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PLS. ~~REC~~ REVIEW
LET'S DISCUSS &
PREPARE APPROPRIATE
RESPONSE FOR JEANNE'S SIGNATURE
BY 11/21
RICH

October 31, 1997

Jeanne M. Fox, Regional Administrator
US EPA, Region II
290 Broadway
New York, NY 10007-1866

Dear Ms. Fox:

I enclose a recent article from the New England Journal of Medicine that studied the relationship between exposure to DDT and PCBs, and the incidence of breast cancer in several hundred women and a like number of controls. The study concludes: "Our data do not support the hypothesis that exposure to DDT and PCBs increases the risk of breast cancer." The study further noted that PCBs are "very weak estrogens" which require concentrations of up to 100,000 times more than natural estrogen to achieve equivalent activity.

I also enclose an editorial from the same issue of the Journal by Dr. Stephen Safe, who is a noted expert in this field and a member of EPA's Science Advisory Board. Dr. Safe makes the point that to link environmental exposure to a toxic or carcinogenic effect there must be "... correlation between the level of exposure and the magnitude or incidence of the response, consistent results from several studies, biologic plausibility based on results of studies in laboratory animals, and if possible, evidence based on high levels of exposure in humans." Dr. Safe notes that the Hunter et al study is consistent with the epidemiological data on breast cancer and states that this should "... reassure the public that weakly estrogenic organochlorine compounds such as PCBs, DDT and DDE are not the cause of breast cancer." He further says:
"... there is no increase in the risk of breast cancer among women who are exposed to relatively high levels of PCBs at work."

I thought you would find this information useful as you think and speak about the risks which may or may not be presented by PCBs.

Sincerely,

Stephen D. Ramsey

SDR/a
Enclosures

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PLASMA ORGANOCHLORINE LEVELS AND THE RISK OF BREAST CANCER

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ABSTRACT

Background Exposure to "environmental estrogens" such as organochlorines in pesticides and industrial chemicals has been proposed as a cause of increasing rates of breast cancer. Several studies have reported higher blood levels of 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE) and polychlorinated biphenyls (PCBs) in patients with breast cancer than in controls.

Methods We measured plasma levels of DDE and PCBs prospectively among 240 women who gave a blood sample in 1989 or 1990 and who were subsequently given a diagnosis of breast cancer before June 1, 1992. We compared these levels with those measured in matched control women in whom breast cancer did not develop. Data on DDE were available for 236 pairs, and data on PCBs were available for 230 pairs.

Results The median level of DDE was lower among case patients than among controls (4.71 vs. 5.35 parts per billion, P = 0.14), as was the median level of PCBs (4.49 vs. 4.68 parts per billion, P = 0.72). The multivariate relative risk of breast cancer for women in the highest quintile of exposure as compared with women in the lowest quintile was 0.72 for DDE (95 percent confidence interval, 0.37 to 1.40) and 0.66 for PCBs (95 percent confidence interval, 0.32 to 1.37). Exposure to high levels of both DDE and PCBs was associated with a nonsignificantly lower risk of breast cancer (relative risk for women in the highest quintiles of both DDE and PCBs as compared with women in the lowest, 0.43; 95 percent confidence interval, 0.13 to 1.44).

Conclusions Our data do not support the hypothesis that exposure to 2,2-bis(*p*-chlorophenyl)-1,1,1-trichloroethane (DDT) and PCBs increases the risk of breast cancer. (N Engl J Med 1997;337:1253-8.)

THE fivefold variation in the rates of breast cancer around the world,[1] combined with the observation that the daughters of women who migrate from a country with a low incidence of breast cancer to a country with a high incidence acquire the breast-cancer risk prevailing in the high-incidence country,[2] strongly suggests that environmental and lifestyle factors are the major causes of breast cancer. The incidence of breast cancer in the United States has risen by 1 percent per year since 1940,[3] and there is uncertainty about the extent to which established risk factors can explain the increase. Environmental pollutants have been suggested as potential causes.[4,5]

The hypothesis that among these pollutants, hormonally active organochlorine chemicals may be responsible has garnered wide attention. Many pesticides and industrial chemicals have the potential to act as "environmental estrogens" and have been shown to affect wildlife adversely. The most abundant organochlorine contaminants are the pesticide 2,2-bis(*p*-chlorophenyl)-1,1,1-trichloroethane (DDT) and certain polychlorinated biphenyls (PCBs). DDT, which was introduced in the United States in 1945 and banned in 1972,[6] has been implicated as the cause of eggshell thinning in bald eagles,[7] and certain PCBs used in a wide variety of industrial products and manufactured between 1929 and 1977[6] can alter sex determination in animals.[8] In vitro assays demonstrate that 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE), the main metabolite of

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DDT, and certain PCB congeners have estrogen-like activity.[9]

Many of these compounds accumulate in the body because of their lipid solubility and resistance to metabolism. They are also present in human adipose tissue and breast milk.[10] In a nationwide study of breast milk in the 1970s, 99 percent of samples had detectable levels of DDT and PCBs.[11] DDT promotes the growth of mammary tumors in some rodent models.[12,13] Limited data are available to assess possible associations with breast cancer in humans. Two small case–control studies reported higher levels of DDE among women with breast cancer than among controls.[14,15] In another study the association was limited to women with estrogen-receptor–positive breast cancer.[16] One of these studies[15] also found higher levels of PCBs among the women with breast cancer than among controls. In a recent case–control study from Europe, concentrations of DDE in adipose tissue were lower in patients with breast cancer than in controls.[17] A prospective study of 58 cases of breast cancer in New York[18] found a significant increase in the risk of breast cancer with higher serum levels of DDE and a nonsignificant positive association with PCBs. In a larger prospective study of 150 cases in the San Francisco Bay area, Krieger et al.[19] observed no overall elevation in risk with higher serum levels of either DDE or PCBs, but some have argued that the findings were not clearly null.[20]

To test the hypothesis that higher blood levels of DDE or PCBs are associated with an increased risk of breast cancer, we measured levels of these organochlorines in 240 women with breast cancer and 240 control women in the Nurses' Health Study, using blood samples prospectively collected from 1989 to 1990.

METHODS

Study Population

In 1976, 121,700 married registered nurses from 11 states were enrolled in the Nurses' Health Study and subsequently followed by questionnaire every two years. Self-reported diagnoses of breast cancer are confirmed by a review of medical records.[21] The completeness of follow-up as a proportion of potential person-years through 1992 is 95 percent.[21] Information on risk factors for breast cancer, such as family history (updated in 1982 and 1988) and reproductive history (updated until 1984), is obtained by questionnaire. Menopausal status was defined on the basis of a woman's response to the question whether her periods had ceased permanently. Women who had had a hysterectomy with one or both ovaries left intact were classified as premenopausal until the age at which 10 percent of the cohort had undergone natural menopause (46 years for smokers and 48 years for nonsmokers) and as postmenopausal at the age at which 90 percent of the cohort had undergone natural menopause (54 for smokers and 56 for nonsmokers); in the intervening years these women were classified as being of uncertain menopausal status and excluded from menopause-specific analyses.

From 1989 to 1990, 32,826 women sent us a blood sample, which was separated into aliquots of plasma, red cells, and buffy coat. Women who sent a blood sample were very similar to other women in the cohort with respect to reproductive risk factors for breast cancer such as age at menarche, parity, and age at the birth of their first child. Women who gave a blood specimen were slightly more likely to have a history of benign breast disease or a family history of breast cancer. These differences should not influence the internal validity of comparisons between case patients and controls in the subcohort of women who gave a blood specimen.

We defined case patients as women who did not have a diagnosis of cancer (other than nonmelanoma skin cancer) when they sent in the blood specimen and in whom breast cancer was subsequently diagnosed before June 1, 1992. There were 240 eligible case patients: 200 women had invasive cancer, 39 had carcinoma in situ, and 1 had cancer with uncertain histologic features. For each case patient we matched a control subject who had not reported a diagnosis of cancer according to the year of birth, menopausal status at the time of blood sampling, month in which the blood sample was returned, time of day that the blood sample was obtained, fasting status at blood sampling, and for postmenopausal women, postmenopausal hormone use.

Laboratory Analyses

The laboratory methods have been described in detail elsewhere.[16,22] Briefly, a polar extract of plasma lipids was further treated with a step involving chromatographic cleanup and enrichment of the column and then analyzed by gas chromatography with electron-capture detection. All steps were scaled appropriately for 0.50-ml aliquot volumes. We have previously demonstrated using Nurses' Health Study specimens that the precision with the use of this volume and an optimized analytic procedure is similar to that with previous procedures using 1-ml and 2-ml aliquots.[22] The amount of methanol was optimized (0.3 ml) to create a good interface between the aqueous layer and the ether–hexane extractant (1.25 ml). Results are reported as parts per billion (ppb) of DDE (which is equivalent to nanograms of DDE per milliliter) and of the sum of the higher PCB congeners — compounds with retention times longer than that of DDE (pentachlorobiphenyls, hexachlorobiphenyls, and heptachlorobiphenyls). The limits of detection were less than 1 ppb for both DDE and PCBs, on the basis of a value that was three times the standard deviation[24] of 24 determinations over the course of sample analyses of a quality-control plasma pool with approximately 1 ppb of both DDE and PCBs. Both DDE and PCBs are stable in frozen blood; organochlorine levels in serum frozen at −20°C were unchanged over a period of one year[25] (and unpublished data). Plasma cholesterol was determined with the procedure of Allain et al.[26]

Serum samples from pairs of case patients and controls (with the order of samples randomized) were sent to the laboratory in batches of 12 pairs; each batch included 2 unidentifiable split samples from pooled plasma from premenopausal or postmenopausal women. For each batch we calculated the coefficient of variation; the median coefficient of variation was 4.3 percent for DDE and 13.2 percent for PCBs. DDE values were missing for one member of four case–control pairs, and PCB values were missing for one member of an additional six pairs because the samples were lost or contaminated.

Statistical Analysis

Since both DDE and PCBs are correlated with blood lipid content,[20] linear regression analysis of log-transformed DDE and PCB values was performed to adjust for plasma cholesterol concentration. We used these adjusted values in our principal analyses; we also used the unadjusted values in supplementary analyses.

We assessed the relations of plasma DDE and PCBs using Spearman correlation coefficients for continuous variables and by examining the distribution of risk factors for breast cancer within thirds of plasma organochlorine levels among the controls, testing for statistical significance with the Kruskal–Wallis test.[27] We used the Wilcoxon signed-rank test for paired data and the Wilcoxon rank-sum test for unpaired data to compare plasma DDE and

PCB levels between case patients and controls.[27] We divided the control distribution into quintiles and calculated the relative risk and 95 percent confidence interval for each quintile relative to the lowest quintile using conditional logistic regression,[28] controlling for established risk factors for breast cancer in addition to the matched factors. To assess the potential synergism between organochlorine compounds, we compared women in the highest quintile of both DDE and PCBs with women in the lowest quintile of both. To examine whether the associations between organochlorines were modified by conventional risk factors for breast cancer, we conducted unconditional analyses within strata of the other risk factors for breast cancer, controlling for the matched variables. All P values are two-sided.

RESULTS

The median age of the subjects was 59 years (range, 43 to 69), 68 percent of both case patients and controls were postmenopausal, and the median age at menopause was 49 years for the case patients and 50 years for the controls. Differences in other risk factors for breast cancer between case patients and controls were not statistically significant, with the exception of maternal history of breast cancer (reported by 11 percent of case patients and 5 percent of controls, P = 0.01), history of breast cancer in a sister (8 percent of case patients and 3 percent of controls, P = 0.03), and history of benign breast disease (56 percent of case patients and 41 percent of controls, P = 0.001).

Plasma levels of both DDE ($r = 0.31$, $P<0.001$ by Spearman rank correlation) and PCBs ($r = 0.25$, $P<0.001$) increased with age (Table 1). The only statistically significant association of either DDE or PCBs with established or suspected risk factors for breast cancer (Table 1) was a positive association between body-mass index and plasma DDE levels. Among parous women, more women in the lowest thirds than in the highest thirds of DDE and PCB levels had breast-fed their children for more than six months; however, these associations were not sig-

TABLE 1. RELATION BETWEEN ESTABLISHED OR SUSPECTED RISK FACTORS FOR BREAST CANCER AND PLASMA LEVELS OF DDE AND PCBS AMONG 236 NURSES' HEALTH STUDY PARTICIPANTS WITHOUT DIAGNOSED BREAST CANCER.*

RISK FACTOR	LOWER THIRD, ≤4.02 ppb OF DDE	MIDDLE THIRD, >4.02–7.22 ppb OF DDE	UPPER THIRD, >7.32 ppb OF DDE	P VALUE
Median age (yr)	54	59	63	<0.001†
Median age at menarche (yr)	12	12	13	0.28†
Median no. of children	3	3	3	0.67†
Median age at birth of 1st child (yr)‡	24	24	25	0.05†
Median body-mass index§	23.2	24.3	25.0	0.01†
Lactation for >6 mo total (%)‡	31	32	17	0.25¶
Family history of breast cancer (%)	8	9	6	0.87¶
History of benign breast disease (%)	36	46	40	0.48¶
	LOWER THIRD, ≤3.99 ppb OF PCBs	**MIDDLE THIRD, >3.99–5.40 ppb OF PCBs**	**UPPER THIRD, >5.40 ppb OF PCBs**	
Median age (yr)	56	59	62	<0.001†
Median age at menarche (yr)	12	12	13	0.56†
Median no. of children	3	3	3	0.09†
Median age at birth of 1st child (yr)‡	24	25	24	0.23†
Median body-mass index§	24.4	24.1	24.9	0.43†
Lactation for >6 mo total (%)‡	37	15	29	0.08¶
Family history of breast cancer (%)	5	7	13	0.31¶
History of benign breast disease (%)	44	41	36	0.57¶

*The plasma levels of DDE and PCBs were measured after adjustment for plasma cholesterol concentrations. The subjects ranged in age from 43 to 69 years. Levels of DDE and PCBs were divided into thirds. Data on PCBs were based on 230 women.

†The Kruskal–Wallis test was used.

‡Only parous women were included in the analysis.

§The body-mass index is calculated as the weight in kilograms divided by the square of the height in meters.

¶The chi-square test was used.

TABLE 2. PLASMA LEVELS OF DDE AND PCBs AMONG CASE PATIENTS WITH BREAST CANCER AND CONTROLS IN THE NURSES' HEALTH STUDY.*

	CASE PATIENTS AND CONTROLS†	MEAN (±SD) VALUE	MEDIAN VALUE	P VALUE‡
	no.	parts per billion		
DDE				
Case patients	236	6.01±4.56	4.71	
Controls	236	6.97±5.99	5.35	0.14
PCBs				
Case patients	230	5.08±2.51	4.49	
Controls	230	5.16±2.26	4.68	0.72

*The plasma levels of DDE and PCBs were measured after adjustment for plasma cholesterol concentrations.

†DDE values were missing for one member of four case–control pairs, and PCB values were missing for an additional six pairs due to lost samples or evidence of contamination.

‡The Wilcoxon signed-rank test was used.

nificant. Results were similar in analyses that were not adjusted for plasma cholesterol concentration.

Women who were given a diagnosis of breast cancer after providing a blood sample in 1989 or 1990 had lower levels of plasma DDE than controls (Table 2); the median level was 4.71 ppb in case patients and 5.35 ppb in controls ($P=0.14$). Plasma PCB levels were essentially the same in case patients and controls. Results were similar in analyses that were not adjusted for plasma cholesterol concentration: the unadjusted median for DDE was 5.07 ppb in case patients and 5.59 ppb in controls ($P=0.14$); the unadjusted median for PCBs was 4.58 ppb in case patients and 4.73 ppb in controls ($P=0.60$). Levels of DDE and PCBs were similar among women with and those without axillary-lymph-node involvement at diagnosis. The exclusion of 101 pairs in which the case patient was given a diagnosis of breast cancer within one year after blood sampling had little effect on these findings. After restriction of the analyses to 197 patients with invasive cancer and their controls for whom data were available, the median value for DDE among case patients was 5.02 ppb, as compared with 5.60 ppb among controls ($P=0.20$). For PCBs the median value among both patients with invasive cancer and controls was 4.69 ppb ($P=0.87$). In analyses restricted to 139 case patients with estrogen-receptor–positive disease and their controls, the results were similar.

We found no evidence of a positive association between high levels of plasma DDE or PCBs and a risk of breast cancer (Table 3). The multivariate relative risk for the highest decile of plasma DDE levels as compared with the lowest decile was 0.38 (95 percent confidence interval, 0.13 to 1.09); for PCBs the risk was 0.44 (95 percent confidence interval, 0.15 to 1.29). Even among women with high levels of both DDE and PCBs, there was still no evidence of a positive association. As compared with women who were in the lowest quintiles of both DDE and PCBs, women in the highest quintiles were at nonsignificantly lower risk of breast cancer (multivariate relative risk = 0.43; 95 percent confidence interval, 0.13 to 1.44).

Among 48 premenopausal case patients and 53 controls with values for DDE, the median level was 3.72 ppb among case patients and 3.30 ppb among controls ($P=0.95$). For PCBs the median was 3.91 ppb among 47 premenopausal case patients and 4.11 ppb among 51 premenopausal controls ($P=0.54$). The results for postmenopausal women were similar to the overall results. The absence of an association between DDE, PCBs, and breast cancer was similar within strata of age, age at menarche, age at birth of first child, number of children, and history of lactation.

DISCUSSION

In this prospective study, we did not observe any evidence of an increased risk of breast cancer among women with relatively high levels of plasma DDE or PCBs. Most of the relative risks we observed for higher levels of exposure were less than 1, and the upper bounds of the 95 percent confidence intervals generally excluded all but small increases in risk. Moreover, women with high levels of both DDE and PCBs were not at higher risk than women with the lowest levels of these compounds.

The hypothesis that environmental organochlorine contaminants cause breast cancer is based largely on indirect evidence. Some but not all studies have shown that DDE and PCBs act as estrogens in vitro and in animals. Indeed, some PCB congeners and organochlorines, such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, have antiestrogenic activity. In general, these compounds are very weak estrogens in in vitro assays, requiring concentrations of up to 100,000 times more than the natural estrogen 17β-estradiol to achieve equivalent estrogenic activity.[9] On the basis of these in vitro assays, it has been estimated that humans are exposed to naturally occurring estrogenic compounds in our diet in amounts that are many orders of magnitude higher than those of environmental organochlorine estrogens.[29] Nevertheless, given that organochlorines are fat soluble, persist in adipose tissue, and are excreted in breast milk,[30] it may be that ductal and other cells in the breast are exposed to these compounds over a period of many decades. Such prolonged exposure may counterbalance the low estrogenic potency of organochlorines.

Because they are highly lipophilic and metabolically resistant, DDE and PCBs undergo lifelong sequestration in human adipose tissue. Blood levels of

TABLE 3. RELATIVE RISK OF BREAST CANCER ACCORDING TO QUINTILE OF PLASMA DDE AND PCB LEVELS AT BASE LINE IN THE NURSES' HEALTH STUDY, 1989 TO 1992.*

VARIABLE	QUINTILE 1, ≤2.78 ppb of DDE	QUINTILE 2, >2.78–4.54 ppb of DDE	QUINTILE 3, >4.54–6.25 ppb of DDE	QUINTILE 4, >6.26–9.46 ppb of DDE	QUINTILE 5, >9.46 ppb of DDE	P VALUE FOR TREND
No. of case patients	61	54	35	43	43	
No. of controls	47	46	49	47	47	
Relative risk						
Matched	1.0‡	0.88	0.56	0.73	0.66	0.22
(95% CI)†		(0.52–1.50)	(0.31–0.99)	(0.42–1.27)	(0.36–1.22)	
Multivariate	1.0‡	0.80	0.47	0.74	0.72	0.47
(95% CI)§		(0.45–1.43)	(0.25–0.90)	(0.40–1.36)	(0.37–1.40)	
	QUINTILE 1, ≤3.59 ppb of PCBs	QUINTILE 2, >3.59–4.28 ppb of PCBs	QUINTILE 3, >4.28–6.12 ppb of PCBs	QUINTILE 4, >6.12–8.31 ppb of PCBs	QUINTILE 5, >8.31 ppb of PCBs	
No. of case patients	64	40	39	41	46	
No. of controls	46	45	46	45	48	
Relative risk						
Matched	1.0‡	0.57	0.54	0.55	0.59	0.26
(95% CI)†		(0.31–1.06)	(0.29–1.00)	(0.29–1.05)	(0.31–1.12)	
Multivariate	1.0‡	0.62	0.52	0.54	0.66	0.47
(95% CI)§		(0.32–1.20)	(0.25–1.06)	(0.26–1.10)	(0.32–1.37)	

*The plasma levels of DDE and PCBs were measured after adjustment for plasma cholesterol concentrations. CI denotes confidence interval.

†Case patients and controls were matched for year of birth, menopausal status, month in which blood sample was returned, time of day blood sample was drawn, fasting status at blood sampling, and for postmenopausal women, postmenopausal hormone use.

‡This was the reference group.

§After control for matching variables, conditional logistic-regression analyses were adjusted for a history of breast cancer in a mother or sister, a history of benign breast disease, age at menarche (<11 years, 11 to 14, and ≥15), number of children and age at birth of first child (nulliparous, 1 to 2 children and age ≤24 at first birth, 1 to 2 children and age >24 at first birth, ≥3 children and age ≤24 at first birth, and ≥3 children and age >24 at first birth), duration of lactation (0, 1 to 6 months, and >6 months), and body-mass index (<21, 21 to 24.9, 25 to 29.9, and ≥30).

these compounds are among the most stable biologic markers of exposure known. In blood samples collected before and after treatment for breast cancer (an average of 56 days apart), the r values for the lipid-adjusted correlations between the first and second samples were 0.99 for DDE and 0.96 for PCBs.[31] Among 31 healthy women who provided two blood samples two months apart, the r values were 0.96 for DDE and 0.89 for PCBs.[32] The half-life of plasma DDE is approximately 10 years (Wolff M, Toniolo P: unpublished data). Among workers with occupational exposure to organochlorines, the length of time that highly chlorinated PCBs persist in the body varies widely; the most long-lived congeners have half-lives of 7 to 30 years.[33] These data, and the consistent correlation of DDE and PCBs with age, suggest that the blood levels of DDE and PCBs we measured reflect exposure that occurred over a period of many years.

Epidemiologic data regarding possible relations of organochlorines with breast cancer are limited. Several small case–control studies reported higher levels of DDE[14] or PCBs[15] among case patients than controls. A recent European case–control study (264 case patients) reported a significant inverse trend between levels of adipose DDE and the risk of breast cancer; data on PCBs were not available.[17] In a prospective study of 14,290 women in New York,[18] levels in serum were compared in 58 women given a diagnosis of breast cancer within one to six months after blood collection in 1985 to 1991 and 171 controls. The adjusted relative risk for the highest quintile of DDE as compared with the lowest was 3.68 (95 percent confidence interval, 1.10 to 13.50); for PCBs the risk was 4.35 (95 percent confidence interval, 0.92 to 20.47). In the largest prospective study to date, Krieger et al.[19] examined serum from 150 case patients selected from a cohort of 57,040 San Francisco Bay area women who had provided blood between 1964 and 1971. Little association was seen between organochlorine levels and the risk of breast cancer.

A strength of the three available prospective studies (including this study) is that the analyses of DDE and PCBs were all performed in the same laboratory;

neither laboratory technique nor a variation in accuracy is likely to account for differences in findings. The levels of DDE we observed in this study among women who provided blood samples in 1989 or 1990 were similar to those observed in samples obtained in 1985 to 1991 from New York women,[18] but the median was six times lower than the medians for women in the San Francisco Bay area in the late 1960s.[19] This finding is compatible with the long-term decline in DDE levels since the compound was banned in 1972 and suggests that there is no relation with breast cancer at either the levels currently prevailing or the higher levels that were present when DDT was still being used. The PCB levels we observed were similar to those observed in both of the previous prospective studies, underlining the persistence of these compounds in our environment even after production ceased in 1977.

Although we cannot exclude the possibility that exposure in utero or during childhood could increase the risk of breast cancer decades later, because DDT and PCBs were introduced into the environment largely in the 1940s and 1950s, exposure very early in life could not have accounted for most of the increase in the incidence of breast cancer over the past several decades, which has been greatest in postmenopausal women who were already adults when the compounds were being most widely used. The absence of an association with DDE and PCBs does not rule out the possibility that other pesticides and environmental contaminants may be associated with breast cancer. There are good ecologic reasons to avoid the release of DDT and PCBs into our environment, but on the basis of our results the use of these compounds does not explain the high and increasing rates of breast cancer.

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REFERENCES

1. Armstrong B, Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. Int J Cancer 1975;15:617-31.
2. Buell P. Changing incidence of breast cancer in Japanese-American women. J Natl Cancer Inst 1973;51:1479-83.
3. Harris JR, Lippman ME, Veronesi U, Willett W. Breast cancer. N Engl J Med 1992;327:319-28.
4. Davis DL, Bradlow HL, Wolff M, Woodruff T, Hoel DG, Anton-Culver H. Medical hypothesis: xenoestrogens as preventable causes of breast cancer. Environ Health Perspect 1993;101:372-7.
5. Wolff MS, Toniolo PG. Environmental organochlorine exposure as a potential etiologic factor in breast cancer. Environ Health Perspect 1995; 103:Suppl 7:141-5.
6. Kutz FW, Wood PH, Bottimore DP. Organochlorine pesticides and polychlorinated biphenyls in human adipose tissue. Rev Environ Contam Toxicol 1991;120:1-82.
7. Wiemeyer SN, Lamont TG, Bunck CM, et al. Organochlorine pesticide, polychlorobiphenyl, and mercury residues in bald eagle eggs — 1969-1979 — and their relationships to shell thinning and reproduction. Arch Environ Contam Toxicol 1984;13:529-49.
8. Bergeron JM, Crews D, McLachlan JA. PCBs as environmental estrogens: turtle sex determination as a biomarker of environmental contamination. Environ Health Perspect 1994;102:780-1.
9. Soto AM, Sonnenschein C, Chung KL, Fernandez MF, Olea N, Serrano FO. The E-SCREEN assay as a tool to identify estrogens: an update on estrogenic environmental pollutants. Environ Health Perspect 1995;103: Suppl 7:113-22.
10. Rogan WJ, Gladen BC, McKinney JD, et al. Polychlorinated biphenyls (PCBs) and dichlorodiphenyl dichloroethene (DDE) in human milk: effects on growth, morbidity, and duration of lactation. Am J Public Health 1987;77:1294-7.
11. Savage EP, Keefe TJ, Tessari JD, et al. National study of chlorinated hydrocarbon insecticide residues in human milk, USA. I. Geographic distribution of dieldrin, heptachlor, heptachlor epoxide, chlordane, oxychlordane, and mirex. Am J Epidemiol 1981;113:413-22.
12. Scribner JD, Mottet NK. DDT acceleration of mammary gland tumors induced in the male Sprague-Dawley rat by 2-acetamidophenanthrene. Carcinogenesis 1981;2:1235-9.
13. Robison AK, Sirbasku DA, Stancel GM. DDT supports the growth of an estrogen-responsive tumor. Toxicol Lett 1985;27:109-13.
14. Wassermann M, Nogueira DP, Tomatis L, et al. Organochlorine compounds in neoplastic and adjacent apparently normal breast tissue. Bull Environ Contam Toxicol 1976;15:478-84.
15. Falck F Jr, Ricci A Jr, Wolff MS, Godbold J, Deckers P. Pesticides and polychlorinated biphenyl residues in human breast lipids and their relation to breast cancer. Arch Environ Health 1992;47:143-6.
16. Dewailly E, Dodin S, Verreault R, et al. High organochlorine body burden in women with estrogen receptor-positive breast cancer. J Natl Cancer Inst 1994;86:232-4.
17. van't Veer P, Lobbezoo IE, Martin-Moreno JM, et al. DDT (dichlorophane) and postmenopausal breast cancer in Europe: case-control study. BMJ 1997;315:81-5.
18. Wolff MS, Toniolo PG, Lee EW, Rivera M, Dubin N. Blood levels of organochlorine residues and risk of breast cancer. J Natl Cancer Inst 1993; 85:648-52.
19. Krieger N, Wolff MS, Hiatt RA, Rivera M, Vogelman J, Orentreich N. Breast cancer and serum organochlorines: a prospective study among white, black, and Asian women. J Natl Cancer Inst 1994;86:589-99.
20. Anderson LE. DDT and breast cancer: the verdict isn't in. J Natl Cancer Inst 1994;86:576-7.
21. Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. N Engl J Med 1995;332:1589-93.
22. Wolff MS, Rivera M, Baker DB. Detection limits of organochlorine pesticides and related compounds in blood serum. Bull Environ Contam Toxicol 1991;47:499-503.
23. Laden F, Wolff MS, Nigiduka NJ, Spiegelman D, Hankinson SE, Hunter DJ. Reduced aliquot size for a plasma organochlorine assay for use in epidemiological studies. Cancer Epidemiol Biomarkers Prev 1997;6:333-8.
24. Long GL, Winefordner JD. Limit of detection: a closer look at the IUPAC definition. Anal Chem 1983;55:712A-724A.
25. Allain CC, Poon LS, Chan CS, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. Clin Chem 1974;20:470-5.
26. Phillips DL, Pirkle JL, Burse VW, Bernert JT Jr, Henderson LO, Needham LL. Chlorinated hydrocarbon levels in human serum: effects of fasting and feeding. Arch Environ Contam Toxicol 1989;18:495-500.
27. Rosner B. Fundamentals of biostatistics. 4th ed. Belmont, Calif.: Duxbury Press, 1995:551-84.
28. Breslow NE, Day NE. Statistical methods in cancer research. Vol. 1. The analysis of case-control studies. Lyon, France: International Agency for Research on Cancer, 1980:249-79. (IARC scientific publications no. 32.)
29. Safe SH. Environmental and dietary estrogens and human health: is there a problem? Environ Health Perspect 1995;103:346-51.
30. Rogan WJ, Gladen BC, McKinney JD, et al. Polychlorinated biphenyls (PCBs) and dichlorodiphenyl dichloroethene (DDE) in human milk: effects of maternal factors and previous lactation. Am J Public Health 1986; 76:172-7.
31. Gammon MD, Wolff MS, Neugut AI, et al. Treatment for breast cancer and blood levels of chlorinated hydrocarbons. Cancer Epidemiol Biomarkers Prev 1996;5:467-71.
32. Gammon MD, Wolff MS, Neugut AI, et al. Temporal variation in chlorinated hydrocarbons in healthy women. Cancer Epidemiol Biomarkers Prev 1997;6:327-32.
33. Wolff MS, Fischbein A, Selikoff IJ. Changes in PCB serum concentrations among capacitor manufacturing workers. Environ Res 1992;59:202-16.

Editorials

XENOESTROGENS AND BREAST CANCER

CHEMOPHOBIA, the unreasonable fear of chemicals, is a common public reaction to scientific or media reports suggesting that exposure to various environmental contaminants may pose a threat to health. The specter of cancer, birth defects, and irreversible effects on infants and children invariably scares people and leads to demands for action. During the past five to six years, there has been widespread scientific debate and media coverage concerning a new potential threat to human health — environmental exposure to chemicals with endocrinologic activity. Attention has focused primarily on the weakly estrogenic organochlorine pollutants, including commercially produced chemicals such as polychlorinated biphenyls (PCBs), the pesticide 2,2-bis(*p*-chlorophenyl)-1,1,1-trichloroethane (DDT), and its stable breakdown product 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE). Both PCBs and DDE are persistent environmental contaminants that have been identified throughout the global ecosystem, including in fish, wildlife, and human tissue, blood, and milk. Some have suggested that organochlorine xenoestrogens and related compounds contribute to the increased incidence of breast cancer in women, a worldwide decrease in sperm counts and male reproductive capacity, and neurodevelopmental deficits in children.[1-3]

Specific compounds have been linked to various health problems, including cancer, as a result of occupational exposure to high levels of these chemicals; however, scientific evidence of adverse effects of low-level environmental exposure to chemicals is difficult to obtain and validate. In order to link environmental exposure to a toxic or carcinogenic effect there must be correlations between the level of exposure and the magnitude or incidence of the response, consistent results from several studies, biologic plausibility based on results of studies in laboratory animals, and if possible, evidence based on high levels of exposure in humans.

In 1993, Wolff and coworkers[4] analyzed DDE and PCB levels in serum samples from 58 women in whom breast cancer was diagnosed within six months after enrollment in the New York University Women's Health Study. In this nested case–control study, the mean (±SD) DDE and PCB levels were 11.0±9.1 and 8.0±4.1 ng per milliliter, respectively, in patients with breast cancer and 7.7±6.8 and 6.7±2.9 ng per milliliter in controls. Further analysis showed a fourfold increase in the risk of breast cancer as DDE levels increased from 2.0 ng per milliliter (10th percentile) to 19.1 ng per milliliter (90th percentile). The authors concluded that "these findings suggest that environmental contamination with organochlorine residues may be an important etiologic factor in breast cancer" and that "the implications are far-reaching for public health intervention worldwide."

Previous studies included relatively small numbers of patients with breast cancer, and the correlations with organochlorine levels were variable. The correlations reported between DDE levels and breast cancer attracted national media coverage and contributed to the belief that exposure to industrially derived xenoestrogens was a risk factor for breast cancer in women.[5] This hypothesis is one reason that Congress recommended that the National Cancer Institute initiate studies of clusters of breast cancer on Long Island and in the Northeast.

Although the degree of exposure to estrogens over a lifetime is known to be a risk factor for breast cancer, the biologic plausibility of the xenoestrogen hypothesis can be criticized on several counts.[6-8] Most of the organochlorine pollutants, including PCBs and DDT or DDE, are only weakly estrogenic, and these compounds can both exacerbate and protect against mammary cancer in laboratory animals. High levels of exposure to DDT have not previously been associated with an increased risk of breast cancer, and there is no increase in the risk of breast cancer among women who are exposed to relatively high levels of PCBs at work.[8] Moreover, the incidence of breast cancer has increased in industrialized countries over the past 20 years, but the environmental levels of most organochlorine contaminants have decreased as a consequence of strict regulations regarding their use and disposal. In addition, the average diet contains very low concentrations of antiestrogenic organochlorine compounds, such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (dioxin), and higher levels of naturally occurring estrogenic and antiestrogenic compounds, which are abundant in fruits, nuts, and vegetables.

In this issue of the *Journal*, Hunter and coworkers[9] report on blood levels of DDE and PCBs in women with breast cancer and matched controls from the Nurses' Health Study, which includes 121,700 women from 11 states. The mean (±SD) level of DDE was 6.01±4.56 ng per milliliter in 236 women with breast cancer and 6.97±5.99 ng per milliliter in their matched controls, and the mean level of PCBs was 5.08±2.51 ng per milliliter in 230 women with breast cancer and 5.16±2.26 ng per milliliter in controls. After extensive analysis, the authors concluded that their "data do not support the hypothesis that exposure to DDT and PCBs increases the risk of breast cancer."

Krieger and coworkers[10] used a nested case–control design to study serum DDE and PCB levels in 150 patients with breast cancer (50 white, 50 black,

and 50 Asian women) from the San Francisco Bay area, another high-risk area for breast cancer, and matched controls. Serum levels of DDE and PCBs were not significantly different in the two groups, and the investigators concluded that their data "did not support the hypothesis that exposure to DDE and PCBs increases the risk of breast cancer."

A recent European study[11] compared DDE levels in adipose tissue in 265 postmenopausal women with breast cancer and 341 controls from centers in Germany, the Netherlands, Northern Ireland, and Spain. The mean DDE levels were 1.35 μg per gram of tissue in patients with breast cancer and 1.5 μg per gram in the controls. Again, the conclusion was that the study "does not support the hypothesis that DDE increases risk of breast cancer in postmenopausal women in Europe."

Serum or adipose-tissue levels of DDE are relatively low in North American and European women because DDT has been banned for over 20 years. This has not been the case in all countries. In Mexico DDT is still used as an insecticide, and environmental levels of DDE are higher than in the United States. A recent study[12] reported that mean serum levels of DDE in 141 patients with breast cancer from three referral hospitals in Mexico City and 141 age-matched controls were 562.48±676.18 and 505.46±567.22 parts per billion, respectively. These values are not significantly different, and the investigators concluded that the findings "do not lend support to the hypothesis that DDT is causally related to breast cancer at body burden levels found in our study population."

Robbins and coworkers[13] recently showed that the high incidence of breast cancer in women from the San Francisco Bay area can be accounted for by known risk factors, including parity, age at first full-term pregnancy, months of breast-feeding, age at menopause, age at menarche, and alcohol consumption. It is possible that the confirmed clusters of breast cancer on Long Island and in other regions of the Northeast[14] may also be explained by known risk factors. The results of Hunter et al.[9] along with those of other recent studies[10-12] should reassure the public that weakly estrogenic organochlorine compounds such as PCBs, DDT, and DDE are not a cause of breast cancer. The public has a right to be responsibly informed about both confirmed and hypothesized threats to health, particularly from environmental exposure. However, it is incumbent on scientists, the media, legislators, and regulators to distinguish between scientific evidence and hypothesis, and not to allow a "paparazzi science" approach to these problems.

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REFERENCES

1. Hunter DJ, Kelsey KT. Pesticide residues and breast cancer: the harvest of a silent spring? J Natl Cancer Inst 1993;85:598-9.
2. Colborn T, vom Saal FS, Soto AM. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. Environ Health Perspect 1993;101:378-84.
3. Sharpe RM, Skakkebaek NE. Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? Lancet 1993;341: 1392-5.
4. Wolff MS, Toniolo PG, Lee EW, Rivera M, Dubin N. Blood levels of organochlorine residues and risk of breast cancer. J Natl Cancer Inst 1993; 85:648-52.
5. Davis DL, Bradlow HL, Wolff M, Woodruff T, Hoel DG, Anton-Culver H. Medical hypothesis: xenoestrogens as preventable causes of breast cancer. Environ Health Perspect 1993;101:372-7.
6. Safe SH. Environmental and dietary estrogens and human health: is there a problem? Environ Health Perspect 1995;103:346-51.
7. *Idem*. Is there an association between exposure to environmental estrogens and breast cancer? Environ Health Perspect 1997;105:Suppl 3:675-8.
8. Adami HO, Lipworth L, Titus-Ernstoff L, et al. Organochlorine compounds and estrogen-related cancers in women. Cancer Causes Control 1995;6:551-66.
9. Hunter DJ, Hankinson SE, Laden F, et al. Plasma organochlorine levels and the risk of breast cancer. N Engl J Med 1997;337:1253-8.
10. Krieger N, Wolff MS, Hiatt RA, Rivera M, Vogelman J, Orentreich N. Breast cancer and serum organochlorines: a prospective study among white, black, and Asian women. J Natl Cancer Inst 1994;86:589-99.
11. van't Veer P, Lobbezoo IE, Martin-Moreno JM, et al. DDT (dichlorodiphenyltrichloroethane) and postmenopausal breast cancer in Europe: case-control study. BMJ 1997;315:81-5.
12. López-Carrillo L, Blair A, López-Cervantes M, et al. Dichlorodiphenyltrichloroethane serum levels and breast cancer risk: a case-control study from Mexico. Cancer Res 1997;57:3728-32.
13. Robbins AS, Brescianini S, Kelsey JL. Regional differences in known risk factors and the higher incidence of breast cancer in San Francisco. J Natl Cancer Inst 1997;89:960-5.
14. Kulldorff M, Feuer EJ, Miller BA, Freedman LS. Breast cancer clusters in the northeast United States: a geographic analysis. Am J Epidemiol 1997;146:161-70.

LIMITING THERAPY FOR LIMITED CHILDHOOD NON-HODGKIN'S LYMPHOMA

DURING the first half of this century, surgery and radiation were the only effective treatments for cancer, and cure was possible only in patients with localized disease. The introduction of chemotherapy in the late 1940s has had a disappointingly limited effect on overall cancer mortality rates but a dramatic effect on mortality rates for specific cancers. In children with lymphomas, for example, the expectancy of cure is excellent. Several chemotherapy protocols now offer a chance of permanent eradication of the disease in 80 to 90 percent of patients, depending on the histologic subtype.[1-4] This remarkable result has not been achieved without cost or without a certain reluctance to abandon the treatments that once offered the only chance of survival. In Hodgkin's disease, for example, the addition of chemotherapy to radiation therapy has been associated with both excellent survival rates and a high frequency of secondary effects, including heart disease