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Organochlorine concentrations in breast milk and prevalence of allergic disorders in Japanese women

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ABSTRACT

Persistent organic pollutants have been shown to have immunomodulating effects in humans. However, epidemiological evidence regarding the relationships between organochlorine compound exposure and allergic disorders coming from studies of children has been limited and inconsistent. The current cross-sectional study examined the associations between the concentrations of β -hexachlorocyclohexane (HCH), hexachlorobenzene (HCB), *p,p'*-dichlorodiphenyldichloroethylene (DDE), and *trans*-nonachlordane in breast milk and the prevalence of allergic disorders in 124 adult Japanese women. The definition of wheeze and asthma was based on criteria from the European Community Respiratory Health Survey whereas that of eczema and rhinoconjunctivitis was based on criteria from the International Study of Asthma and Allergies in Childhood. Adjustment was made for age, smoking, family history of allergic disorders, and education. The prevalence values of wheeze, asthma, eczema, and rhinoconjunctivitis in the past 12 months were 9.7%, 4.8%, 13.7%, and 29.8%, respectively. The median concentrations of β -HCH, HCB, *p,p'*-DDE, and *trans*-nonachlordane in breast milk were 28.3, 7.0, 71.6, and 23.9 ng g⁻¹ lipid, respectively (range, 4.5–253, 2.1–14.5, 7.5–362, and 1.8–130 ng g⁻¹ lipid, respectively). When the exposures were treated as continuous variables, no significant associations were found between concentrations of HCB, β -HCH, *p,p'*-DDE, or *trans*-nonachlordane and the prevalence of wheeze, asthma, eczema, or rhinoconjunctivitis. Our results suggest that concentrations of β -HCH, HCB, *p,p'*-DDE, and *trans*-nonachlordane in breast milk are not evidently associated with the prevalence of wheeze, asthma, eczema, or rhinoconjunctivitis in young female Japanese adults.

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1. Introduction

Persistent organic pollutants (POPs) have been shown to have immunomodulating effects. Of 188 German adults who had been exposed for more than 6 months to pentachlorophenol-containing pesticides, 65% exhibited impaired lymphocyte stimulation (Daniel et al., 1995). A significant inverse correlation was found between blood levels of hexachlorobenzene (HCB) and plasma INF- γ levels in 141 German individuals who had been occupationally exposed primarily to polychlorinated biphenyls (PCBs) for more than 6 months (Daniel et al., 2001). Plasma levels of 4,4'-dichlorodiphenyltrichloroethane (DDT) and 4,4'-dichlorodiphenyldichloroethylene (DDE) were positively associated with plasma IL-4 levels in 49 farmers or farmhands in the former German Demo-

cratic Republic (Daniel et al., 2002). Among 137 African-American male farmers, plasma *p,p'*-DDE levels were significantly inversely related to serum IgG levels (Cooper et al., 2004). Another US study showed that individuals with higher plasma DDE levels had lower mitogen-induced lymphoproliferative activity and increased total lymphocytes and IgA levels (Vine et al., 2001). A cross-sectional study of German children showed increased IgE levels and a higher IgE count on basophils at higher DDE levels in blood (Karmaus et al., 2005). The immunomodulating effects of perinatal exposure to POPs have also been observed (Reichrtová et al., 1999; Weisglas-Kuperus et al., 2000; Bilrha et al., 2003; Noakes et al., 2006; Glynn et al., 2008).

Epidemiological evidence regarding the relationships between exposure to POPs and allergic disorders has been limited and inconsistent (Weisglas-Kuperus et al., 2000, 2004; Karmaus et al., 2001, 2003; ten Tusscher et al., 2003; Sunyer et al., 2005, 2006). To our knowledge, no studies of such relationships have been conducted on adults or in non-Western countries. In the current

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study, we examined the associations between the concentrations of β -hexachlorocyclohexane (HCH), HCB, *p,p'*-DDE, and *trans*-nonachlordane in breast milk and the prevalence of allergic disorders among Japanese women using data from a part of the Kyushu Okinawa Maternal and Child Health Study (KOMCHS).

2. Subjects and methods

2.1. Study subjects

The KOMCHS is an ongoing prospective prebirth cohort study that investigates risk and preventive factors for maternal and child health problems such as allergic disorders. The KOMCHS requested that 131 obstetric hospitals in Fukuoka Prefecture, the largest prefecture on Kyushu Island in southern Japan with a total population of approximately 5.04 million, provide all pregnant women, as far as was possible, with a set of leaflets explaining the KOMCHS, an application form to participate in the study, and a self-addressed and stamped return envelope during the period from April 2007 to March 2008. From May 2007 to March 2008, the KOMCHS also requested that 40 obstetric hospitals in Okinawa Prefecture, an island in the southernmost area in Japan with a total population of almost 1.37 million, provide pregnant women with a similar such set. In addition, to increase the sample size, from August 2007 to March 2008, pregnant women living in six prefectures on Kyushu Island other than Fukuoka Prefecture with a total population of approximately 8.22 million were provided with a similar such set at 252 obstetric hospitals. Pregnant women who intended to participate in the KOMCHS returned the application form to the data management center. When all responses were tallied, a total of 1757 pregnant women between the 5th and 39th week of pregnancy had given their fully informed written consent to participate and had completed the baseline survey. Around 1 month after delivery, we asked study subjects to provide breast milk based on the order in which they had given birth, so the mothers of the subgroup of 124 participants took samples of their breast milk while nursing their infants. Milk sampling could not be continued due to lack of financial resources, leaving data on only those 124 women available for the current analysis. The ethics committee of the Faculty of Medicine, Fukuoka University approved the KOMCHS.

2.2. Questionnaire

In the baseline survey, each participant filled out a self-administered questionnaire which they mailed to the data management center. Research technicians completed missing or illogical data by telephone interview.

The self-administered questionnaire included questions on wheeze and asthma based on the European Community Respiratory Health Survey (European Community Respiratory Health Survey, 1996) and those on eczema and rhinoconjunctivitis based on the International Study of Asthma and Allergies in Childhood (ISAAC) (Strachan et al., 1997; Williams et al., 1999). The definition of wheeze was determined by a positive response to the question, 'Have you had wheezing or whistling in your chest at any time in the last 12 months?' The presence of asthma was defined as the existence of either of two conditions: an asthma attack during the last 12 months or current use of asthma medication. Affirmative answers to the following three questions were required to indicate the presence of eczema: 'Have you ever had an itchy rash which was coming and going for at least 6 months?', 'Have you had this itchy rash at any time in the last 12 months?' and 'Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under

the buttocks, or around the neck, ears, or eyes?' Rhinoconjunctivitis was defined as present based on a positive response to the following two questions: 'In the last 12 months, have you had a problem with sneezing or a runny or blocked nose when you did not have a cold or flu?' and 'In the last 12 months, has this nose problem been accompanied by itchy-watery eyes?' The questionnaire also elicited information on age, smoking habits, family history of asthma, atopic eczema, allergic rhinitis, and education. A family history of allergic disorders was considered to be present if one or more parents or siblings of the study subjects had been diagnosed by a physician as having asthma, atopic eczema, and/or allergic rhinitis (including Japanese cedar pollinosis).

2.3. Organochlorine compound analysis

About 100 mL of human breast milk was collected in a glass bottle using a manual breast pump and stored at -20°C until analysis. Samples were analyzed at the Institute of Environmental Ecology, IDEA Consultants, Inc., Shizuoka, Japan. Approximately 5 g of breast milk was weighed and spiked with a known amount of $^{13}\text{C}_6$ -labeled β -HCH, $^{13}\text{C}_6$ -labeled HCB, $^{13}\text{C}_{12}$ -labeled *p,p'*-DDE, and $^{13}\text{C}_{10}$ -labeled *trans*-nonachlordane. The liquid-liquid extraction was performed using 1:1 ethanol:hexane. After the hexane layer was separated, the residue was extracted with hexane. The sample extract was defatted with acetonitrile saturated with hexane. The purified extract was placed on a florisil cartridge column and analyzed by gas chromatography-mass spectroscopy (GC/MS) (HP6890, HP5973, Agilent technologies Inc., CA, USA) equipped with a 30 m $\times$ 0.25 mm DB-1 ms (Agilent technologies Inc.). The detection limit was 0.08 ng g^{-1} fresh weight for β -HCH, 0.04 ng g^{-1} fresh weight for HCB, 0.3 ng g^{-1} fresh weight for *p,p'*-DDE, and 0.05 ng g^{-1} fresh weight for *trans*-nonachlordane. All exposures are expressed on a lipid basis. It was discovered that all women exhibited detectable concentrations of the organochlorine compounds under investigation in their breast milk.

2.4. Statistical analysis

Age, smoking, family history of allergic disorders, and education were *a priori* selected as potential confounding factors. Age and education were significantly inversely associated with the prevalence of any of the allergic disorders under study while there were significant positive relationships between smoking and family history of allergic disorders and any of the outcomes in our entire population who participated in the baseline survey of the KOMCHS. Smoking was classified into two categories (never and ever) and education into two (less than 15 years and 15 or more years). Age was used as a continuous variable.

We assessed whether or not concentrations of β -HCH, HCB, *p,p'*-DDE, and *trans*-nonachlordane in breast milk were linearly related to the log-odds of the binary outcomes under study in a restricted cubic spline model. Estimations of crude odds ratios (ORs) and their 95% confidence intervals (CIs) of allergic disorders in relation to organochlorine compound concentrations in breast milk were made by means of logistic regression analysis. Multiple logistic regression analysis was used to adjust for potential confounding factors. All computations were performed using STATA/SE software version 11.0 (StataCorp, College Station, TX, USA).

3. Results

The mean age of the participants at baseline was 31.3 years (Table 1). The prevalence values of wheeze, asthma, eczema, and rhinoconjunctivitis in the past 12 months were 9.7%, 4.8%, 13.7%, and 29.8%, respectively, among 124 women. The

Table 1

Distribution of selected characteristics of the 124 female participants.

Variable	n (%) or mean (SD)
Age (years)	31.3 (3.5)
Smoking (%)	34 (27.4)
Family history of allergic disorders ^a (%)	65 (52.4)
Fifteen years or more of education (%)	57 (46.0)
Wheeze (%)	12 (9.7)
Asthma (%)	6 (4.8)
Eczema (%)	17 (13.7)
Rhinoconjunctivitis (%)	37 (29.8)

^a Asthma, atopic eczema, or allergic rhinitis.**Table 2**Organochlorine concentrations in breast milk (ng g⁻¹ lipid) in 124 women.

	Minimum	p25	p50	p75	Maximum
β-HCH	4.5	18.3	28.3	45.3	253
HCB	2.1	5.2	7.0	9.1	14.5
<i>p,p'</i> -DDE	7.5	47.5	71.6	97.0	362
<i>trans</i> -Nonachlordane	1.8	15.6	23.9	39.2	130

HCH – hexachlorocyclohexane; HCB – hexachlorobenzene; DDE – dichlorodiphenyldichloroethylene.

distribution of organochlorine compounds was skewed toward high values (Table 2). The median concentrations of β-HCH, HCB, *p,p'*-DDE, and *trans*-nonachlordane in breast milk were 28.3, 7.0, 71.6, and 23.9 ng g⁻¹ lipid, respectively (range, 4.5–253, 2.1–14.5, 7.5–362, and 1.8–130 ng g⁻¹ lipid, respectively). The coefficients of variation were 88.5% for β-HCH, 38.0% for HCB, 69.4% for *p,p'*-DDE, and 76.5% for *trans*-nonachlordane. There were significant positive correlations among the organochlorine compound concentrations examined: the Pearson's correlation coefficients ranged from 0.35 (β-HCH and *trans*-nonachlordane) to 0.71 (β-HCH and *p,p'*-DDE).

There were linear relationships between concentrations of β-HCH, HCB, *p,p'*-DDE, and *trans*-nonachlordane and the log-odds of wheeze, asthma, eczema, and rhinoconjunctivitis ($P = 0.26$ [*p,p'*-DDE and rhinoconjunctivitis] to 0.99 [HCB and wheeze]). Therefore, the exposures were treated as continuous variables in the following logistic regression analysis.

Table 3 provides crude and adjusted ORs and their 95% CIs for the prevalence of wheeze and asthma according to organochlorine compound concentrations in breast milk. There were no significant relationships between concentrations of β-HCH, HCB, *p,p'*-DDE, or *trans*-nonachlordane and the prevalence of wheeze. Concentrations of β-HCH, HCB, *p,p'*-DDE, and *trans*-nonachlordane were not related to the prevalence of asthma.

Results for eczema and rhinoconjunctivitis are given in Table 4. No significant associations were found between concentrations of β-HCH, HCB, *p,p'*-DDE, or *trans*-nonachlordane and the prevalence of eczema or rhinoconjunctivitis.

Table 3Odds ratios and 95% confidence intervals of wheeze and asthma in relation to each increase in 1 ng g⁻¹ lipid of organochlorine concentrations in breast milk in 124 women.

Variable	Wheeze		Asthma	
	Odds ratio (95% confidence interval)		Odds ratio (95% confidence interval)	
	Crude	Adjusted ^a	Crude	Adjusted ^a
β-HCH	0.98 (0.96–1.01)	0.98 (0.95–1.01)	1.00 (0.97–1.02)	1.00 (0.97–1.02)
HCB	0.92 (0.74–1.15)	0.94 (0.74–1.18)	1.01 (0.76–1.36)	1.01 (0.76–1.36)
<i>p,p'</i> -DDE	1.00 (0.98–1.01)	1.00 (0.98–1.01)	1.00 (0.98–1.01)	1.00 (0.98–1.01)
<i>trans</i> -Nonachlordane	1.01 (0.99–1.03)	1.01 (0.99–1.03)	1.01 (0.99–1.04)	1.01 (0.98–1.04)

HCH – hexachlorocyclohexane; HCB – hexachlorobenzene; DDE – dichlorodiphenyldichloroethylene.

^a Adjusted for age, smoking, family history of allergic disorders, and education.

4. Discussion

The current study showed that concentrations of β-HCH, HCB, *p,p'*-DDE, and *trans*-nonachlordane in breast milk were not significantly associated with the prevalence of any of the allergic disorders under study after adjustment for confounders. In a cohort study in Spain, higher concentrations of DDE in cord serum were significantly related to an increased risk of wheeze at 4 years of age and asthma at 6.5 years of age whereas concentrations of DDE in blood measured at 4 years were not associated with those outcomes; neither did HCB concentrations in cord serum show a significant association with wheezing (Sunyer et al., 2005, 2006). A cross-sectional study of German children aged 7–10 years showed that higher DDE blood concentrations were significantly associated with a higher prevalence of ever having asthma based on the ISAAC and elevated total serum IgE levels (Karmaus et al., 2001). In another cross-sectional study of German children aged 7–8 years, DDE blood concentrations were not related to the prevalence of ever having asthma based on the ISAAC and physician-diagnosed asthma, atopic eczema, and hay fever, although significant inverse associations between breastfeeding duration and the prevalence of ever having asthma and physician-diagnosed asthma were observed among children with DDE blood concentrations below the median of 0.29 μg L⁻¹, but not among those with DDE concentrations of 0.29 μg L⁻¹ and higher (Karmaus et al., 2003). The current results are in partial agreement with those observations regarding the null associations; however, because different mechanisms might be involved in the effects of perinatal exposure to POPs and such exposure during adulthood on allergic disorders, the interpretation of the comparison between our results and previous findings should be made with caution.

Among 27 healthy 8-year-old Dutch children, perinatal dioxin exposure through mother's breast milk was significantly inversely related to a history of allergy, which was defined by hay fever and allergic reactions to animals and to dust, but not asthma or eczema (ten Tusscher et al., 2003). Another study of 175 42-month-old Dutch children found that current levels of PCBs in plasma were significantly associated with a lower prevalence of allergic reactions, but not eczema, asthma or bronchitis (Weisglas-Kuperus et al., 2000). However, in a follow-up study at the age of 7 years, no association was observed between lactational PCB exposure and a history of allergic reactions although prenatal PCB exposure was significantly inversely related to one or more attacks of shortness of breath with wheeze (Weisglas-Kuperus et al., 2004). The non-significant inverse association between HCB exposure and eczema in the current study might be explained by immunological suppression via HCB. Alternatively, given a positive association between HCB exposure and marine origin *n*-3 polyunsaturated fatty acid intake, the observed non-significant inverse relationship might be confounded by such intake. In our previous study, a significant inverse association was found between docosahexaenoic acid intake and the prevalence of atopic eczema in Japanese pregnant women (Miyake et al., 2008).

Table 4
Odds ratios and 95% confidence intervals of eczema and rhinoconjunctivitis in relation to each increase in 1 ng g⁻¹ lipid of organochlorine concentrations in breast milk in 124 women.

Variable	Eczema		Rhinoconjunctivitis	
	Odds ratio (95% confidence interval)		Odds ratio (95% confidence interval)	
	Crude	Adjusted ^a	Crude	Adjusted ^a
β-HCH	0.98 (0.96–1.01)	0.98 (0.96–1.01)	1.00 (0.98–1.01)	1.00 (0.98–1.01)
HCB	0.84 (0.69–1.03)	0.85 (0.69–1.04)	0.97 (0.84–1.11)	0.95 (0.82–1.09)
p,p'-DDE	0.99 (0.98–1.004)	0.99 (0.98–1.005)	1.00 (0.99–1.01)	1.00 (0.99–1.005)
trans-Nonachlordane	1.01 (0.99–1.03)	1.01 (0.99–1.03)	1.00 (0.98–1.01)	0.99 (0.98–1.01)

HCH – hexachlorocyclohexane; HCB – hexachlorobenzene; DDE – dichlorodiphenyldichloroethylene.

^a Adjusted for age, smoking, family history of allergic disorders, and education.

Weaknesses in the current study should be considered. Definitions of wheeze and asthma were based on the questions in the European Community Respiratory Health Survey. However, the prevalence of eczema and rhinoconjunctivitis was estimated by the questions in the ISAAC: validation tests of such questions have not been performed for young Japanese adults. The participation rate could not be calculated because the exact number of eligible pregnant women who were provided with a set of leaflets explaining the KOMCHS, an application form, and a self-addressed and stamped return envelope by the 423 collaborating obstetric hospitals was not available. Moreover, we selected a subgroup for organochlorine compound analysis due to budget constraints. The current study did not have substantial statistical power. Our subjects were likely not a representative sample of Japanese women in the general population. In fact, educational levels in the current study population were higher than in the general population. According to the 2000 population census of Japan, the proportions of women aged 30–34 years in Fukuoka Prefecture with years of education of <13, 13–14, ≥15, and unknown were 52.0%, 31.5%, 11.8%, and 4.8%, respectively (Statistics Bureau, Ministry of Public Management, Home Affairs, Posts and Telecommunications, Japan, 2002). The corresponding figures for the current study were 13.7%, 40.3%, 46.0%, and 0.0%, respectively. The present population might have had a greater awareness about health than the general population. The prevalence values of the outcomes under study in this population might represent those in the general population. A nationwide cross-sectional study of Japanese adults reported that the prevalence values of wheeze and asthma based on the European Community Respiratory Health Survey questionnaire were 9.3% and 5.3%, respectively, among young adults aged 20–44 years (Fukutomi et al., 2010). The prevalence values of wheeze, eczema, and rhinoconjunctivitis based on the ISAAC criteria were 6.7%, 14.5%, and 23.9%, respectively, among Japanese junior high school students aged 12–15 years who lived in an urban area (Miyake et al., 2003). In a study of 1540 Japanese aged 20–49 years who lived in a rural area, the prevalence of allergic rhinitis symptom was 44.2% (Sakashita et al., 2010). The nature of cross-sectional studies prevents conclusions from being drawn about causality.

To our knowledge, this is the first epidemiological study on the association of organochlorine compound exposure with allergic disorders in a non-Western population. Our results suggest that concentrations of β-HCH, HCB, p,p'-DDE, and trans-nonachlordane in breast milk are not evidently associated with the prevalence of wheeze, asthma, eczema, or rhinoconjunctivitis in young female Japanese adults. Further evidence from well-designed epidemiological studies is needed.

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