Mortality from Cancer of the Male Reproductive Tract and Environmental Exposure to the Anti-Androgen \( p,p' \)-Dichlorodiphenyl dichloroethylene in the United States

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**Key Words**  
Environment  
Epidemiology  
Dichlorodiphenyltrichloroethane (DDT)  
\( p,p' \)-Dichlorodiphenyldichloroethylene (\( p,p' \)-DDE)  
Prostate cancer  
Testicular cancer

**Abstract**  
The association of prostate cancer mortality and testicular cancer mortality with environmental exposure to the antiandrogen dichlorodiphenyldichloroethane (DDT) derivative \( p,p' \)-dichlorodiphenyldichloroethylene (\( p,p' \)-DDE) in the USA was explored in the period 1971–1994 using multiple linear regression analysis. Environmental \( p,p' \)-DDE contamination by state was estimated by \( p,p' \)-DDE concentrations in the subcutaneous fat of population samples and by measurements of \( p,p' \)-DDE in tree bark. On average, African Americans had adipose \( p,p' \)-DDE levels 74% higher than Whites (8.49 vs. 4.88 μg/g; \( p < 0.001 \)). Neither prostate cancer mortality nor testicular cancer mortality showed a positive association with either indicator of \( p,p' \)-DDE environmental contamination. On the contrary, the regression coefficient for prostate cancer was constantly inverse for adipose \( p,p' \)-DDE along the period of study, although it approached statistical significance only for African Americans in 1981–1985 (\( \beta = -0.755; 0.10 > p > 0.05 \)). This ecologic study does not provide support to the hypothesis of a link between environmental exposure to DDT derivatives and cancer of the male reproductive tract.

**Introduction**  
Patterns of mortality from cancer of the male reproductive tract present some similarities: (1) both prostatic and testicular cancers have the lowest incidence rates among Asian countries and the highest among US or European countries, respectively [1], and (2) mortality rates of Asian emigrants to the USA are intermediate between the country of origin and US Whites for both cancers [1]. These geographic patterns suggest an etiologic role of environmental factors.

Also of interest are the contrasting rates of these cancers among Whites and African Americans in the USA. African Americans have the highest mortality rates from prostate cancer in the world (ranging between 65 and 102 \( \times 10^{-5} \)) [1]. These rates are about 50% higher than those among US Whites. In addition, prostate cancer mortality increased among African Americans between 1950 and 1980 [2] but not among Whites [3]. On the other hand, mortality from testicular cancer is 5–6 times higher among US Whites compared to African Americans [1–3], and it decreased between 1950 and 1980 among both...
Whites and African Americans [2, 3], although this was likely due to improved survival, as a global increase in testicular cancer incidence has been reported [4, 5]. These two cancers also peak at different ages, with prostate cancer mortality increasing sharply after the age of 65 years [6], while testicular cancer occurs most frequently at the age of 20–35 years [7]. In addition, while prostate cancer is considered as an androgen-dependent tumor [8], cryptorchidism and other genital anomalies related to a deficiency in adrogen action or biosynthesis during the fetal development [9] are major risk factors for testicular cancer [7, 10].

Recently, an ability of the major and most persistent derivative of dichlorodiphenyltrichloroethane (DDT), p,p′-dichlordiphenyl dichloroethylene (p,p′-DDE), to bind the androgen receptor in male rats has been reported [11, 12], and concern has been expressed that environmental chemicals with hormonal activity may be responsible for a global increase in testicular cancer [4]. However, to the best of our knowledge, no epidemiologic studies have appeared in the literature focusing on this issue. Since binding of p,p′-DDE to androgen receptors could have important effects on prostate and testicular cancer, we thought it would be of interest to evaluate the geographic patterns of mortality of these cancers in relation to environmental exposure to the antiandrogen DDT derivative p,p′-DDE. Associations of occupational exposure to DDT [13, 14] or the body burden of its derivatives [15] with other cancers have been suggested. They are beyond the scope of this paper and will be investigated in the future.

**Methods**

Data on p,p′-DDE concentration in the subcutaneous fat of population samples of 22 US states [16] and data on the concentration of p,p′-DDE in the tree bark of 18 US states [17] were used to explore the association of prostate cancer and testicular cancer mortality with environmental exposure to p,p′-DDE. Adipose p,p′-DDE was measured in 1968 under the US EPA Human Monitoring Program in 22 US states. Average p,p′-DDE (µg/g) and sample size by state and race were available from the US Department of Health, Education and Welfare [16]. Sampling procedure, standard errors, range and gender distribution were not described in this report, and we were unable to retrieve the information elsewhere. We assumed these values to reflect the nationwide variation in global DDT intake in the preceding years, including dietary intake. Based upon the estimated half-life of DDT and its derivatives in the human body [18] and upon considerations of latency between exposure to a carcinogen and diagnosis of tumor disease, we plotted state-specific adipose p,p′-DDE levels in 1968 against standardized mortality rates from prostate cancer and testicular cancer by quinquennium in 1971–1990. Data on tree bark p,p′-DDE were collected by Simonich and Hites [17] worldwide in 1992–1995 and were kindly provided to us upon request. Overall, 24 measurements were available in 18 US states. The methods of collection of tree bark samples were not described with enough detail in Simonich and Hites [17] for us to assess the representativeness of the measurements. When more than one measurement was available in one state, we attributed the median value to that state. Data in nanograms per gram of lipids were log-transformed to approximate a normal distribution more closely. We plotted these data against prostate cancer and testicular cancer mortality in 1986–1994.

Age-adjusted mortality rates from prostate cancer and testicular cancer by quinquennium in 1971–1994, specific by US state, and race were provided by the National Center for Health Statistics in computerized form. The 1970 US population was the standard. Because deaths from testicular cancer among African Americans were too few in several states to provide stable rates, the analysis of this cancer was limited to Whites.

Multiple linear regression analysis was conducted with SAS® using the PROC GLM procedure. Information on possible confounders of the association between p,p′-DDE environmental contamination and prostate cancer or testicular cancer mortality was available from public resources [19]. Selected variables of interest were: population density, percent age of state population resident in metropolitan areas, percent increase in resident population between 1980 and 1990, percentage of population aged ≤18 years, birth rate, marriage rate, infant mortality rate, abortion rate per 1,000 live births, average per capita income, agricultural production as percent gross state product, electric power production and electric power installed in million kilowatts, number of farms, average farm size in acres and circulating automobiles per 1,000 residents. As a surrogate for human fertility, for each state the pregnancy rate per 1,000 residents (Pr) was calculated as Pr = Br + (Br·Ar/1,000), where Br and Ar are the birth rate per 1,000 residents and the legal abortion rate per 1,000 live births for that year, respectively. Variables showing a significant correlation with prostate cancer mortality and testicular cancer mortality include: pregnancy rate and average annual income for both cancers, marriage rate for prostate cancer and percent state population resident in metropolitan areas for testicular cancer. These covariates were fitted in the multiple linear regression model together with adipose p,p′-DDE or tree bark p,p′-DDE. The State of Nevada was not considered for the multiple linear regression analyses of prostate cancer mortality, since its marriage rate was 6 times greater than the average across the other US states, more likely reflecting a common behavior in the US population instead of a demographic characteristic of the local population. No adipose p,p′-DDE measurements were available in three states for African Americans, and one of these was Nevada. Therefore, the analysis of prostate cancer mortality in relation to adipose p,p′-DDE levels was conducted in 21 states for Whites and in 19 states for African Americans. All 22 states contributed to the analysis of testicular cancer in relation to adipose p,p′-DDE levels. These analyses were conducted using a weighted regression procedure, with the size of the population sample surveyed by EPA in each state in 1968 as the weight. The analyses of prostate cancer and testicular cancer in relation to tree bark p,p′-DDE were conducted in 17 states (again Nevada was excluded) and 18 states, respectively. 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

At least one \( p,p' \)-DDE measurement was available for 30 US states. Both adipose \( p,p' \)-DDE and tree bark \( p,p' \)-DDE were available for 10 states for Whites and 8 states for African Americans (table 1). The two measurements showed a weak positive correlation among Whites (\( r = 0.358; p = \text{n.s.} \)) but not among African Americans (\( r = 0.172; p = \text{n.s.} \)). Adipose \( p,p' \)-DDE levels among Whites and among African Americans showed a strong positive correlation (\( r = 0.746; p = 0.0002 \)), indicating that interstate variations were in the same direction in both race groups. This provided partial reassurance about our decision to use those measurements as indicators of environmental contamination from DDT across US states, in spite of the unknown reliability. Also, exposure to DDT was greater among African Americans, whose adipose \( p,p' \)-DDE levels were 74% higher than those of Whites over the 19 US states with measurements available for both race groups (African Americans: \( 8.49 \pm 4.16 \mu g/g; \) Whites: \( 4.88 \pm 1.87 \mu g/g; t = 6.69; p < 0.001 \)).

The results of the multivariate analyses are reported in tables 2 and 3 for prostate cancer and in table 4 for testicular cancer. The same regression model was applied to mortality data in 5 consecutive 5-year periods in 1971–1994, using adipose \( p,p' \)-DDE levels through 1990 and tree bark \( p,p' \)-DDE concentrations from 1986 onwards, as indicators of environmental exposure to DDT. In all regression models for prostate cancer mortality, the regression coefficient for adipose \( p,p' \)-DDE was consistently inverse among both race groups, although it approached statistical significance only for African Americans in 1981–1985, who also showed steeper slopes all along the period of study. None of the other covariates showed a similar consistency by race, although significant inverse regression coefficients were observed for marriage rate (Whites and African Americans) and income (African Americans).

Among regression coefficients of \( p,p' \)-DDE in the regression model predicting testicular cancer mortality among Whites, all but one were inverse, and none approached statistical significance. Among the other covariates, testicular cancer mortality increased significantly with percent metropolitan population and it decreased significantly with average per capita income in 1986–1990, while results of opposite sign were observed in 1971–1980.

| Table 1. Average adipose \( p,p' \)-DDE among Whites and African Americans, tree bark \( p,p' \)-DDE by state in the USA |
|---------------------------------|-----------------|-----------------|
| **State** | **Adipose \( p,p' \)-DDE, \( \mu g/g \)** | **Tree bark \( p,p' \)-DDE** |
| | **Whites** | **African Americans** | **ng/g lipids** | **ln 10- ng/g lipids** |
| Alabama | 4.90 | 10.20 | 7.44 | 2.01 |
| Alaska | 8.75 | 19.75 | 2,550.35 | 10.15 |
| Arizona | 6.66 | 9.28 | 32.23 | 5.78 |
| Arkansas | 3.48 | 6.85 | 6.85 | 7.62 |
| California | 6.85 | 10.56 | 38.63 | 5.96 |
| Connecticut | 2.78 | 3.92 | 11.70 | 4.76 |
| Delaware | 3.45 | 6.39 | 71.86 | 6.58 |
| Georgia | 6.24 | 10.56 | 2.97 |
| Hawaii | 6.85 | 10.56 | 181.89 | 7.51 |
| Illinois | 2.90 | 5.82 | 89.40 | 6.80 |
| Indiana | 2.98 | 5.82 | 8.75 | 4.47 |
| Louisiana | 3.50 | 3.31 | 833.25 | 9.03 |
| Massachusetts | 5.50 | 8.29 | 477.30 | 8.47 |
| Michigan | 3.44 | 5.13 | 181.89 | 7.51 |
| Missouri | 3.11 | 6.50 | 0.00 | 0.00 |
| Nevada | 3.66 | 14.56 | 10.36 | 4.64 |
| New Mexico | 7.86 | 13.28 | 859.25 | 9.06 |
| New York | 2.95 | 4.26 | 55.30 | 6.31 |
| Ohio | 3.97 | 4.26 | 17.44 | 5.16 |
| Oregon | 17.44 | 5.16 | 17.44 | 5.16 |

Discussion

The ability of \( p,p' \)-DDE, the major and most persistent DDT derivative, to antagonize androgens by linking to the same receptor has recently been reported [11]. In an experimental study, \( p,p' \)-DDE was the most potent inhibitor of \([3H]5\alpha\)-dihydrotestosterone among all xenobiotics tested, causing a 100% dihydrotestosterone inhibition by binding to the androgen receptor prepared from frozen rat prostates [12]. Early animal studies have suggested a causative association between environmental endocrine disruptors and decreased testicular weight and an increased frequency of genital malformations [20]. Therefore, since cryptorchidism, the major risk factor for this
### Table 2. Regression parameters of prostate cancer mortality among Whites and African Americans in 1971–1990

| Years   | Race   | Intercept | Adipose \(p,p\)-DDE | Income   | Marriage rate | Pregnancy rate |
|---------|--------|-----------|-----------------------|----------|---------------|----------------|
| 1971–1975 | Whites | 20.282 (2.919) | –0.220 (0.150) | 0.285 (0.477) | 0.207 (0.122) | –0.122 (0.072) |
|         | AAs    | 61.867 (19.589) | –0.372 (0.562) | –1.124 (3.293) | –1.319 (0.996) | –0.004 (0.006) |
| 1976–1980 | Whites | 21.754 (3.216) | –0.012 (0.153) | 0.565 (0.401) | –0.092 (0.106) | –0.160 (0.075)* |
|         | AAs    | 81.012 (12.524) | –0.620 (0.365) | –1.846 (1.571) | –1.357 (0.550)* | –0.519 (0.325) |
| 1981–1985 | Whites | 19.987 (2.985) | –0.187 (0.175) | 0.213 (0.248) | –0.123 (0.157) | 0.068 (0.109)  |
|         | AAs    | 83.832 (12.524) | –0.755 (0.373) | –2.674 (1.075)* | –0.992 (0.680) | 0.132 (0.491)  |
| 1986–1990 | Whites | 28.373 (3.289) | –0.131 (0.210) | –0.153 (0.214) | –0.334 (0.225) | 0.008 (0.098)  |
|         | AAs    | 91.295 (20.267) | –0.440 (0.643) | –1.125 (1.550) | –0.703 (0.597) |

Standard errors are given in parentheses. The regression model includes adipose \(p,p\)-DDE as the indicator of exposure to DDT. AAs = African Americans. * \(p < 0.05\).

### Table 3. Regression parameters of prostate cancer mortality among Whites and African Americans in 1986–1994

| Years   | Race   | Intercept | Tree bark \(p,p\)-DDE | Income   | Marriage rate | Pregnancy rate |
|---------|--------|-----------|------------------------|----------|---------------|----------------|
| 1986–1990 | Whites | 37.570 (6.384) | –0.073 (0.207) | –0.717 (0.846) | –0.669 (0.301)* | 0.037 (0.230)  |
|         | AAs    | –32.050 (51.110) | –0.865 (1.660) | 9.422 (6.770) | –1.219 (2.407) | –0.370 (1.844) |
| 1991–1994 | Whites | 41.156 (5.025) | 0.017 (0.173) | –0.571 (0.353) | –0.644 (0.258)* | –0.054 (0.187) |
|         | AAs    | 11.328 (29.011) | –0.773 (0.875) | 2.801 (1.911) | 1.368 (1.385)  | –0.587 (0.926) |

Standard errors are given in parentheses. The regression model includes tree bark \(p,p\)-DDE as the indicator of exposure to DDT. AAs = African Americans. * \(p < 0.05\).

### Table 4. Regression parameters of testicular cancer mortality among Whites

| Years   | Model | Intercept | \(p,p\)-DDE | Income | % metropolitan residents | Pregnancy rate |
|---------|-------|-----------|-------------|--------|--------------------------|---------------|
| 1971–1975 | 1     | 0.570 (0.271) | –0.007 (0.020) | 0.139 (0.088) | –0.003 (0.002) | –0.005 (0.009) |
| 1976–1980 | 1     | 0.100 (0.274) | –0.006 (0.017) | 0.082 (0.060) | –0.001 (0.002) | 0.003 (0.008)  |
| 1981–1985 | 1     | 0.329 (0.106) | –0.005 (0.007) | –0.015 (0.015) | 0.002 (0.001)* | 0.002 (0.004)  |
| 1986–1990 | 2     | 0.544 (0.139) | –0.018 (0.011) | –0.068 (0.016)* | 0.004 (0.001)* | 0.010 (0.006)  |
|         | 2     | 0.536 (0.227) | –0.001 (0.008) | –0.058 (0.030) | 0.004 (0.001)* | 0.005 (0.008)  |
| 1991–1994 | 2     | 0.281 (0.233) | 0.014 (0.010) | –0.020 (0.021) | –0.00009 (0.002) | 0.011 (0.010)  |

Standard errors are given in parentheses. Model 1: with adipose \(p,p\)-DDE; model 2: with tree bark \(p,p\)-DDE. * \(p < 0.01\).

1 Approaching statistical significance: 0.10 > \(p > 0.05\).
cancer, is reportedly related to a deficient androgen activity during the fetal development, one of the study hypotheses was a positive association between testicular cancer and exposure to \( p,p'-\text{DDE} \) [9]. Indeed, hypotheses linking a worldwide increase in testicular cancer incidence to environmental exposure to organochlorines have been made [21, 22] but remain controversial [23]. On the contrary, prostate cancer is an androgen-dependent tumor [8], and therefore it would be expected to decrease in relation to environmental exposure to \( p,p'-\text{DDE} \), if its levels are or have been biologically effective.

Our results do not support the hypothesis of a causal link between environmental exposure to DDT derivatives and mortality from cancer of the male reproductive tract. On the contrary, the most regression coefficients of both \( p,p'-\text{DDE} \) measurements were inverse for prostate cancer mortality in either race group and for testicular cancer among Whites. However, the modest reliability of exposure indicators and the lack of statistically significant findings prevent discussing the hypothesis of an inverse association between environmental exposure to \( p,p'-\text{DDE} \) and prostate cancer occurrence based solely on the present results. Due to its biological plausibility, testing such a hypothesis with analytic studies is warranted.

Two measures of DDT contamination were used in the present study to explore the association between prostate cancer and testicular cancer mortality with environmental exposure to \( p,p'-\text{DDE} \). Adipose \( p,p'-\text{DDE} \) was measured in 1968 when the pesticide was still in use; we considered nationwide differences as reflecting the geographical variation of global DDT intake in the immediately preceding years, including dietary intake. Tree bark \( p,p'-\text{DDE} \) concentration in 1992–1995 may be related to past local use of the pesticide and/or to drift of volatile compounds through the atmosphere from warm regions of the world, where the pesticide is still produced and used, to colder latitudes where volatile atmospheric contaminants more easily condense [17]. The weak positive correlation between the two measurements perhaps results from their different meaning, as well as from the long time interval separating them. Measures of DDT alone as well as total DDT, including DDT, DDE and dichlorodiphenyldichloroethane, were also available from the same sources. We used \( p,p'-\text{DDE} \) because it is the major and most persistent DDT derivative, and it may better resume historic contamination, while total DDT and DDT alone would be more representative of contamination from recent uses of the pesticide [1]. Also, tree bark DDT readings gave null values in two thirds of the measurements (16 out of 24) further pointing to \( p,p'-\text{DDE} \) as the most suitable indicator of past contamination from DDT.

As DDT deposition is also a function of latitude [17], we might have adjusted the regression coefficients associated with tree bark \( p,p'-\text{DDE} \) also by latitude. This strategy would be mostly suitable if a strong association existed between latitude and mortality from prostate cancer and testicular cancer. We are not aware of this association worldwide, although the highest incidence rates of testicular cancer are being reported in northern and western Europe [5]. Also, the geographic pattern of prostate cancer mortality among African Americans in the USA seems more related to farming than latitude [24].

Ecologic studies are only a first step in the epidemiologic inquiry of human health effects following exposure to environmental contaminants. The advantages of low cost and quick execution are counterbalanced by the potential for bias [25], resulting from assuming that the whole population of a given geographic area shares the same level of exposure to environmental contaminants, a problem referred to as the ‘ecologic fallacy’. Clearly, low social class, low annual income and race are important determinants of geographic variability in environmental exposure [26]. Indeed, based on the EPA Human Monitoring data, African Americans had adipose \( p,p'-\text{DDE} \) levels 74% higher than Whites on average.

Another weakness of this analysis is that we used mortality rather than incidence rates. This could be misleading in view of the high survival from testicular cancer and, to a lesser extent, from prostate cancer [9]. The positive, although not statistically significant, correlation between 1973–1977 incidence [27] and 1976–1980 mortality rates observed (testicular cancer: \( r = 0.403, p = 0.25 \); prostate cancer: \( r = 0.560, p = 0.09 \)) is of partial reassurance in this respect.

In conclusion, we did not find evidence of a positive association of prostate cancer mortality and testicular cancer mortality with \( p,p'-\text{DDE} \) environmental contamination. Furthermore, these results suggest that higher incidence and mortality from prostate cancer among African Americans compared to Whites is not explained by their higher level of environmental exposure to DDT derivatives. Weaknesses inherent to the ecologic study design, the limited statistical power of the present analysis and the uncertain reliability of exposure indicators prevent interpreting our findings as more than a mere suggestion of an inverse association of cancer of the male reproductive tract with environmental exposure to \( p,p'-\text{DDE} \). However, in view of the biological plausibility of this association for prostate cancer, further research is warranted.
Male Reproductive Cancer and \( p,p'-\text{DDE} \)

**Acknowledgements**

This work was initiated while P.C. was a guest researcher and J.B. an investigator at the Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Md., USA. The work of P.C. was supported by funding from the International Union against Cancer (Geneva, Switzerland) and the NCI/EORTC Exchange Program (Brussels, Belgium). The authors are also grateful to Mr. Dan Grauman, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Md., USA, for his collaboration in providing data on mortality rates by state in the USA, and to Dr. Ronald A. Hites, Indiana University, Bloomington, Ind., USA, who kindly provided data on levels of tree bark \( p,p'-\text{DDE} \) in the USA.

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