Cancer Mortality and Environmental Exposure to DDE in the United States

Pierluigi Cocco,[1] Neely Kazerouni,[2] and Shelia Hoar Zahm[2]

[1]Institute of Occupational Medicine, University of Cagliari, Cagliari, Italy; [2]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA

To explore the role of DDE, the major and most persistent DDT derivative, in cancer etiology, we examined the association of the 1968 adipose DDE levels of population samples from 22 U.S. states with age-adjusted mortality rates between 1975 and 1994 for multiple myeloma; non-Hodgkin lymphoma (NHL); and cancer of the breast, corpus uteri, liver, and pancreas. Separate analyses were conducted by gender and race. Covariates in the regression models included average per-capita income, percent metropolitan residents, and the population density. Liver cancer mortality increased significantly with adipose DDE levels in both sexes among whites, but not among African Americans. No association was observed for pancreatic cancer and multiple myeloma. Breast cancer mortality was inversely correlated with adipose DDE levels among both white and African American women. Significant inverse correlations were also observed for uterine cancer among white women, whereas no association was observed for African Americans and for NHL among whites (men and women) and African American women. The results for pancreatic cancer, multiple myeloma, NHL, breast cancer, and uterine cancer did not support the hypothesis of an association with past adipose levels of the DDT derivative DDE. The multivariate analysis confirmed most findings. The association between liver cancer and DDE observed among whites, particularly in view of the occurrence of hepatic neoplasms in laboratory animals exposed to DDT, warrants further investigation. *Key words*: breast cancer, cancer of the corpus uteri, DDE, DDT, environment, epidemiology, liver cancer, multiple myeloma, non-Hodgkin lymphoma, pancreatic cancer. *Environ Health Perspect* 108:1–4 (2000). [Online 22 November 1999]
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Agricultural use of the insecticide DDT was banned in 1973 in the United States and in most Western countries. However, some Eastern European countries and numerous developing countries still use DDT, primarily in the prevention of malaria, typhus, yellow fever, and sleeping sickness (*1*). The current industrial production of DDT is only a small fraction of the 80,000 tons produced in 1963. However, concern exists over possible health consequences of its indiscriminate use in the past because of its prolonged half-life and biologic persistence, which may extend over several decades, particularly in temperate climates (*1*). The ability of the prevalent isomer of the major and most persistent DDT derivative, p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE), to bind to the androgen receptor in male rats has been reported (*2*). In 1991, the International Agency for Research on Cancer evaluated the evidence of DDT carcinogenicity as sufficient in experimental animals (*1*). Subcutaneous injection and oral administration of DDT and its metabolites such as DDE and dichlorodiphenyldichloroethane were followed by a dose-related increase of liver tumors in mice and rats. Results were less consistent for malignant lymphomas, lung carcinomas, and thyroid tumors (*1*). Concern has been expressed about the possible link between

environmental exposure to organochlorines and an increase in incidence of various cancers among humans (*3*).

Epidemiologic data on cancer risk associated with exposure to DDT are suggestive, but limitations in the exposure assessment and the finding of small and inconsistent excesses complicate the interpretation. Elevated risks of non-Hodgkin lymphoma (NHL) in relation to potential exposure to DDT has been found in Washington State (*4*) and in Sweden (*5*). A slight increase of leukemia occurred among Iowa farmers that used DDT and had other agricultural exposures (*6*). A case–control study on pancreatic cancer found a strong dose-related association with exposure to DDT (*7*) although its positive results have not been replicated thus far. Breast cancer risk has also been repeatedly associated with increased adipose and serum levels of DDE in the general population (*8–11*), although more recent studies yield contradictory or negative results (*12–16*). The p,p'-DDE concentration was elevated in the tumor tissue of patients suffering from uterine cancer as compared to the surrounding normal tissue (*17*), although the risk of endometrial cancer was not increased in relation to serum p,p'-DDE concentrations (*18*). A preliminary study of the mortality experience of DDT applicators in Sardinia, Italy, found an

increase in mortality from liver cancer and multiple myeloma (*19*).

To explore the hypothesis of a link between mortality from six cancer sites, namely liver, pancreas, breast, corpus uteri, multiple myeloma, and NHL, and exposure to the DDT derivative DDE in the United States, we examined the correlation between cancer mortality rates and the past DDE concentration in the subcutaneous adipose tissue of population samples from 22 states in the United States.

Methods

Data on DDE concentrations in the subcutaneous fat of population samples of 22 U.S. states (Alabama, Arkansas, California, Connecticut, Delaware, Georgia, Illinois, Indiana, Louisiana, Massachusetts, Missouri, Nevada, New Mexico, New York, North Carolina, Ohio, Pennsylvania, South Dakota, Tennessee, Texas, Washington, and Wisconsin) were obtained from a U.S. Environmental Protection Agency (EPA) human monitoring program report of 1968 data (*20*). The report provided data on average level of DDE (micrograms per gram) and sample size by state and race. Based on the estimated half-life of organochlorines in the human body (7 years for DDT, several decades for DDE) (*21*), and on latency considerations in human cancerogenesis, we compared state-specific adipose DDE levels in 1968 to standardized mortality rates in 1975–1994.

Age-adjusted mortality rates from cancers of the liver, pancreas, breast, and corpus uteri;

multiple myeloma; and NHL in 1975–1994, overall and every 5 years, specific by U.S. state and by race, were provided by the National Center for Health Statistics in computerized form. The 1970 U.S. population was the standard. Multiple linear regression analysis was conducted with SPSS (SPSS, Inc., Chicago, IL), using the REGRESSION feature.

Information on possible confounders of the association between DDE environmental contamination and mortality from the six cancers was available from public resources (22). We selected average per capita income, percent of state population living in metropolitan areas, population density, birth rate, and abortion rate per 1,000 live births. The two last variables were used to construct a pregnancy rate. Only three covariates (per capita income, metropolitan residence, and population density) were correlated with one or more cancer sites and they were included in the multiple linear regression models. No adipose DDE measurements were available in three states for African Americans; therefore, analyses for African Americans were restricted to 19 states. These analyses were conducted using a weighted regression procedure, with the size of the population sample surveyed by the U.S. EPA in each state in 1968 as the weight.

The statistical significance of the regression coefficients (β) was calculated from the ratio of β and its standard error, which has a *t* distribution under the null hypothesis. Two-tailed tests were used to assess statistical significance.

Results

Adipose DDE levels showed a strong positive correlation ($r = 0.746$; $p = 0.0002$) between whites and African Americans, indicating that interstate variations were in the same direction in both race groups (Figure 1). In addition, such high correlation provides partial reassurance for our decision to use those measurements as indicators of environmental contamination from DDT across U.S. states. Adipose DDE levels were 74% higher among
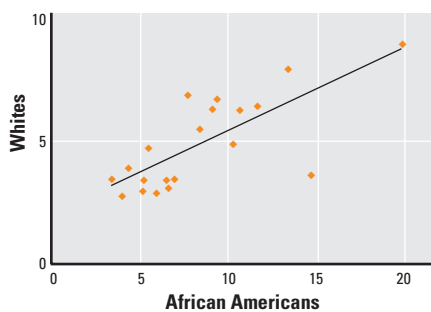
African Americans as compared to whites over the 19 U.S. states with measurements available for both race groups (African Americans 8.49 μg/g ± 4.16; whites 4.88 μg/g ± 1.87; $t = 6.69$; $p < 0.001$) (Figure 2).

Table 1 shows the correlation matrix of socioeconomic variables and adipose DDE with mortality from each cancer site in the four study groups. Annual income and metropolitan residence showed a significant correlation with liver cancer mortality among African Americans and with pancreatic cancer mortality among white women. Annual income, metropolitan residence, and population density were significantly correlated with breast cancer mortality among white women, whereas only metropolitan residence showed a significant association among African

American women. Pregnancy rate was not related to breast cancer mortality in either race group. None of the socioeconomic variables were correlated with mortality from uterine cancer. Population density was associated with NHL mortality among men, but not among women. Metropolitan residence was inversely related with multiple myeloma among African American men and white women. A weak positive correlation was also observed with population density among white men.

In the univariate analysis (Table 1), liver cancer mortality increased with increasing levels of adipose DDE among white men and women, but not among African Americans. Mortality from pancreatic cancer and multiple myeloma did not vary according to DDE
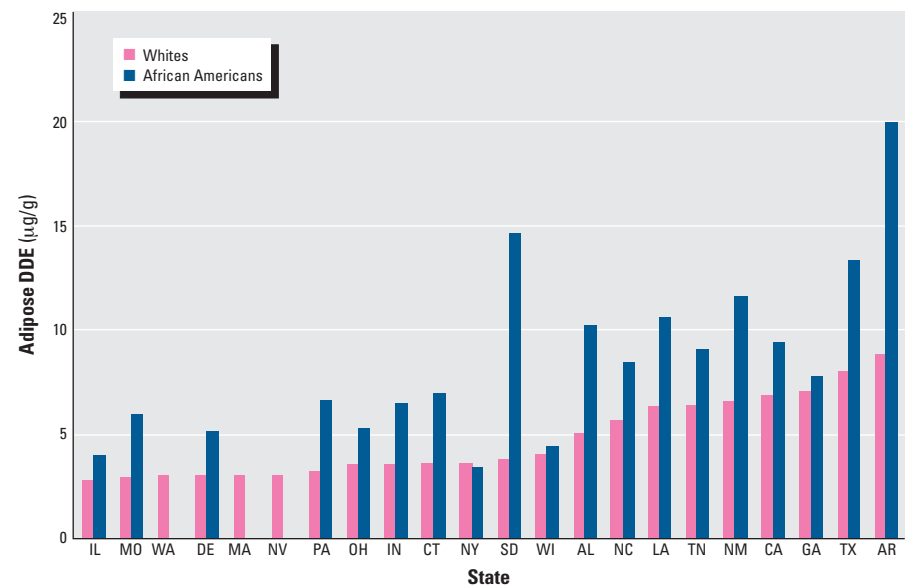
Figure 2. Adipose DDE levels in population samples of 22 U.S. states (*20*).

Table 1. Mortality from six cancers associated with socioeconomic factors and adipose DDE in 22 U.S. states: correlation coefficients from univariate analysis.

Cancer site	Study group	Annual income	Metropolitan residence	Population density	Pregnancy rate	Adipose DDE
Liver	White men	0.193	0.263	0.190	–	0.416*
	African American men	0.439**	0.547**	0.162	–	-0.378
	White women	-0.197	0.245	0.066	–	0.413*
	African American women	0.377*	0.525**	0.229	–	-0.250
Pancreas	White men	-0.082	0.107	0.063	–	0.041
	African American men	-0.272	-0.183	-0.001	–	-0.199
	White women	0.457**	0.361*	0.083	–	-0.126
	African American women	-0.080	-0.100	-0.070	–	-0.118
Breast	White women	0.573**	0.539**	0.553**	0.112	-0.731**
	African American women	0.299	0.565*	0.258	0.142	-0.501*
Corpus uteri	White women	0.022	0.183	0.143	0.064	-0.632**
	African American women	0.115	0.129	0.242	0.221	0.023
Multiple myeloma	White men	0.097	0.199	0.311	–	0.205
	African American men	0.330	-0.448*	-0.117	–	0.026
	White women	0.293	-0.329	0.149	–	-0.123
	African American women	0.213	-0.018	-0.080	–	0.053
Non-Hodgkin lymphoma	White men	-0.037	0.240	0.394*	–	-0.471*
	African American men	0.273	0.114	0.301	–	-0.218
	White women	0.137	0.118	0.013	–	-0.507*
	African American women	0.053	-0.293	0.068	–	-0.497*

*$p < 0.05$. **$p < 0.01$.

Figure 1. Correlation between adipose *p,p´*-dichlorodiphenyldichloroethylene levels among whites and African Americans in 19 U.S. states (*20*). $R = 0.746$, $p < 0.001$.

levels in any of the study groups. Breast cancer mortality among women showed a significant inverse correlation with DDE levels among either race group. Mortality from cancer of the corpus uteri was also inversely correlated with adipose DDE levels, but only among whites. An inverse correlation was also observed with NHL mortality in three of the four study groups.

The multivariate analysis (Table 2) confirmed the increase in liver cancer mortality with increasing adipose DDE levels among whites, which was significant only among men, whereas no association was observed among African Americans. None of the other cancer sites under investigation showed a positive association with DDE levels. Cancer of the breast and corpus uteri were both inversely affected by DDE levels, and the regression coefficients were highly significant among white women. NHL mortality also decreased with increasing DDE levels, but only among whites. With regard to socioeconomic covariates in the regression models, metropolitan residence was significantly associated with NHL mortality and liver cancer mortality, respectively, in three and two of four study groups. The association was still positive, although nonsignificant, in the remaining study groups for either cancer site. Breast cancer mortality was also positively associated with metropolitan residence, but only among white women. In the multivariate models, state population density did not affect cancer mortality rates, perhaps because of the adjustment for metropolitan residence. Average annual income was inversely associated with liver cancer mortality in three of four study groups, but the regression coefficient was significant only among white

women. We also explored the same associations by 5-year periods from 1975 onward. The results confirmed our observation using mortality rates over the entire study period.

Discussion

Our exploratory epidemiologic exercise showed no evidence of a consistently significant increase in mortality with increasing adipose DDE levels measured in 1968. A positive association was observed for liver cancer, but only among whites. Mortality from breast cancer, uterine cancer, and NHL was inversely related to DDE levels in one or more study groups. Remarkably, the association between adipose DDE and liver cancer mortality was not significant in the first decade, but it became statistically significant from 1985 onward among white women and in 1990–1994 among white men.

Ecologic analysis—such as the one reported here—is only a preliminary step in the epidemiologic inquiry of human health effects after exposure to environmental contaminants. The advantages of low cost and quick execution are counterbalanced by the potential for bias, resulting from assumptions that the whole population of a given geographic area shares the same level of exposure to environmental contaminants, a problem referred to as the "ecological fallacy" (23). Race and low social class are important determinants of geographic variability in environmental exposure and risk of disease (24). Indeed, based on the EPA human monitoring data, African Americans had adipose DDE levels 74% higher than whites on average. We used state average annual income in the multivariate model to account for this confounding effect. Another weakness of this analysis is that we used mortality rather than incidence rates.

Results for cancers with better survival rates, such as breast cancer and NHL, could have been more severely affected.

An association between exposure to DDT and liver cancer was suggested by experimental studies (1) and a recent proportional mortality study (19). Our results are only partially consistent with these reports because of differences in race. Earlier reports of an increase in breast cancer risk associated with increasing adipose and serum DDE levels (8–11) were not supported by other recent studies showing no association (13–16). Our results are consistent with these latter reports. The risk of endometrial cancer was not increased in relation to serum p,p'-DDE levels (18), whereas levels of DDT and its derivatives were higher in the leiomyomatous tissue as compared to the surrounding normal uterine tissue (17). Cancers arising from the endometrium and from the muscular walls of the corpus uteri are jointly considered in the *International Classification of Diseases, 9th revision* (World Health Organization, Geneva) coding of the causes of death on which the death statistics were based. In our analysis, mortality from cancer of the corpus uteri was not associated with adipose DDE levels. A pooled analysis of three case–control studies of NHL among U.S. male farmers did not show consistent evidence for an association with exposure to DDT (25). In our study, we found a negative association, if any. We did not find evidence of a positive association with pancreatic cancer and multiple myeloma, in contrast to previous epidemiologic and pathologic reports (7,19). Although our study may provide partial reassurance on the magnitude of cancer risk associated with environmental exposure to the DDT derivative DDE, its limitations and the vast public

Table 2. Mortality from six cancers associated with socioeconomic risk factors and adipose DDE in 22 U.S. states: multivariate analysis.

Cancer site	Study group	Constant	Annual income	Metropolitan residence	Population density	Adipose DDE
Liver	White men	1.553 (0.978)	0.015 (0.121)	0.013 (0.010)	–	0.163 (0.065)*
	African American men	7.002 (2.584)*	-0.479 (0.294)	0.065 (0.028)*	–	-0.096 (0.088)
	White women	2.043 (0.353)**	-0.147 (0.044)**	0.013 (0.004)**	–	0.034 (0.023)
	African American women	2.741 (1.064)*	-0.203 (0.121)	0.027 (0.011)*	–	-0.021 (0.036)
Pancreas	White men	9.625 (1.093)**	0.037 (0.135)	0.001 (0.011)	–	0.026 (0.073)
	African American men	2.562 (4.112)**	0.702 (0.468)	-0.072 (0.044)	–	-0.104 (0.140)
	White women	5.062 (0.910)**	0.077 (0.112)	0.013 (0.009)	–	0.014 (0.060)
	African American women	8.056 (2.228)**	0.213 (0.253)	-0.003 (0.024)	–	0.010 (0.076)
Breast	White women	24.294 (3.761)**	0.237 (0.502)	0.057 (0.030)	0.001 (0.003)	-0.947 (0.205)**
	African American women	34.656 (7.817)**	-0.633 (1.018)	0.065 (0.063)	-0.001 (0.007)	-0.401 (0.196)
Corpus uteri	White women	1.262 (0.742)	0.135 (0.099)	-0.001 (0.006)	-0.001 (0.001)	-0.130 (0.040)*
	African American women	3.171 (2.981)	0.216 (0.388)	-0.032 (0.024)	0.000 (0.003)	-0.028 (0.075)
Multiple myeloma	White men	3.808 (0.398)**	-0.062 (0.053)	0.002 (0.003)	–	-0.009 (0.022)
	African American men	6.846 (2.856)**	0.036 (0.372)	-0.007 (0.023)	–	0.008 (0.072)
	White women	2.401 (0.243)**	-0.027 (0.032)	0.001 (0.002)	–	-0.010 (0.013)
	African American women	4.362 (4.349)	0.249 (0.566)	-0.023 (0.035)	–	-0.022 (0.109)
Non-Hodgkin lymphoma	White men	6.829 (0.452)**	–	0.015 (0.006)*	-0.001 (0.001)	-0.135 (0.055)*
	African American men	3.404 (0.923)**	–	0.018 (0.011)	-0.001 (0.001)	0.023 (0.044)
	White women	4.842 (0.241)**	–	0.006 (0.003)**	-0.000 (0.000)	-0.073 (0.030)*
	African American women	2.066 (0.536)**	–	0.014 (0.006)	-0.000 (0.001)	-0.018 (0.025)

*$p < 0.05$. **$p < 0.01$.

concern on this matter point toward the need for more analytic research to confirm or reject the hypotheses raised by the few positive reports published to date.

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