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Environmental Organochlorine Exposure and Risk of Breast Cancer

Polychlorobiphenyls (PCB's) and dichlorodiphenyl-trichloroethane (DDT) are persistent organic pollutants in the Great Lakes and other aquatic ecosystems. Currently in North America, human exposure to these compounds occurs primarily through the ingestion of contaminated fish, meat and dairy products. Many of these compounds have interacted with the estrogen receptor, but the interactions are complex. Some congeners of both PCB and DDT, as well as other organochlorine pollutants, have weakly estrogenic activity, stimulating estrogen receptors in both animal and human tissue. Yet others of these compounds have anti-estrogenic capacity. Consequences of the estrogenic effect of xenobiotics in wildlife include an altered male:female sex ratio among California gulls exposed to DDT.[1]

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A quarterly summary of recent findings in the scientific literature on human health effects and environmental pollutants, with an emphasis on pollutants of the Great Lakes ecosystem. Prepared under the direction of the Health Professionals Task Force of the International Joint Commission. This newsletter does not represent the official position of the International Joint Commission.

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The large variations in international breast cancer rates, and the sustained rise in incidence in most countries, have prompted research into possible environmental etiologies for this disease. Among known risk factors for breast cancer are those related to the duration of breast exposure to physiologic estrogen (early age at menarche, late menopause); prolonged lactation, which interrupts this exposure, is protective. Thus, there is interest in whether "environmental estrogens" can contribute to the development of breast cancer. This newsletter reviews ten recent papers which have addressed DDT, PCB or other organochlorine exposure and breast cancer risk in women.

The first study, by Wolff, *et al.* at Mount Sinai, was a nested case-control study which examined the relationship between serum DDE (the stable metabolite of DDT) and PCB levels and breast cancer.[2] The study was conducted within a large cohort study, the New York University Women's Health Study. Between 1985 and 1991, 14,290 women were enrolled in the cohort, had screening mammography, and blood drawn and frozen. From this group, women found to have breast cancer within six months of entry into the study were identified as cases (n=58). Controls were randomly selected from the cohort and matched for age at entry into the study and menopausal status (n=171). Serum DDE and PCB concentrations were determined in cases and controls. Results: Mean DDE concentrations among breast cancer cases compared to their matched controls; this difference was significant (11.0 ng/ml$\pm$ 9.1 vs 7.7 ng/ml$\pm$6.8; mean difference = 2.7 ng/ml, t =2.22; P = .031). Analyses adjusting for family history of breast cancer, lactation history, and age at first full term pregnancy, showed that OR's for breast cancer increased markedly with increasing quintile of DDE concentration [upper vs. lowest quintile OR 3.68 (95% C.I. = 1.01-13.50)]. There was a significant trend of increasing risk for breast cancer as the DDE concentration increased. The association between DDE concentration and breast cancer risk was strengthened by controlling for lactation history. Although mean PCB concentration was increased in cases compared to controls, the difference was not statistically significant, and the test for trend was also not significant. The authors conclude that a strong association between DDE and breast cancer was found and that there was a significant dose-response relationship. They note that failing to control for lactation history would weaken the association observed; they suggest that a possible reduction of DDE serum levels associated with lactation could produce this effect.

Another nested case-control study, by Krieger, *et al.*, examined prospectively the relationship between serum DDE and PCB concentrations and the subsequent development of breast cancer.[3] They study population was a subset of 46,629 female members of a regional health plan in northern California who had chosen to take a multiphasic health examination between 1969 and 1971; blood was sampled at that time. From among 1805 white, 230 black, and 62 Asian women identified as having developed breast cancer during the follow-up period (through 1990), random samples of fifty from each racial/ethnic group were selected as the cases. Matched controls were identified from the cohort. Serum DDE and PCB concentrations were determined for cases and controls. Results: Mean differences in DDE and PCB serum concentrations did not differ between cases and controls, for the racial/ethnic groups combined. Serum levels of both agents tended to be higher among black patients compared to black controls, and slightly lower among Asian cases compared to Asian controls. PCB levels were somewhat lower in white cases, compared to white controls. Adjusting for known risk factors did not alter the result. The authors note several limitations of the study, including a relatively small sample size (which would decrease the likelihood of identifying a small relative risk, if it exists) and inability to control for lactation history. They also note that the DDE levels measured in this group of northern Californian women were much higher that those reported by Wolf, *et al*., and raise the possibility of a "leveling-off" effect at higher exposure levels. They note that any alterations in DDE and PCB serum levels associated with the cancer itself would be avoided by the prospective design of this study. The authors conclude that the current data do not support an association between DDT and PCB exposure and subsequent development of breast cancer. They recommend that future research should address the possibility of a "leveling-off" effect at high exposure levels, and the effects that lactation and estrogen/progesterone receptor status have on the relationship between organochlorine exposure and breast cancer risk.

A hospital-based case-control study was conducted by Lopez-Carrillo, *et al*., to examine the relationship between DDT exposure and breast cancer in Mexico, where DDT is still used for malaria control.[4] The study took place at three referral hospitals in Mexico City, from 1994 to 1996. Cases were women at three referral hospitals, between 1994-1996, with a new diagnosis of histologically confirmed breast cancer. There were 141 cases, with age-matched controls, who underwent interviews regarding reproductive, lactation, diet and occupational histories, evaluation of Body Mass Index, and blood sampling for DDE and *p,p*-DDT determinations. Results: The mean DDE levels were not significantly different between cases and controls. There were also no differences between the cases and controls regarding *p,p*-DDT levels. OR's for the higher tertiles of DDE levels versus for the lowest tertile was low (0.97; 95% C.I. 0.38-1.24), thus indicating that there was no dose response relationship between DDE levels and breast cancer risk. The authors note that in contrast to other case-control studies, they were able to control for multiple known

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variables associated with breast cancer risk. They conclude that their data do not support an association between DDT exposure and breast cancer, but that the possibility of an etiologic role at higher DDT concentrations is not excluded.

European investigators (van't Veer, *et al.*) conducted a multi-centered case-control study to examine the relationship between DDE levels in adipose tissue and the presence of breast cancer in women in Germany, the Netherlands, Northern Ireland, Switzerland and Spain.[5] Incident cases of histologically proven ductal breast cancer without clinically evident distant metastases were included. Controls were matched for age and study center. Cases and controls underwent needle aspiration of subcutaneous buttock fat; samples were available for 265 cases and 341 controls for analysis of DDE. Results: Body mass index (kg/m^2) was positively associated with DDE concentration among controls, as expected. Mean DDE concentration was 1.35 ug/g (95% C.I. 1.15-1.58) for cases and 1.51 ug/g (95% C.I. 1.31-1.73) for controls; thus the mean was 10.5% lower in the women with breast cancer. The OR for breast cancer for the highest quartile of DDE concentration vs. lowest was 0.73, with a trend that was not significant (P=0.16). Adjusting for body mass index, age at first birth and current alcohol use strengthened the inverse relationship between DDE concentration and breast cancer risk (P for trend = 0.02). The multivariate OR, adjusted for age, study center, body mass index, age at first birth and alcohol consumption, was 0.48 (highest vs. lowest quartile DDE level). The authors conclude that their data do not support the hypothesis that DDE levels in fat tissue are associated with breast cancer, but that associations with other organochlorines are not excluded.

Recently, a large study, by Hunter, et. al., examined the hypothesis that higher blood PCB and DDT levels are associated with breast cancer risk, using prospectively collected blood samples for both breast cancer cases and controls.[6] The study was carried out among enrollees in the Nurses' Health Study, who entered the study in 1976, and supplied blood samples in 1989-1990. From among 32,826 women, 240 cases were identified who had a subsequent new diagnosis of breast cancer by 1992. For each case, a control subject was identified from the cohort who was matched for factors including age, menopausal status, and post-menopausal hormone use. DDE and PCB levels were cholesterol-adjusted. Results: Both DDE and PCB concentration rose with age. There was a positive association between body-mass index and plasma DDE; otherwise there were no associations between known or suspected breast cancer risk factors and DDE or PCB levels. Among parous women, women in the lowest thirds of PCB and DDE concentrations were more likely to have breast-fed for more than 6 months compared to women in the highest thirds (association not significant). Cases had lower levels of plasma DDE compared to controls (4.71 ppb vs.5.35 ppb, P=0.14). There was no difference between PCB levels among cases and controls. Restricting the analysis to those with invasive breast cancer, or to those with estrogen-receptor-positive tumors, did not change the results. A multivariate relative risk of breast cancer for the highest decile of plasma DDE compared with the lowest decile was 0.38 (95% C.I., 0.13-1.09). For PCB's, the risk was 0.44 (95% C.I. 0.15-1.29). Thus, there was no evidence for an increased risk of breast cancer from higher levels of either organochlorine. The authors *conclude* that although there are sound ecologic concerns about the release of these organochlorines into the environment, the current data do not support an association between DDT and PCB exposure and the recent increases in breast cancer.

Objections to the conclusions of the Hunter study were raised by several investigators. One was that exposure to more highly estrogenic DDT and PCB components may have occurred earlier in life during critical developmental periods, and would not have been accounted for by measuring the persistent *in vivo* metabolites that were studied.[7] Another was that measured serum DDE levels may not reflect the large concentration of this compound found in breast fat, and that the relationship between fat and serum levels is highly variable.[8]

A case-control study of post-menopausal breast cancer risk and organochlorine exposure was carried out among women in western New York state by Moysich, *et al.*[9] Cases were postmenopausal women with breast cancer who provided a blood sample after diagnosis, generally within 3 months of surgery but before chemotherapy or radiation. They were compared to 192 age-matched community controls. Analysis was done for serum DDE, HCB, mirex, and PCB congeners. Results: DDE, mirex, HCB and total PCB's were not associated with increased risk of breast cancer in the group as a whole. However, there was a slight increased risk with PCB'S among women who had never lactated (3rd tertile OR, 2.87; 95% C.I. 1.01-7.29). There was also a suggestion, in women who had never lactated, of increased risk with levels of mirex above the limit of detection, compared to those with levels below (OR 2.42, 95% C.I. 0.98-4.32).

Finally, a recent nested case-control study by Hoyer, *et al.*, reports on the experience of Danish women enrolled in the Copenhagen City Heart Study (CCHS).[10] These were 7712 women who enrolled in the study in 1976 and provided a blood sample at that time. Cases were women who developed breast cancer from the beginning of the study until 1993 and were identified using the Danish Cancer Registry; two age-matched controls per case were identified from the CCHS cohort. The serum of cases and controls were analyzed for 28 PCB congeners, and 18 organochlorine pesticides or metabolites (mirex, dieldrin, aldrin, endrin, "-chlordane, ?-chlordane, heptachlor, heptachlor epoxide, oxychlordane, transnonachlor, ?-HCH, ß-HCH, HCB, and five DDT-related compounds). The study included 240 cases and 477 controls. Results: The risk of breast cancer was related to dieldrin levels, with a dose-response relationship seen (OR 2.25, 95% C.I. 1.32-3.84, p for trend 0.003). There was a slight risk with increasing concentrations of ß-HCH. The risk from these two agents were strengthened when excluding cases diagnosed within five years of serum sampling. There was no association seen for DDT isomers, PCB congeners, or other the organochlorines examined. The authors note that there is experimental evidence for estrogenicity of dieldrin; they suggest that their results regarding ß-HCH require replication and further evidence of biological plausibility. They note that their data do not support a relationship between DDT or PCB'S and risk.

Conclusion: The observation of risk for breast cancer from dieldrin and beta-HCH in a single study is interesting and requires confirmation. The weight of current epidemiologic evidence collected to date is not sufficient to support an association between DDT or PCB exposure and the development of breast cancer in women. One possibility is that DDT and some PCB congeners do not increase the risk of breast cancer. Another possibility is that, if such an association exists, it may be a weak one, and the cited negative studies had insufficient power

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