Null Results in Brief

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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 (PCB) 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 U.S. women, we measured concentrations of PCBs and *p,p′*-DDE in blood samples from 145 women diagnosed with NHL at least 6 months after blood draw and 290 age- and race-matched controls. We used conditional logistic regression to estimate the odds ratios and 95% confidence intervals 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. *Cancer Epidemiol Biomarkers Prev; 19(5); 1381–4. ©2010 AACR.*

Introduction

Polychlorinated biphenyls (PCB) and organochlorine pesticides such as dichlorodiphenyl trichloroethane have been the focus of several recent investigations into the etiology of non–Hodgkin lymphoma (NHL; refs. 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 dichlorodiphenyl trichloroethane 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), the primary metabolite of dichlorodiphenyl trichloroethane, with risk of NHL among women in a case-control study nested in the Nurses' Health Study.

Materials and 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 Nurses' Health Study blood cohort (11). NHL diagnoses, including chronic lymphocytic leukemia/small lymphocytic lymphoma, were identified by annual follow-up questionnaires and all cases were confirmed by a review of medical records and pathology reports. Women with a diagnosis of NHL before or within 6 months of blood collection and those with a prior diagnosis of cancer (other than nonmelanoma skin cancer) were excluded. Histologic subtype was determined according to the 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 (that is, International Union of Pure and Applied Chemistry 66, 74, 105, 118, 156, and 167; ref. 15). We also evaluated other groupings including the sum of PCBs (ΣPCB) and the sum of the four most prevalent congeners (that is, 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

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Table 1. ORs and 95% CIs 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_{trend}‡
∑PCB						
1	406.9	33	72	Reference	Reference	
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	Reference	Reference	
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
∑ (118, 138, 153, 180)						
1	185.7	33	72	Reference	Reference	
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	Reference	Reference	
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	Reference		
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	Reference	Reference	
2	91.2	33	73	0.87 (0.49-1.54)	0.85 (0.47-1.54)	
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	Reference	Reference	
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	Reference	Reference	
2	779.6	43	73	1.38 (0.79-2.43)	1.41 (0.76-2.60)	
3	1,327.0	27	73	0.86 (0.45-1.63)	0.77 (0.39-1.52)	
4	2,325.2	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 and 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 and no breastfeeding, parous and some breastfeeding), and height (missing indicator method for BMI, parity).

‡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.

case-control triplets to estimate odds ratios (OR) and 95% confidence intervals (CI) for risk of NHL associated with each quartile of exposure relative to the lowest quartile. Tests for trend were done 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, and South), smoking history (never, past, and current), body mass index (BMI; tertiles based on the control distribution), and alcohol intake (≥1 time/d, 1-6 times/wk, 1-3 times/mo, rarely/never) were used to adjust simultaneously for potential confounding by these factors. Additional analyses of individual PCB congeners and congener groups were done 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 (that is, diffuse large B-cell lymphoma, follicular lymphoma, and chronic lymphocytic leukemia/small lymphocytic lymphoma).

Table 2. ORs and 95% CIs for NHL subtypes in relation to tertile of lipid-adjusted organochlorine exposure

Exposure, in thirds	Controls	DLBCL		Follicular lymphoma		CLL/SLL		$P_{difference}$*
		Cases	OR† (95% CI)	Cases	OR† (95% CI)	Cases	OR† (95% CI)	
∑ PCB								
1	96	12	Reference	8	Reference	11	Reference	
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	Reference	9	Reference	11	Reference	
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
∑ (118, 138, 153, 180)								
1	96	12	Reference	7	Reference	12	Reference	
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	Reference	8	Reference	14	Reference	
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	Reference	8	Reference	12	Reference	
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	Reference	8	Reference	11	Reference	
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	Reference	11	Reference	11	Reference	
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
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	Reference	7	Reference	10	Reference	
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

Abbreviations: DLBCL, diffuse large B-cell lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma.
*Test for heterogeneity for diffuse large B-cell lymphoma versus follicular versus chronic lymphocytic leukemia only.
†Polytomous logistic regression models controlling for age at blood draw, year and month of blood draw, and fasting status at blood draw.
‡The immunotoxic congeners include PCBs 66, 74, 105, 118, 156, and 167.

Results

Cases and controls, ranged in age from 44 to 69 years 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 with 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; interquartile range (IQR), 252.0; max, 1,957.5; min, 279.5; ΣPCB controls: median, 625.0; IQR, 322.2; max, 3,012.2; min, 221.6; $P = 0.35$; DDE cases: median, 996.2; IQR, 1,293.7; max, 6,079.4; min, 7.5; DDE controls: median, 1,002.3; IQR, 1,152.4; max, 7,042.1; 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 ($P_{trend} = 0.09$). However, this is based on only 20 cases.

Discussion

Previous reports (2, 4, 6, 7, 16), including pilot analyses in this cohort using 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 1 year versus 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.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Cocco P, Brennan P, Ibba A, et al. Plasma polychlorobiphenyl and organochlorine pesticide level and risk of major lymphoma subtypes. Occup Environ Med 2008;65:132–40.
2. De Roos AJ, Hartge P, Lubin JH, et al. Persistent organochlorine chemicals in plasma and risk of non-Hodgkin's lymphoma. Cancer Res 2005;65:11214–26.
3. Engel LS, Laden F, Andersen A, et al. Polychlorinated biphenyl levels in peripheral blood and non-Hodgkin's lymphoma: a report from three cohorts. Cancer Res 2007;67:5545–52.
4. Engel LS, Lan Q, Rothman N. Polychlorinated biphenyls and non-Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev 2007;16:373–6.
5. Hardell E, Eriksson M, Lindstrom G, et al. Case-control study on concentrations of organohalogen compounds and titers of antibodies to Epstein-Barr virus antigens in the etiology of non-Hodgkin lymphoma. Leuk Lymphoma 2001;42:619–29.
6. Rothman N, Cantor KP, Blair A, et al. A nested case-control study of non-Hodgkin's lymphoma and serum organochlorine residues. Lancet 1997;350:240–4.
7. Spinelli JJ, Ng CH, Weber JP, et al. Organochlorines and risk of non-Hodgkin lymphoma. Int J Cancer 2007;121:2767–75.
8. Quintana PJ, Delfino RJ, Korrick S, et al. Adipose tissue levels of organochlorine pesticides and polychlorinated biphenyls and risk of non-Hodgkin's lymphoma. Environ Health Perspect 2004;112:854–61.
9. Vineis P, D'Amore F, Working Group on the Epidemiology of Hematolymphopoietic Malignancies in Italy. The role of occupational exposure and immunodeficiency in B-cell malignancies. Epidemiology 1992;3:266–70.
10. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for Polychlorinated Biphenyls (PCBs). Atlanta (GA): US Department of Health and Human Services; 2000.
11. Hankinson SE, Willett WC, Manson JE, et al. Plasma sex steroid hormone levels and risk of breast cancer in postmenopausal women. J Natl Cancer Inst 1998;90:1292–9.
12. Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. WHO Classification of Tumours: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Lyon (France): International Agency for Research on Cancer (IARC) Press; 2001.
13. Bertrand K, Spiegelman D, Aster J, et al. Plasma organochlorine levels and risk of non-Hodgkin lymphoma in the Physicians' Health Study. Epidemiology 2010;21:172–80.
14. Phillips DL, Pirkle JL, Burse VW, et al. Chlorinated hydrocarbon levels in human serum: effects of fasting and feeding. Arch Environ Contam Toxicol 1989;18:495–500.
15. Wolff MS, Camann D, Gammon M, Stellman SD. Proposed PCB congener groupings for epidemiological studies (letter). Environ Health Perspect 1997;105:13–4.
16. Hardell L, Lindstrom G, van Bavel B, et al. Adipose tissue concentrations of dioxins and dibenzofurans, titers of antibodies to Epstein-Barr virus early antigen and the risk for non- Hodgkin lymphoma. Environ Res 2001;87:99–107.