CEBP Focus: Update on Lymphoma

Polychlorinated Biphenyls and Non-Hodgkin Lymphoma

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Abstract

Several epidemiologic studies suggest that polychlorinated biphenyl (PCB) levels measured in peripheral blood or adipose tissue are related to increased risk of non-Hodgkin lymphoma (NHL) and, therefore, may be at least partially responsible for the rising incidence of NHL unrelated to HIV infection in recent decades. Case-control studies that measured PCBs in blood, adipose tissue, or household carpet dust, at the time of diagnosis, have observed elevated NHL risk associated with concentrations of either total PCBs or of specific congeners. Similar associations have been found in a number of prospective cohorts. These associations do not seem to be due to confounding by other organochlorines or by other known NHL risk factors. These results support evidence of PCB carcinogenicity from animal studies. However, interpretation of the epidemiologic evidence is limited by the wide range in measurement precision across congeners and by the moderate to high correlation among many congeners. Occupational cohort studies provide very limited support for a relationship between PCBs and NHL. In conclusion, there is mounting evidence of a relationship between certain PCBs and risk of NHL, but important questions remain, especially regarding the magnitude, timing, and causality of that relationship. (Cancer Epidemiol Biomarkers Prev 2007;16(3):373–6)

Introduction

The incidence of non-Hodgkin lymphoma (NHL) rose dramatically in the United States, Europe, and elsewhere in the latter half of the 20th century (1, 2). Changes in diagnostic patterns, increased rates of HIV infection, and use of immunosuppressive drugs only partially explain this increase (2, 3).

Organochlorines are receiving increased attention in relation to NHL risk. Organochlorines such as polychlorinated biphenyls (PCB) and certain pesticides are of particular interest due to the appreciable persistent exposure to these chemicals experienced by the general population in many industrialized countries in the latter half of the 20th century. These lipophilic chemicals tend to persist in the environment, have long biological half-lives, and bioaccumulate in the food chain. Consequently, exposure of the general population to these chemicals has occurred primarily through diet and through employment in certain occupations. Because of the weight of evidence and because of space constraints, this paper focuses on PCBs.

PCBs were widely used in various industries in the United States from the 1930s until their production was banned in 1977 because of concerns about their environmental and biological persistence and their possible health effects (4). Of 209 possible congeners, only about 36 show sufficient toxicity, environmental prevalence, and relative abundance in animal tissues to be considered potentially important for public health (5). The different congeners exhibit a variety of biological activities, including estrogenicity, antiestrogenicity, dioxinlike effects, immunotoxicity, and induction of bioactivating enzyme systems (5, 6). The number of chlorine atoms in a congener, which is partly related to its biological activity, also affects a congener's rate of metabolism and bioaccumulation (5).

The U.S. Environmental Protection Agency (USEPA) and the IARC have listed PCBs as probable human carcinogens, based largely on animal studies with some supporting epidemiologic evidence (4, 7). *In vivo* and *in vitro* studies indicate that the carcinogenic effects of these structurally diverse chemicals may be mediated by more than one mechanism, depending on the structure of the congener and the anatomic site of the tumor. These include binding to the AhR receptor (8), promotion of cell proliferation or inhibition of apoptosis (9), alterations of the immune system (10, 11), inhibition of gap-junctional intercellular communication (12), and formation of DNA adducts (13).

Prospective Cohort Studies Carried Out in the General Population. Rothman et al. (14) reported that total PCB levels measured in serum were strongly associated with increased risk of NHL in a case-control study nested within the CLUE I cohort from Maryland. A recent study examined lipid-corrected PCB concentrations in prospectively collected serum or plasma from NHL cases and controls in the community-based Janus cohort from Norway and the multistate Nurses' Health Study cohort and combined results with a reanalysis of the CLUE I cohort that focused on specific PCB congeners (15). This latest report found exposure-response trends for several congeners (International Union of Pure and Applied Chemistry 118, 138, and 153) across the three cohorts. More limited evidence also suggested exposure-response trends for several other congeners.

Exposure-response trends in the above cohorts were strongest in the period closest to blood draw. In studies of organ transplant patients, the median time from start of associated immunosuppressive therapy to NHL diagnosis was only 1 to 5 years (16, 17). Moreover, in a prospective study of AIDS-related lymphoma, the median time from HIV infection

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to NHL diagnosis was 6 to 8 years both before and after highly active antiretroviral therapy was introduced (18). However, population-based studies of PCB exposure and disease risk generally lack data on temporal patterns of exposure among subjects, thus limiting interpretation.

Case-Control Studies. Two previous case-control studies of incident, untreated NHL patients also observed associations between body burden of PCBs at diagnosis and risk of NHL (19, 20). Hardell et al. (19), in a study of 51 cases and 41 controls, found an OR of 1.8 (0.9-3.9) for blood or adipose levels of total PCBs above the median, although this effect disappeared after adjustment for age, sex, body mass index, and type of specimen. The authors did not report risk estimates for individual congeners, although they did report a relative risk of 3.2 (1.4-7.4) for the group of immunotoxic congeners. De Roos et al. (20), in a population-based study of 100 cases and 100 controls, found exposure-response trends for several congeners, including 156, 180, and 194; ORs for the highest fourth of plasma concentration relative to the lowest fourth ranged from 2.7 (1.0-6.9) for 194 to 3.5 (1.3-9.2) for 180. A case-control study, based on the same parent study and examining PCB concentrations in carpet dust collected at the time of diagnosis, also found a statistically significant dose-response trend for 180, with ORs of 1.3 (0.8-2.1), 1.5 (0.9-2.3), and 1.7 (1.1-2.6; p trend = 0.03) for increasing thirds of concentration compared with samples with concentrations below the limit of detection (21).

Many of the congeners related to increased risk in the above studies are proposed to be immunotoxic (6). As previously indicated, Hardell et al. (19) observed a stronger risk associated with the group of immunotoxic congeners than with all congeners combined. PCBs have been shown to alter immune function in humans and animal models (22, 23). Lastly, evidence suggests that infection by the EBV may potentiate the effects of PCB exposure on NHL risk (14, 19).

In contrast to the above findings, a case-control study nested within the EPA National Human Adipose Tissue Survey (24) found no association between adipose levels of PCBs and NHL risk. That study was based on adipose samples randomly collected from cadavers and surgical patients and analyzed for organochlorines between 1969 and 1983. However, the study had several important methodologic limitations, including use of samples collected postdiagnosis and primarily postmortem, chemical analyses done in various laboratories over many years, and a nonrepresentative case group consisting primarily of patients with more aggressive or fatal disease. A population-based case-control study of incident NHL in Australia also found no relationship with PCB exposure, based on expert assessment of likely exposure using self-reported job histories (25). However, because most people are likely to receive their primary exposure to PCBs through diet, job histories probably do not provide an adequate measure of cumulative exposure for the majority of the general population.

Occupational Cohort Studies. Although most biospecimen-based studies have found an association between PCB levels and NHL risk, retrospective cohort mortality studies of electric utility or capacitor-manufacturing workers with likely PCB exposure have found only weak and inconsistent evidence of an association. PCB-exposed workers (n = 2,100) employed for at least 1 week at a capacitor-manufacturing plant in Italy were followed for mortality between 1946 and 1991 by Tironi et al. (26); standardized mortality ratios (SMRs) of 2.02 (0.41-5.91) among males (3 observed, 1.5 expected) and 1.41 (0.46-3.30) among females (5 observed, 3.5 expected) were reported for lymphatic/hematopoietic malignancies. Similarly elevated risks were observed by Gustavsson et al. (27) in a study of 242 male Swedish capacitor manufacturing workers exposed to PCBs for at least 6 months between 1965 and 1978 and followed until 1991; that study found an overall SMR for NHL of 2.54 (0.07-14.16). Among the highly exposed, the SMR was 9.09 (0.23-50.70), and the standardized incidence ratio (SIR) was 5.26 (0.13-29.30), based on one case. A study of 1,939 men employed for at least 1 month at a Canadian transformer manufacturing plant and followed for mortality between 1946 and 1975 also observed a nonsignificantly elevated risk of lymphoma, with a SMR of 2.54 (0.29-9.17), based on two cases (28). Prince et al. (29) examined mortality among 2,572 highly exposed workers employed for at least 90 days in two capacitor manufacturing plants in the United States, between 1946 and 1977 in one plant and between 1939 and 1976 in the other plant, with follow-up through 1998. SMRs for NHL were 1.98 (0.91-3.77) and 0.32 (0.01-1.80) in the two plants, based on nine cases and one case, respectively. There was no clear exposure-response trend based on duration of employment. At the same time, several large mortality studies of workers exposed to PCBs through employment in electrical utilities (30) or capacitor manufacturing (31-33), and with long-term follow-up, have found no increased risk of lymphatic/hematopoietic malignancies. In addition, a study of cancer mortality and incidence among Swedish fishermen with differing intakes of PCB-contaminated fish found no increase in risk of NHL among the fisherman consuming the more contaminated fish, although their risk of multiple myeloma was elevated [SMR = 3.08 (1.24-6.35) and SIR = 2.08 (0.76-4.53) based on six cases; ref. 34].

Limitations of Studies to Date and Future Research Needs. Certain aspects of the occupational cohort studies published to date limit interpretation of their findings. First, none assessed individual exposures in blood or tissue; these are likely to provide a better measure of cumulative exposure to such long-lived bioaccumulating compounds. In addition, virtually all of them examined cancer mortality rather than incidence. Moreover, the number of expected NHL cases in most studies was low. Nevertheless, substudies (35-37) showed that serum PCB concentrations in some of the exposed workers were appreciably higher than those found in the general-population cohorts described above during the same time period. The discrepancy between findings among workers with occupational exposure to industrial-grade PCB mixtures and among general-population cohorts with primarily environmental exposure to PCBs needs further exploration before conclusions can be made about the carcinogenicity of PCBs. However, the discrepancy may be related to differences in the composition of PCB mixtures to which each group was exposed, in the accuracy of exposure measurements, or in the statistical power to observe associations with a relatively rare disease like NHL.

It is possible that the associations between PCBs and NHL risk observed in biospecimen-based studies are due to confounding by other persistent, bioaccumulating chemicals such as organochlorine pesticides, dioxins, furans, or coplanar PCBs. However, several pieces of evidence argue against this. First, although strong associations between NHL risk and several of these chemicals were observed in the population-based study by De Roos et al. (20), neither they nor any lifestyle factors confounded the observed relationship between PCBs and NHL. Moreover, dichlorodiphenyltrichloroethane (DDT), the most extensively studied pesticide in this context, has not been associated with NHL risk in most studies when considered singly (20, 38) or when accounting for other chemical exposures (14, 19, 24, 39-41). On the other hand, Engel et al. (15) observed that adjustment for levels of p,p'-dichlorodiphenyldichloroethylene, the main DDT metabolite, modestly attenuated risk estimates between several PCB congeners and NHL, although

conversely, risk estimates for *p,p'*-dichlorodiphenyldichloroethylene were attenuated much more by PCB levels, and trends in the PCB risk estimates remained significant. In addition, DDT levels in carpet-dust samples collected at diagnosis were higher among NHL cases than among controls in another study (21). Limited evidence has also suggested links between several other organochlorine pesticides, including aldrin, chlordane, and dieldrin, and NHL risk even after accounting for other chemical exposures (24, 41, 42).

Another limitation of the above biospecimen-based studies is that the PCB congeners that have been most strongly and consistently associated with NHL risk tend to be found at higher levels than other congeners in the populations studied, which can improve the precision with which they are measured. It is possible that the stronger associations observed for these congeners may reflect lower measurement error, and that other less well-measured congeners may be similarly associated with risk. In addition, moderate to high correlations among many of the well-measured congeners limit our ability to tease apart the effects of individual congeners. Nonetheless, the apparent lack of a relationship between several well-measured congeners and NHL risk suggests some degree of congener specificity for the associations. Also, although measurement of PCBs in blood or adipose tissue is believed to provide the best estimate of cumulative exposure, it does not allow the assessment of timing of exposure. The fact that NHL risk is elevated primarily in the period closest to sample collection in biospecimen-based prospective studies is consistent with other established risk factors for NHL; however, existing studies do not allow the assessment of the relationship of timing of exposure itself with disease risk. Moreover, PCB levels measured in biospecimens probably reflect not only cumulative environmental exposure to these chemicals, but also endogenous processes that affect their storage, dilution, and elimination (43). Thus, measured PCB levels, especially when based on a single biospecimen, may be, at least partly, a surrogate for endogenous processes that may be risk factors for NHL. Finally, differences in laboratory methods across biospecimen-based studies have prevented direct quantitative comparison of the observed risks.

Although the epidemiologic evidence increasingly suggests an association between exposure to certain PCB congeners and NHL risk, limitations in those studies necessitate caution in their interpretation and indicate the need for further investigation. The findings need to be evaluated in other cohorts of similar populations to determine if the association can be replicated. In addition, future biospecimen-based studies of PCBs and NHL risk would benefit by studying populations with appreciably different patterns of exposure to individual PCB congeners and other organochlorines than those studied to date to help address concerns about the impact of relative measurement precision and correlated exposures on risk estimates. Examining populations where PCBs and organochlorine pesticides are less correlated would be particularly informative. Studies involving populations with better characterized temporal patterns of exposure and/or availability of multiple prediagnostic biospecimens over time would also help clarify the relevant windows of exposure and/or effect. Such research will allow us to better evaluate the impact of continuing, albeit generally decreasing, exposure to these chemicals.

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