effects of a one year moderate-intensity aerobic exercise intervention, with goal of 225 min/week in a combined facility and home program, *vs*. a stretching control program on sex hormone concentrations (as biomarkers of breast cancer risk) (McTiernan et al., 1999). As previously described, participants were selected to maximize the possible effects of exercise on endogenous sex hormones and to avoid other factors known to affect sex hormones (Irwin et al., 2003). Women were enrolled into the Physical Activity for Total Health study between 1998 and 2000. One hundred and seventy three women from the Seattle, Washington area participated in the study and were evaluated at baseline, three months, and one year. The ancillary study of Immune Function and Exercise (IMEX) was conducted among 115 participants of the Physical Activity for Total Health study that met additional IMEX selection criteria (Shade et al., 2004).

The present study included the IMEX subset of the Physical Activity for Total Health study participants. We excluded participants at baseline or one year who were missing all primary outcome or primary exposure values or total lipid measures necessary to compute lipid-adjusted plasma organochlorine concentrations (Phillips et al., 1989; Schisterman et al., 2005). Six of the 115 IMEX participants were missing these values at baseline, and 17 participants (including three that were lost to follow-up) were missing these values at one year. A sensitivity analysis excluding observations with any missing covariate data in any of the analyses yielded similar results.

2.2. Questionnaires

Information on demographics and smoking history was collected *via* self-administered questionnaire. Questionnaire data also included body weight history, medical history, health habits, medication use, and dietary intake over the past three months. Dietary intake and alcohol consumption over the past three months were assessed using a 120-item food frequency questionnaire designed and validated at the FHCRC (Patterson et al., 1999).

2.3. Body composition measures

Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, using a balance-beam scale and a stadiometer at corresponding clinic visits. Both measurements were taken in duplicate and averaged. Body mass index (BMI) was calculated as (weight[kg]/height[m]^2).

2.4. Blood draw

Blood samples were collected for previously described studies conducted in the same population as our study population (Shade et al., 2004; Troen et al., 2006; Campbell et al., 2008). Blood draws took place at the UW Department of Laboratory Medicine. Fasting blood samples were taken between 7:30 and 8:30 AM. Samples were processed within one hour of collection.

2.5. Immune function measures

Assays of cellular immunity were conducted by the UW Department of Laboratory Medicine on blood samples from the baseline and one year IMEX visits. NK cytotoxicity was measured in fresh NK cells using a flow-cytometric assay. NK cells were isolated from peripheral blood mononuclear cells (PBMCs) by the Ficoll-Hypaque separation. Cells were washed and diluted to a mononuclear cell concentration of 7.7×10^6 cells/mL. K562 target cells were washed in the log phase of growth twice and incubated with label 3,3′-dioctadecyloxacarbocyanine perchlorate (DiO; Live/Dead cytotoxicity kit no. L7010; Molecular Probes, Eugene, OR). Cells were incubated, washed, and re-suspended to a concentration of 1×10^6 cells/mL and then filtered through a 35-μm strainer. Culture-suspended NK cells were diluted to four effector-to-target cell (E:T) ratios of 50:1, 25:1, 12.5:1, and 6.25:1, pelleted, and incubated. Propidium iodide was added to a final concentration of 0.03 mg/mL, and cells were transferred to a polypropylene tube for flow cytometric analysis to identify dead cells. The percentage of dead target cells among a total DiO-identified target cells was used as the measure of NK cytotoxicity.

T-lymphocyte proliferation was assessed using cryopreserved PBMCs with ^{3}H-thymidine incorporation in response to the mitogen phytohemagglutinin (PHA), as previously described (Boynton et al., 2007; Campbell et al., 2008). Cells were prepared by the Ficoll-Hypaque separation and frozen in 30% fetal calf serum, 60% RPMI medium, and 10% dimethyl sulfoxide (Gibco, Gaithersburg, MD). For the

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