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Plasma organochlorine levels and risk of non-Hodgkin lymphoma in the Nurses' Health Study

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Abstract

Numerous studies have reported positive associations of environmental exposure to polychlorinated biphenyls (PCBs) and *p,p′*-dichlorodiphenyldichloroethylene (*p,p′*-DDE) with the risk of non-Hodgkin lymphoma (NHL). In a case-control study nested within the Nurses' Health Study, a prospective cohort of US women, we measured concentrations of PCBs and *p,p′*-DDE in blood samples from 145 women diagnosed with NHL at least six months after blood draw, and 290 age- and race-matched controls. We used conditional logistic regression to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for each quartile of exposure relative to the lowest quartile. We also evaluated these associations for major histologic subtypes of NHL. There was no consistent evidence of an association of *p,p′*-DDE, total PCBs, immunotoxic or individual PCB congeners with risk of NHL. These results do not support the hypothesis of a positive association between PCB exposure and development of NHL.

Keywords

organochlorine; polychlorinated biphenyl; PCB; DDT; non-Hodgkin lymphoma

Introduction

Polychlorinated biphenyls (PCBs) and organochlorine pesticides such as dichlorodiphenyl trichloroethane (DDT) have been the focus of several recent investigations into the etiology of NHL (1–8). It has been hypothesized that the organochlorine-NHL association may be mediated through immunotoxic mechanisms (9). Although manufacturing and new uses of PCBs and DDT were banned in the United States in the 1970s, these compounds persist in the environment and store in adipose tissue and the lipid components of blood and breast milk. Because they are resistant to metabolism and have long half-lives, measurements of these compounds in biological media represent cumulative exposures over time (10). We examined the association of blood levels of PCBs and *p,p′*-dichlorodiphenyl dichloroethane (*p,p′*-DDE),

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the primary metabolite of DDT, with risk of NHL among women in a case-control study nested in the Nurses' Health Study (NHS).

Methods

NHL cases (n=145) and two controls per case, matched on age, race, month of blood draw, and fasting status, (n=290) were identified from participants in the NHS blood cohort (11). NHL diagnoses, including chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), were identified by annual follow-up questionnaires and all cases were confirmed by review of medical records and pathology reports. Women with a diagnosis of NHL prior to or within six months of blood collection and those with a prior diagnosis of cancer (other than non-melanoma skin cancer) were excluded. Histologic subtype was determined according to the World Health Organization (WHO) classification of lymphomas (12,13).

Organochlorine analyses for 51 individual PCB congeners and *p,p′*-DDE were done at the Harvard School of Public Health Organic Chemistry Analytical Laboratory. The laboratory methods have been described in detail elsewhere (13). Plasma PCB and *p-p*-DDE concentrations were adjusted for total serum lipids calculated using the formula by Phillips et al. (14) and are reported in units of nanograms of organochlorine per gram of lipid (ng/g).

Our primary interest was in *p-p*-DDE and a priori groupings of PCB congeners based on suspected immunotoxicity (i.e., IUPAC 66, 74, 105, 118, 156, 167) (15). We also evaluated other groupings including sum of PCBs (ΣPCB) and the sum of the four most prevalent congeners (i.e., 118, 138, 153, and 180) as well as these individual PCB congeners. The difference between the means of the cases and those of their matched controls was computed using generalized estimating equations, adjusting for the matching factors. We categorized organochlorine concentrations into quartiles based on the distribution among controls. In separate models for each organochlorine or group of organochlorines, we used conditional logistic regression, stratifying on the matched case-control triplets to estimate odds ratios (OR) and 95% confidence intervals (CIs) for risk of NHL associated with each quartile of exposure relative to the lowest quartile. Tests for trend were performed using the natural log-transformed lipid-adjusted organochlorine concentrations as continuous variables.

Multivariable conditional logistic regression models including height as a continuous variable and indicator variables for region of residence (Northeast, Midwest, West, South), smoking history (never, past, current), body mass index (BMI) (tertiles based on the control distribution), and alcohol intake (≥ 1 time/day, 1–6 times/week, 1–3 times/month, rarely/never) were used to adjust simultaneously for potential confounding by these factors. Additional analyses of individual PCB congeners and congener groups were performed including *p-p*-DDE in the model. We also examined whether the associations between organochlorines and NHL were modified by known or suspected risk factors for NHL as well as region of residence, in unconditional logistic regression models. Tertiles of organochlorines rather than quartiles were used in the stratified analyses because of the decreased sample size in each stratum. Additionally, we performed polytomous logistic regression to test for heterogeneity in effect estimates for the most common NHL subtypes (i.e., diffuse large B-cell lymphoma [DLBCL], follicular lymphoma, and CLL/SLL).

Results

Cases and controls, ranged in age from 44 to 69 years old at blood draw, were 96% white, and were similar with respect to height, and BMI. Cases were more likely to reside in the South and less likely to reside in the Northeast, Midwest, or West compared to controls. Additionally, cases were slightly more likely to be current smokers than controls. The median time to

diagnosis among cases was 5.8 years. The distributions (in ng/g lipid) of PCBs and DDE were not statistically significantly different between cases and controls (ΣPCB: cases: median=621.0, IQR=252.0, max=1957.5, min=279.5; controls: median=625.0, IQR=322.2, max=3012.2, min=221.6, p=0.35; DDE: cases: median=996.2, IQR=1293.7, max=6079.4, min=7.5; controls: median=1002.3, IQR=1152.4, max=7042.1, min=54.6, p=0.26). Results from conditional logistic regression analyses of total NHL and the different organochlorine metrics are presented in Table 1. Similar analyses of NHL subtypes are presented in Table 2. There was no evidence of confounding by DDE or effect modification by lactation, current smoking status, region or follow-up period. We observed a suggestive positive linear association of ΣPCB with NHL in obese women (p for trend=0.09). However, this is based on only 20 cases.

Discussion

Previous reports (2,4,6,7,16), including pilot analyses in this cohort utilizing controls selected for a study of breast cancer (3), have found significant evidence of an association between plasma concentrations of PCBs and risk of NHL. In contrast, we observed no association of NHL or NHL subtypes with PCBs or DDE. The levels of organochlorines measured in this general population sample were low; however, they are consistent with or even higher than (7) other studies that have observed positive associations. Different laboratories and laboratory methods were used to measure PCBs in the pilot and this study; however, we observed a significant positive association between PCBs and NHL in men using the same laboratory as this study (13). In the pilot analyses, the median time to diagnosis for cases was only one year vs. 5.8 years here. It is possible that a biased case or control sample was selected by chance in one or both studies. In conclusion, there was no consistent evidence of an association of NHL with prospectively measured blood levels of PCBs or DDE in this population based study of U.S. women.

Abbreviations

NHL	non-Hodgkin lymphoma
PCB	polychlorinated biphenyl
DDT	dichlorodiphenyl trichloroethane
DDE	*p,p′*-dichlorodiphenyl dichloroethanel
PHS	Physicians' Health Study
NHS	Nurses' Health Study

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Table 1

Odds ratios & 95% confidence intervals for NHL in relation to quartile of lipid–adjusted PCB exposure.

Exposure, in fourths	Median (ng/g lipid)	Cases (n=145)	Controls (n=290)	Unadjusted OR* (95% CI)	Adjusted** OR (95% CI)	p for trend[1]
ΣPCB						
1	406.9	33	72	ref	ref	
2	547.8	41	73	1.22 (0.69–2.18)	1.25 (0.68–2.28)	
3	678.0	41	73	1.22 (0.69–2.18)	1.32 (0.71–2.43)	
4	945.4	30	72	0.91 (0.50–1.67)	1.02 (0.53–1.95)	0.76
Immunotoxic congeners†						
1	75.6	34	72	ref	ref	
2	111.5	56	73	1.62 (0.93–2.82)	1.83 (1.01–3.31)	
3	149.6	30	73	0.86 (0.48–1.57)	0.94 (0.51–1.76)	
4	228.7	25	72	0.75 (0.39–1.42)	0.89 (0.45–1.77)	0.48
Σ (118, 138, 153, 180)						
1	185.7	33	72	ref	ref	
2	257.5	36	73	1.05 (0.58–1.89)	1.04 (0.57–1.92)	
3	334.4	48	73	1.45 (0.83–2.53)	1.63 (0.90–2.95)	
4	471.7	28	72	0.84 (0.45–1.54)	0.91 (0.48–1.75)	0.63
PCB 118						
1	27.4	38	72	ref	ref	
2	42.9	49	73	1.26 (0.73–2.19)	1.39 (0.78–2.47)	
3	61.0	31	73	0.80 (0.45–1.44)	0.89 (0.48–1.64)	
4	104.7	27	72	0.69 (0.37–1.29)	0.81 (0.42–1.56)	0.42
PCB 138						
1	34.3	31	72	ref		
2	53.2	39	73	1.26 (0.71–2.22)	1.33 (0.73–2.40)	
3	75.7	48	73	1.53 (0.87–2.69)	1.61 (0.89–2.92)	
4	113.3	27	72	0.88 (0.47–1.63)	0.95 (0.49–1.83)	0.59
PCB 153						
1	64.9	37	72	ref	ref	
2	91.2	33	73	0.87 (0.49–1.54)	0.85 (0.47–1.54)	

Exposure, in fourths	Median (ng/g lipid)	Cases (n=145)	Controls (n=290)	Unadjusted OR* (95% CI)	Adjusted** OR (95% CI)	p for trend[1]
3	120.3	45	73	1.20 (0.69–2.09)	1.38 (0.76–2.51)	
4	170.0	30	72	0.81 (0.45–1.47)	0.82 (0.43–1.56)	0.55
PCB 180						
1	47.8	36	72	ref	ref	
2	63.4	33	73	0.90 (0.50–1.64)	1.02 (0.54–1.93)	
3	80.5	44	73	1.23 (0.69–2.19)	1.24 (0.66–2.31)	
4	109.4	32	72	0.89 (0.49–1.63)	1.03 (0.52–2.02)	0.82
p,p'-DDE						
1	343.6	30	72	ref	ref	
2	779.6	43	73	1.38 (0.79–2.43)	1.41 (0.76–2.60)	
3	1327.0	27	73	0.86 (0.45–1.63)	0.77 (0.39–1.52)	
4	2325.2	45	72	1.52 (0.84–2.73)	1.56 (0.82–2.97)	0.33

*Conditional logistic regression adjusted for matching factors (race (white/non–white), age at blood draw, year & month of blood draw, fasting status at blood draw)

**Multivariate conditional logistic regression further adjusted for region (Northeast, Midwest, West, South), BMI (<25, 25–29.9, 30+), current smoking status (never, past, current), parity/breastfeeding (nulliparous, parous & no breastfeeding, parous & some breastfeeding), & height (missing indicator method for BMI, parity).</p>

[1]Test for trend modeled natural log of lipid–adjusted organochlorine as continuous variable.

†The immunotoxic congeners include PCBs 66, 74, 105, 118, 156, and 167.

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Table 2

Odds ratios & 95% confidence intervals for NHL subtypes in relation to tertile of lipid–adjusted organochlorine exposure.

		DLBCL		Follicular lymphoma		CLL/SLL		p-difference[1]
Exposure, in thirds	**controls**	**cases**	**OR* (95% CI)**	**cases**	**OR* (95% CI)**	**cases**	**OR* (95% CI)**	
Σ PCB								
1	96	12	ref	8	ref	11	ref	
2	97	16	1.29 (0.57, 2.92)	11	1.40 (0.53, 3.69)	9	0.85 (0.33, 2.20)	0.71
3	97	7	0.53 (0.19, 1.42)	9	1.22 (0.44, 3.38)	5	0.51 (0.17–1.57)	0.38
Immunotoxic congeners†								
1	96	12	ref	9	ref	11	ref	
2	97	14	1.16 (0.51, 2.68)	10	1.11 (0.42, 2.88)	10	0.98 (0.39, 2.47)	0.96
3	97	9	0.67 (0.27, 1.71)	9	1.04 (0.39, 2.80)	4	0.42 (0.13, 1.40)	0.50
Σ (118, 138, 153, 180)								
1	96	12	ref	7	ref	12	ref	
2	97	16	1.28 (0.57, 2.87)	13	1.87 (0.71, 4.94)	7	0.62 (0.23, 1.66)	0.25
3	97	7	0.53 (0.20, 1.42)	8	1.22 (0.42, 3.55)	6	0.56 (0.20, 1.58)	0.44
PCB 118								
1	96	11	ref	8	ref	14	ref	
2	97	17	1.47 (0.65, 3.35)	11	1.42 (0.54–3.73)	6	0.47 (0.17, 1.28)	0.15
3	97	7	0.55 (0.20, 1.53)	9	1.19 (0.43, 3.28)	5	0.42 (0.14, 1.23)	0.32
PCB 138								
1	96	11	ref	8	ref	12	ref	
2	97	13	1.16 (0.49, 2.74)	10	1.21 (0.46, 3.22)	7	0.60 (0.22, 1.60)	0.49
3	97	11	0.93 (0.38, 2.28)	10	1.29 (0.49, 3.45)	6	0.55 (0.20, 1.54)	0.46
PCB 153								
1	96	13	ref	8	ref	11	ref	
2	97	15	1.09 (0.49, 2.44)	11	1.37 (0.52, 3.59)	8	0.78 (0.30, 2.05)	0.69
3	97	7	0.48 (0.18, 1.28)	9	1.21 (0.44, 3.32)	6	0.62 (0.22, 1.78)	0.39
PCB 180								
1	96	13	ref	11	ref	11	ref	
2	97	9	0.64 (0.26, 1.60)	7	0.67 (0.25, 1.84)	8	0.80 (0.30, 2.11)	0.94

		DLBCL		Follicular lymphoma		CLL/SLL		p-difference[1]
Exposure, in thirds	**controls**	**cases**	**OR* (95% CI)**	**cases**	**OR* (95% CI)**	**cases**	**OR* (95% CI)**	
3	97	13	0.95 (0.40, 2.21)	10	1.00 (0.39, 2.56)	6	0.58 (0.20, 1.70)	0.70
p,p'-DDE								
1	96	10	ref	7	ref	10	ref	
2	97	11	1.06 (0.43, 2.65)	9	1.28 (0.46, 3.63)	8	0.87 (0.32, 2.32)	0.85
3	97	14	1.34 (0.55, 3.24)	12	1.76 (0.65, 4.77)	7	0.78 (0.28, 2.21)	0.50

*Polytomous logistic regression models controlling for age at blood draw, year & month of blood draw, and fasting status at blood draw

[1]Test for heterogeneity for DLBCL vs. follicular vs. CLL only

†The immunotoxic congeners include PCBs 66, 74, 105, 118, 156, and 167.