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Plasma levels of dichlorodiphenyldichloroethene (DDE) and dichlorodiphenyltrichloroethane (DDT) and survival following breast cancer in the Carolina Breast Cancer Study

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Abstract

Objectives: To examine plasma levels of dichlorodiphenyldichloroethene (DDE) and dichlorodiphenyltrichloroethane (DDT) in association with survival among women with breast cancer who participated in a population-based case-control study.

Methods: Participants included 456 white and 292 black women from the Carolina Breast Cancer Study Phase I who were diagnosed with primary invasive breast cancer from 1993–1996, and who had available DDE/DDT and lipid measurements from blood samples obtained on average 4.1 months after diagnosis. Using the National Death Index, we identified 392 deaths (210 from breast cancer) over a median follow-up of 20.6 years. We used Cox regression to estimate covariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause and breast cancer-specific 5-year mortality, and 20-year mortality conditional on 5-year survival, for lipid-standardized DDE and DDT levels. Associations stratified by race and estrogen receptor (ER) status were also examined.

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Conflict of interest:

The authors declare they have no conflict of interest.

Ethical standards: All procedures performed in the Carolina Breast Cancer Study involving human participants were in accordance with the ethical standards of the Institutional Review Boards of the University of North Carolina at Chapel Hill and were in compliance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Ethical approval: Informed consent was obtained from all individual participants included in the study.

Results: The highest versus lowest DDE tertile and the highest vs non-detectable DDT quantile were associated with HRs of 1.95 (95%CI=1.31–2.92) and 1.64 (95%CI=1.10–2.44), respectively, for 20-year conditional all-cause mortality. DDE levels above versus below the median were associated with a HR of 1.69 (95%CI=1.06–2.68) for 20-year conditional breast cancer-specific mortality among women overall, and HRs were 2.36 (95%CI=1.03–5.42) among black women and 1.57 (95%CI=0.86–2.89) among white women ($P_{\text{Interaction}}=0.42$), and 3.24 (95%CI=1.38–7.58) among women with ER⁻ tumors and 1.29 (95%CI=0.73–2.28) among women with ER⁺ tumors ($P_{\text{Interaction}}=0.03$).

Conclusion: Exposure to DDE/DDT may adversely impact overall and breast cancer-specific survival. DDE exposure may contribute to the racial disparities in breast cancer survival.

Keywords

organochlorine compounds; DDT; DDE; pesticides; breast cancer; survival

Introduction

The broad-spectrum organochlorine insecticide dichlorodiphenyltrichloroethane (DDT) was introduced into the United States (US) in the 1940's for agricultural and residential use (1). DDT was used widely and indiscriminately for decades; however, its use was restricted in the US in the late 1960's and eventually banned in 1972 due to growing environmental and health concerns (1). DDT and its metabolite, dichlorodiphenyldichloroethene (DDE), are lipophilic and thus bioaccumulate in adipose tissues (2). Additionally, DDT is designated as a probable human carcinogen by the International Agency for Research on Cancer (IARC) based on evidence of association with non-Hodgkin lymphoma and testicular and liver cancers (3) while DDE is designated as a probable human carcinogen by the US Environmental Protection Agency (EPA) based on increased incidence of liver tumors in mice and hamsters and of thyroid tumors in female rats (4). Furthermore, DDT and DDE are well-known endocrine disruptors (5). Given these characteristics, it was hypothesized that DDT and DDE exposure may impact risk of developing breast cancer (6), a hormone-dependent tumor and the most frequently diagnosed cancer among US women (7). While initial cohort studies reported elevated risks of breast cancer among women with high blood levels of DDT or DDE (8,9), subsequent studies generally failed to link these chemicals to the development of breast cancer (10,11). However, studies suggest that exposure to DDT and DDE during developmentally sensitive periods, including in utero (12) or early life (13), may increase the risk of developing breast cancer.

Tamoxifen, a selective estrogen receptor (ER) modulator, is a central component of ER⁺ breast cancer treatment as it inhibits cell growth by binding to and inhibiting the ER thereby reducing the likelihood of breast cancer progression and recurrence (14). It is therefore plausible that exposure to exogenous compounds that show hormonal activity including DDT and DDE (15), influences relevant pathways involved in breast cancer progression. The few studies conducted to date to test this hypothesis suggest that these and other organochlorine compounds (16–20) may impact recurrence or survival following breast cancer. Furthermore, despite consistently higher measured DDT/DDE levels among US black women as compared to white women (9,21), including a previous analysis of the

Carolina Breast Cancer Study (CBCS) (22), to our knowledge, no prospective studies have considered whether differences in DDT/DDE exposure contributes to the US racial disparities in breast cancer survival. Today, five-year survival is estimated at 90% among white women, but only 81% among black women (23).

In this study, we examined the associations between plasma levels of organochlorine compounds DDE and DDT and all-cause and breast cancer-specific survival among white and black women who participated in a population-based North Carolina study. Given our previous work identifying higher organochlorine levels (22) and higher mortality rates (24) among black women as compared to white women the CBCS, we hypothesized that higher levels of DDT/DDE would be associated with worse survival following breast cancer diagnosis.

Methods

Study population

This study included 456 white women, 98% of whom were Caucasian, and 292 black women diagnosed with first primary invasive breast cancer from 1993–1996 with available DDT and DDE and lipid measurements available who participated in the CBCS Phase I. The CBCS Phase I was a population-based case-control study of breast cancer with follow-up for mortality among women diagnosed with breast cancer, as previously reported (25). During May 1993–December 1996, the CBCS enrolled and interviewed 861 women with (and 790 women without) breast cancer in 24 counties of North Carolina. Approximately 98% of participants who were interviewed in-person by nurses using a standardized questionnaire provided, on average within 4.1 months of diagnosis (range=0.8–19.2 months), three 10 mL blood samples for laboratory analyses, including analyses of organochlorine compounds DDE and DDT. All procedures performed in the CBCS involving human participants were in accordance with the ethical standards of the Institutional Review Boards of the University of North Carolina at Chapel Hill.

Follow-up for Mortality

Date and cause of death were ascertained by linking participants to the National Death Index (NDI), a centralized database of death record information compiled from state vital statistics records (26). Breast cancer-related deaths were identified using International Statistical Classification of Diseases (ICD) codes ICD-9–174.9 and ICD-10-C-50.9 listed on the death certificate. Follow-up for mortality occurred from date of diagnosis in 1993–1996 until December 31, 2016. The median survival time for the 748 women included in this study was 20.6 years (min=0.4, max=23.7 years). Over the 20 years of follow-up, 392 women died from any cause, and of these, 210 died from breast cancer.

Laboratory Assessment

DDE and DDT levels were measured in plasma samples using gas chromatography/electron capture detection, as previously described (22). In brief, 2.0 mL plasma samples were treated with 1.0 mL methanol, spiked with a surrogate standard, and then extracted with three 2.5 mL portions of hexane:diethyl ether (1:1). The extract was fractionated using

Florisil (R) open-column chromatography and the fraction was eluted with 35 mL of hexane, which contained *p,p'*-DDE, *o,p'*-DDE, and DDT. This fraction was concentrated to 0.5 mL and spiked with octachloronaphthalene as an external quantitation standard. The extract was analyzed by gas chromatography/electron capture detection using a DB-5 column and Hewlett-Packard Model 6890 instrument. Individual compounds were identified based upon chromatographic retention times relative to the internal standards and pattern recognition in the sample extract. Values below the limit of detection (LOD=0.0625 ng/mL), one *p-p'*-DDE value (0.1%) and 473 DDT values (63.2%), were imputed as the LOD divided by the square root of two (27). Because only 1% of participants had detectable levels of *o,p'*-DDE, this isomer was not considered further.

As lipid adjustment of organochlorine levels is recommended to account for non-fasting variation (27) and to more closely approximate adipose tissue levels (28), lipid profiles were measured at the Core Laboratory for Clinical Studies at Washington University School of Medicine (St. Louis, Missouri). As previously described (22), automated enzymatic assays were performed on a Technicon RA-1000 analyzer using cholesterol esterase and lipoprotein lipase. Organochlorine and lipid measurements were available on 748 (84%) women with breast cancer; reasons for failure to obtain laboratory measurements included insufficient plasma and interference in the sample.

Interview and Medical Record Data

As part of the case-control interview, participants were asked about known and suspected breast cancer risk and prognostic factors and demographic characteristics including self-reported race, education, smoking status, and parity and lactation history. At the time of the in-person interview, trained nurses collected anthropometric measurements in duplicate including height (inches) and weight (pounds) to determine body mass index (BMI in kg/m²). Breast cancer disease characteristics including stage at diagnosis, grade, tumor size, nodal status, and ER status, were obtained from medical records.

Statistical Analysis

For our primary analyses, we categorized levels of lipid-standardized DDE into tertiles (0.36, 0.37–1.00, and 1.01 µg/g lipid) and detectable levels of DDT at the median (<LOD, 0.01–0.03, and 0.04 µg/g lipid). We first used Kaplan-Meier survival curves to examine the unadjusted associations between DDE and DDT and all-cause and breast cancer-specific survival and to visually examine the proportional hazards assumption. We also evaluated the proportional hazards assumption by testing interaction terms of the exposure variables with dichotomized time (at 5 years) and by Schoenfeld residuals. We observed a divergence in the survival curves five years following breast cancer diagnosis. This interaction with time was supported by time-by-exposure interactions (all $P < 0.01$) and by the Schoenfeld residuals; residuals were significantly correlated with time, ln-time, or time² for DDE and DDT and all-cause mortality (all $P < 0.05$), but not breast cancer-specific mortality (all $P > 0.10$). Given the violations in the proportional hazards assumption, in multivariable models, examined associations within five years of diagnosis, as well as 20 years after diagnosis conditional on 5-year survival using Cox regression with a Heaviside function. We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between tertiles of lipid-

standardized DDE levels and quantiles of DDT and all-cause and breast cancer-specific mortality. We first adjusted the Cox models for age at diagnosis (continuous in years) and race (black vs. white). We then also included adjustment for smoking status (never, former, and current smoker), education (less than high school, high school, and college or greater), BMI (<25.0, 25.0–29.9, 30.0 kg/m²), parity/lactation history (nulliparous, parous/never lactated, parous/ever lactated), stage (III/IV vs. I/II), and ER status (ER⁺ vs. ER⁻). We used Efron's approximation for tied event times (29). Estimates for linear trends (i.e., HRs and corresponding 95% CIs) used continuous natural log-transformed and log₂-transformed lipid-standardized DDE/DDT levels in age- and race-adjusted and in full covariate-adjusted regression models. For full covariate-adjusted models, we also report the *P*-values for linear trend (*P*_{Trend}). In sensitivity analyses, we examined associations between wet weight concentrations with and without adjustment for lipids in the regression models given that all three approaches may vary depending on the assumptions of the underlying causal structure (30).

For our secondary analyses in which we examined effect measure modification by race and ER status, DDE and DDT levels were categorized at the median (>0.58 vs. 0.58 µg/g lipid) and at the LOD, respectively. We first adjusted the Cox models for age at diagnosis and race, as appropriate. We then included adjustment for smoking status, education, BMI, parity/lactation history, stage, and ER status, as appropriate. For DDT models stratified by race, we also compared models with and without adjustment for ER status, as ER status may mediate the association between DDT and breast cancer-specific mortality (31). Effect modification was evaluated by stratifying the Cox models by race (black vs. white) and ER status (ER⁻ vs. ER⁺). We also evaluated in full covariate-adjusted regression models, continuous log₂-transformed lipid-standardized DDE/DDT levels-by covariate interactions (i.e., *P*_{Interaction}). Last, using results of the Cox model we estimated the partial attributable fractions (PAR_p) and their corresponding 95% CIs for DDE among black women and white women separately for 20-year breast cancer-specific mortality using the publicly available SAS PAR Macro (<https://www.hsph.harvard.edu/donna-spiegelman/software/par/>) as outlined by Hertzmark, Wand, and Spiegelman (32,33).

All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) and were based on participants with complete data (i.e., complete-case analysis).

Results

Participant characteristics for the 748 women with invasive breast cancer included in this study, overall and by DDE tertiles, are reported in Table 1. Black women had mean DDE levels that were three times higher than those of white women (1.96 vs. 0.66 µg/g lipid), as previously reported for this group of women (22). Mean DDE levels were also higher among women aged ≥50 years than those <50 at diagnosis (1.71 vs. 0.78 µg/g lipid), among never smokers than among former smokers (1.28 vs. 0.93 µg/g lipid), among women with a less than high school than some college or greater education (2.37 vs. 0.76 µg/g lipid), and among women with breast cancer stages III/IV than stages I/II (1.57 vs. 1.11 µg/g lipid).

Patterns for lipid-standardized DDT quantiles by participant characteristics were similar to those observed for DDE (Supplemental Table 1).

Breast Cancer-Specific Mortality

In the Kaplan-Meier survival curves, there was no difference in the breast cancer survival rates by DDE tertiles or DDT quantiles within the first five years of diagnosis (Figure 1). After five years of diagnosis, however, the survival curves diverged, with lower survival rates among women with the highest ($1.01 \mu\text{g/g}$ lipid) versus lowest ($0.36 \mu\text{g/g}$ lipid) DDE tertiles and among women with the highest ($0.04 \mu\text{g/g}$ lipid) versus non-detectable DDT quantiles. In the covariate-stratified Kaplan-Meier survival curves, DDE levels above versus below the median were associated with lower survival rates among black women, but not among white women, and DDE-survival associations were more pronounced among women with ER⁻ tumors than among women with ER⁺ tumors (Figure 2).

Detectable versus non-detectable DDT levels were associated with lower survival among white women, but not among black women, and DDT-survival associations were more pronounced among women with ER⁻ tumors than among women with ER⁺ tumors (Supplemental Figure 1).

Consistent with the Kaplan-Meier survival curves, in the Cox regression analyses, lipid-standardized DDE and DDT levels were not associated with 5-year breast cancer-specific mortality. The highest (vs. lowest) tertile of DDE was associated with a HR of 1.79 (95% CI=1.06–3.03) for 20-year conditional breast cancer-specific mortality, in age and race-adjusted models (Table 2). However, this association was attenuated (HR=1.50, 95% CI=0.85–2.65; $P_{\text{Trend}}=0.17$) after further adjustment for demographic and tumor characteristics. When categorized at the median, DDE levels above versus below the median were associated with a HR of breast cancer-specific mortality of 1.69 (95% CI=1.06–2.68) (Table 3). HRs for 20-year conditional breast cancer-specific mortality for DDE levels above versus below the median were elevated more so among black women (HR=2.36, 95% CI=1.03–5.42) than among white women (HR=1.57, 95% CI=0.86–2.89; $P_{\text{Interaction}}=0.42$), and among women with ER⁻ tumors (HR=3.24, 95% CI=1.38–7.58) than among women with ER⁺ tumors (HR=1.29, 95% CI=0.73–2.28; $P_{\text{Interaction}}=0.03$) (Table 3). Furthermore, among black women the attributable fraction (PAR_p) for DDE for 20-year conditional breast cancer-specific mortality was 0.304 (95% CI= -0.103 to 0.624) whereas it was 0.162 (95% CI= -0.142 to 0.439) among white women. That is, among black women and white women, 30.4% and 16.2% of breast cancer-specific deaths, respectively, can be prevented if DDE exposure above versus below the median is eliminated from the population, while the distribution of other modifiable and non-modifiable risk factors is unchanged.

The highest (vs. non-detectable) quantile of DDT was associated with a HR of 1.59 (95% CI=0.91–2.78) for 20-year conditional breast cancer-specific mortality in models adjusted for age and race, but this association was attenuated (HR=1.07, 95% CI=0.56–2.01) after full covariate adjustment. We observed little evidence of effect measure modification for DDT by race and ER status in full covariate-adjusted models (Table 3). However, the HRs adjusted for all covariates except ER status were slightly more elevated among black

women (HR=1.48, 95% CI=0.73–2.99) than among white women (HR=1.43, 95% CI=0.71–2.86), though not after adjustment for ER status (HR among black women=1.31, 95% CI=0.62–2.73 vs. HR among white women=1.37, 95% CI=0.66–2.83) ($P_{\text{Interaction}}=0.70$). Furthermore, HRs were slightly more elevated among women with ER⁻ tumors (HR=1.43, 95% CI=0.64–3.19) than among women with ER⁺ tumors (HR=1.18, 95% CI=0.62–2.26) in full covariate-adjusted models ($P_{\text{Interaction}}=0.76$).

Results using wet weight concentrations with and without covariate adjustment for lipids were similar to those in which we used lipid-standardized concentrations (Supplemental Table 2) with two notable exceptions. First, the HRs for 5-year breast cancer-specific mortality for the highest (versus lowest) tertiles of DDE were 1.19 (95% CI=0.67–2.12) in lipid-adjusted models, 1.13 (95% CI=0.64–1.99) in lipid-unadjusted models, and 1.01 (95% CI=0.58–1.77) in lipid-standardized models. Second, the HRs for 20-year breast cancer-specific mortality for the highest quantile (vs. non-detectable) of DDT were associated with HRs of 1.35 (95% CI=0.72–2.51) in lipid-adjusted models, 1.30 (95% CI=0.70–2.41) in lipid-unadjusted models, and 1.07 (95% CI=0.56–2.01) in lipid-standardized models.

All-Cause Mortality

From the Kaplan-Meier curves, increasing DDE and DDT levels were associated with worse overall survival (Figure 1). In the Cox regression analyses lipid-standardized DDE and DDT levels were not associated with 5-year all-cause mortality; however, the highest (vs. lowest) DDE tertile and the highest detectable (vs. undetectable) DDT quantile were associated with HRs for 20-year conditional all-cause mortality of 1.95 (95% CI=1.31–2.92) and 1.64 (95% CI=1.10–2.44), respectively, after full covariate adjustment (Table 2). These associations exhibited dose-response relationships as supported by the trend analyses. A one-unit increase in ln-transformed DDE levels was associated with an 18% increase in the rate of all-cause mortality [ln(DDE) HR=1.18, 95% CI=1.03–1.36], while a doubling of levels was associated with an 12% increase in the rate of all-cause mortality [$\log_2(\text{DDE})$ HR=1.12, 95% CI=1.02–1.24] ($P_{\text{Trend}}=0.02$). A one-unit increase in ln-transformed DDT levels was associated with an 19% increase in the rate of all-cause mortality [ln(DDT) HR=1.19, 95% CI=1.02–1.39], while a doubling of levels was associated with an 13% increase in the rate of all-cause mortality [$\log_2(\text{DDT})$ HR=1.13, 95% CI=1.01–1.25] ($P_{\text{Trend}}=0.03$). As shown in Supplemental Table 3, patterns of effect measure modification by race for all-cause mortality were similar to those for breast cancer-specific mortality. However, there was little evidence of effect measure modification by race for DDT and all-cause mortality.

Discussion

In this study of organochlorine compounds DDE and DDT and survival following breast cancer, we observed higher rates of long-term (i.e., 20 years post-diagnosis) all-cause and breast cancer-specific mortality among women with high lipid-standardized plasma DDE levels compared to women with low levels. Furthermore, in stratified analyses, breast cancer-specific mortality rates were elevated 136% among black women, but only elevated

57% among white women, and elevated 224% among with ER⁻ tumors, but elevated only 29% among women with ER⁺ tumors. Detectable versus undetectable levels of DDT were also associated with increased rates of long-term all-cause mortality, but not breast cancer-specific mortality.

Few studies have prospectively investigated organochlorine pesticides in association with all-cause or breast cancer-specific mortality following breast cancer (16,17,20), and to our knowledge, no studies have examined these exposures within the context of racial breast cancer survival disparities. In the study by Høyer et al. of overall, but not breast cancer-specific survival among 195 Danish women with breast cancer, women with the highest versus lowest DDE quartile had a two-fold increase in overall mortality risk over a median six year follow-up (17). However, this association was evident only in models in which a second blood sample collected five years after enrollment was considered, and the association was attenuated in models adjusted for tumor characteristics. In a follow-up to their study, Høyer et al. examined organochlorine compounds and overall survival according to ER status (34). The association between DDE and overall breast cancer survival did not vary by ER status; however, their follow-up study was underpowered to examine effect modification by ER status as only 161 ($n=116$ ER⁺ and $n=45$ ER⁻) women were included. In a second study of 633 predominantly Caucasian US women with breast cancer, the highest versus lowest DDT tertile was associated with HRs for all-cause and breast cancer-specific mortality of 2.19 and 2.72, respectively, at five years post-diagnosis; however, the associations were attenuated 15 years post-diagnosis (16), which was not consistent with the pattern for DDT in our study. Also, in contrast to our findings reported here, in that study, the third versus first DDE tertile was inversely associated with 15-year all-cause and breast cancer-specific mortality (16). A recently published study of organochlorine compounds measured in adipose tissue from 399 postmenopausal Danish women and breast cancer survival reported inverse association between increasing DDE/DDT levels and overall mortality over a median follow-up of eight years (20), also in contrast to our findings reported. Reasons for the inconsistencies between previous studies and our results reported here may be due in part to the differences in the exposure distributions and to the type of blood sample used. In the study by Parada et al., 92% of women had detectable DDT levels (16), whereas only 37% of women in our study had detectable DDT levels. Furthermore, women in our study had the highest mean lipid-standardized DDE levels (mean=1.96 µg/lipid) as compared to women in the studies by Parada et al. (mean=0.672 µg/lipid) (16) and Høyer et al. (mean=1.38 µg/lipid) (17). However, we measured DDE and DDT in plasma, whereas Parada et al. and Høyer et al. used serum samples. A previous study comparing organic compound concentrations measured in various types of blood samples from adult volunteers reported consistently higher compound concentrations in plasma as compared to whole blood and dried blood spot samples (35).

Our results for DDE of higher rates of breast cancer-specific mortality and a larger attributable fraction for DDE among black women than among white women may in part be explained by differences in the prevalence or magnitude of exposure or to differences in dietary sources of exposure to DDE/DDT. We observed higher and more extreme DDE levels in black women than among white women, which were associated with worse mortality in black women than among white women thus providing evidence that the excess

for breast cancer mortality among black women may have a contribution from DDT/DDE exposure. Furthermore, our race-stratified models, which were adjusted for ER status, suggest that racial differences in mortality may not be driven entirely by ER status, and vice versa. However, we also note that the ER⁻ basal-like intrinsic subtype is more prevalent among black women compared to white women (24). Thus, the impact of DDE and ER⁻ disease on breast cancer mortality may be synergistic, providing further evidence that DDE exposure contributes to poor breast cancer survival among black women.

As DDT and DDE are endocrine disrupting chemicals (5) and probable human carcinogens (3,4), several biological mechanisms may explain the associations observed here. *In vivo* and *in vitro* laboratory evidence shows that *p,p'*-DDE is not estrogenic (36), but is able to bind to and inhibit androgen binding to the androgen receptor (AR) (37). Previous studies have hypothesized that anti-androgenic chemicals may inhibit breast cancer progression (38), as the AR dimerizes and translocates to the nucleus upon binding of androgen ligands where it binds to androgen response elements (AREs) to promote target gene transcription (39). In the CBCS, we do not have information on AR status; future studies should consider the emerging role of the androgen receptor in the DDE-breast cancer-specific mortality association. Our findings for DDE by ER status are not consistent with mechanisms of endocrine disruption; however, it is possible that DDE/DDT may impact prognosis via other mechanisms including oxidative stress, inflammation, and immune suppression (2). However, in this observational study, we cannot rule out non-causal explanations including random error and bias due to uncontrolled confounding and other sources of error.

Previous studies of women with breast cancer (16,17), as well one study of a national representative sample of US adults 60 years or older (40), have reported increased rates of overall mortality among women with high DDT levels, consistent with our findings reported here. While it is well-established that *p,p'*-DDT is able to bind to the ER (36,41,42), and thus stimulate tumor growth and metastasis in breast cancer, in this study, we observed only modest increases in risk of breast cancer-specific mortality in association with dichotomized DDT. One possible reason for these discrepancies is that most women in the CBCS had non-detectable DDT levels and thus exposure misclassification for DDT, if non-differential with respect to mortality, could have resulted in estimates that were biased towards the null for women of both races. While women in our study were born from 1918–1971, and thus were likely to have been exposed to DDT directly, blood samples were collected in the 1990's. Thus, it is likely that most of the measured DDE was ingested as DDE rather than DDT.

Ours is the largest study to date to prospectively examine the association between DDE/DDT and survival following breast cancer. Additionally, our follow-up of 20+ years allowed us to examine associations with long-term survival, and while previous studies (16,17) have focused on Caucasian women, by design, the CBCS oversampled black women, which allowed us to examine associations by race. Furthermore, ours is the largest study to date to examine these associations by ER status. However, our study had several limitations. First, we relied on a single blood sample measurement taken shortly after diagnosis to examine associations with mortality up to 20+ years post-diagnosis and we only considered two organochlorine compounds. In the study by Høyer et al., repeated exposure assessment improved the accuracy of the measurement (17). However, DDT residues have

biological half-lives ranging from 5–10 years (43,44) and therefore a single measurement may be sufficient to characterize these associations. Additionally, blood samples drawn after diagnosis may also be impacted by breast cancer treatment. However, in the CBCS case-control design, blood DDT/DDE levels were not different when stratified by weight loss or gain, as well as stage of disease (22). Second, although the NDI provides high ascertainment of mortality there is a potential for misclassification of deaths and cause of death. This is likely to be a minor limitation as the sensitivity and specificity of NDI search are estimated to be 98% and approximately 100%, respectively (45). Third, for breast cancer-specific survival estimates, we assumed that censoring was non-informative and we did not consider causes of death other than breast cancer (46). However, our approach accurately estimates the relative hazard (rate) of breast cancer-specific death and thus addresses how death from breast cancer is associated with DDE and DDT (46). Last, the production and use of DDT was banned in the US in 1972 and raises the question of whether these low-level exposures remain relevant to US women diagnosed with breast cancer, though high-level exposure is relevant to women who live in parts of the world where DDT is still actively used for vector control (47). While worldwide DDT and DDE levels have declined since the restriction of DDT production and use (48), diet remains an important source of exposure, albeit at low levels (49) and our results reported here indicate that even at low levels, exposure may be a cause for concern.

Conclusion

In conclusion, in this study of organochlorine compounds DDE and DDT and breast cancer survival among US white and black women, high versus low levels of DDE and DDT were associated with increased rates of long-term all-cause and breast cancer-specific mortality. Furthermore, results of our study indicate that exposure to DDE, but not DDT, may contribute to the racial disparities in breast cancer survival. Breast cancer-specific mortality rates comparing high versus low DDE levels were elevated more so among black women than among white women and among women with ER⁻ tumors than among women with ER⁺ tumors. Because exposure to DDE/DDT may adversely impact overall and breast cancer-specific survival, future studies should consider the impact of other organochlorine compounds, and in particular more contemporary chemicals, alone or in combination, on survival following breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Higher DDE and DDT levels were associated with worse overall survival
- Higher DDE levels were associated with worse breast cancer-specific survival
- Mortality rates were elevated more so among black women than among white women
- Mortality rates were elevated more so among women with ER⁻ than ER⁺ breast cancer

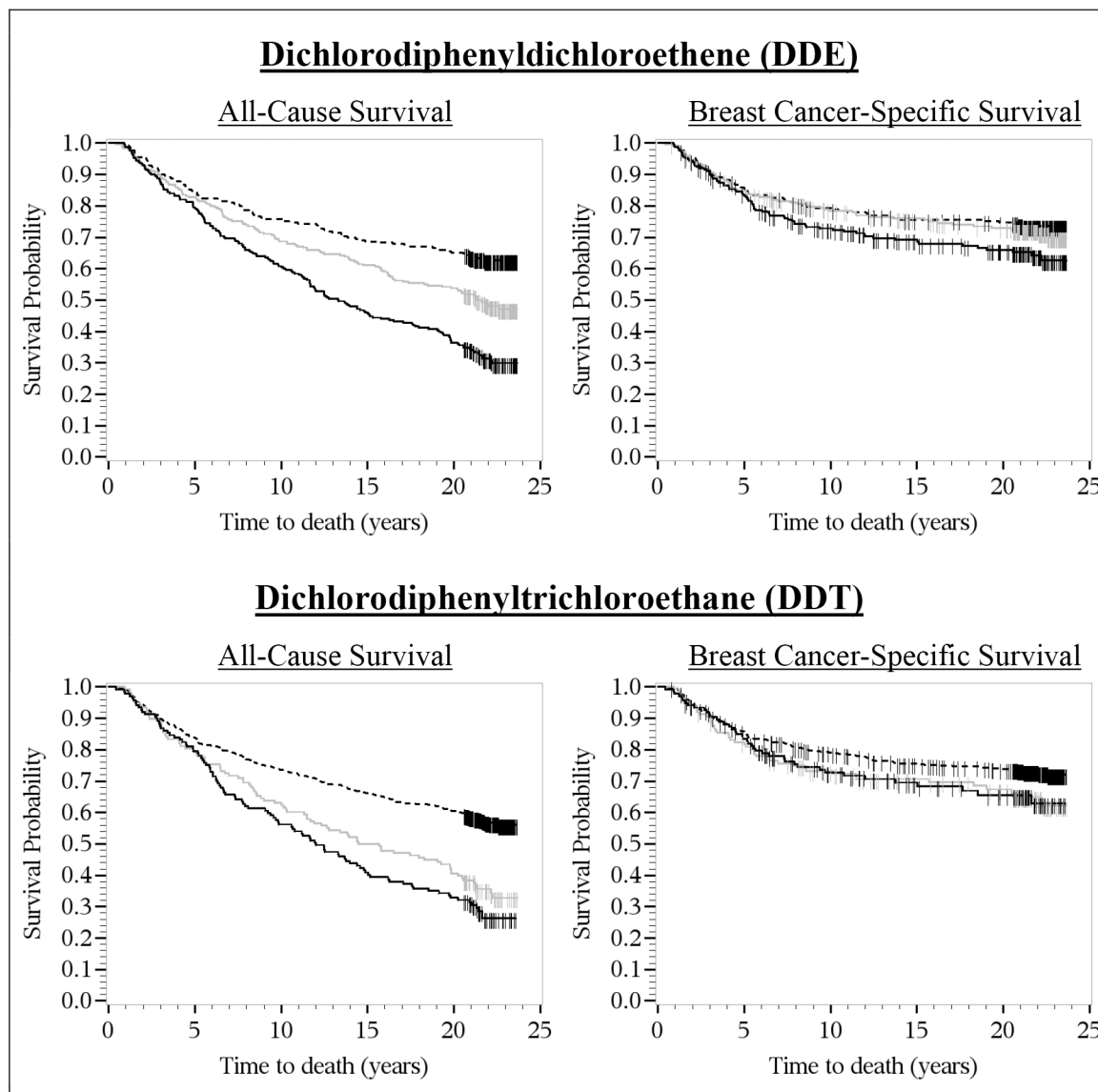


Figure 1.

Kaplan-Meier survival curves for DDE (dashed line, 0.36 µg/g lipid; solid gray line, 0.37–1.00 µg/g lipid; solid black line, 1.01 µg/g lipid) and DDT (dashed line, <LOD; solid gray line, 0.01–0.03 µg/g lipid; solid black line, 0.04 µg/g lipid) and all-cause and breast cancer-specific survival. CBCS women were diagnosed with invasive breast cancer from 1993–1996 and followed-up for vital status through December 31, 2016. The x-axis shows times to death in years; the y-axis shows proportion of participants alive.

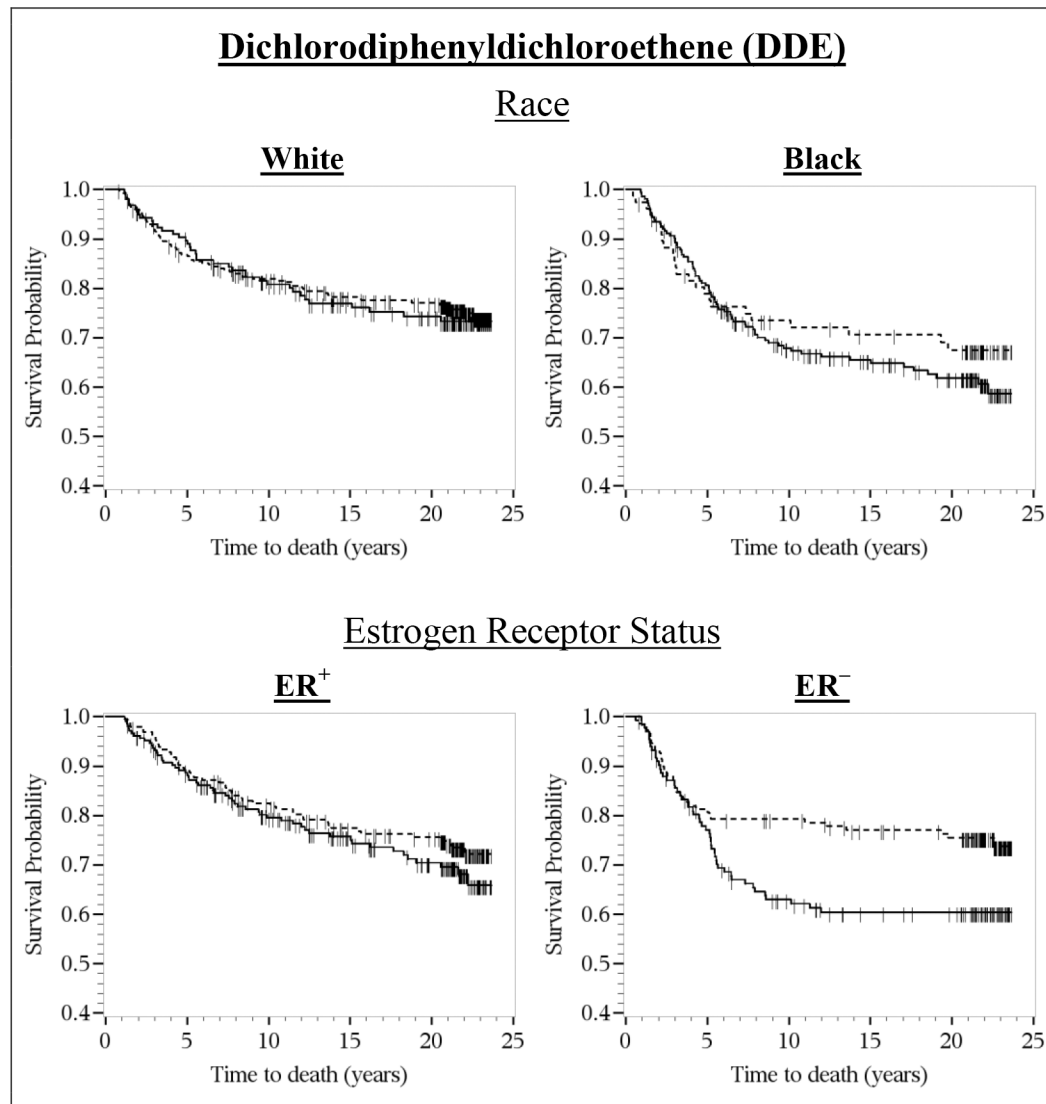


Figure 2.

Kaplan-Meier survival curves for DDE (dashed line, $0.58 \mu\text{g/g}$ lipid; solid line, $>0.58 \mu\text{g/g}$ lipid) and breast cancer-specific survival, overall and by race and estrogen receptor (ER) status. CBCS women were diagnosed with invasive breast cancer from 1993–1996 (Phase I) and followed-up for vital status through December 31, 2016. The x-axis shows times to death in years; the y-axis shows proportion of participants alive.

Table 1.

Characteristics of CBCS Phase I women with invasive breast cancer and with available plasma DDE and lipid data ($n=748$).

Characteristic	<i>n</i> (%)	DDE	DDE Tertiles ($\mu\text{g/g lipid}$)		
		$\mu\text{g/g lipid}$ Mean (SD)	0.36 <i>n</i> (%)	0.37–1.00 <i>n</i> (%)	1.01 <i>n</i> (%)
Race					
White	456 (61.0)	0.66 (0.77)	209 (83.9)	162 (65.1)	85 (34.0)
Black	292 (39.0)	1.96 (2.24)	40 (16.1)	87 (34.9)	165 (66.0)
Age at diagnosis (years)					
<50	438 (58.6)	0.78 (0.93)	197 (79.1)	143 (57.4)	98 (39.2)
50	310 (41.4)	1.71 (2.20)	52 (20.9)	106 (42.6)	152 (60.8)
Education					
Less than high school	137 (18.3)	2.37 (2.85)	25 (10.0)	33 (13.2)	79 (31.6)
High school	281 (37.6)	1.06 (1.18)	74 (29.7)	107 (43.0)	100 (40.0)
Some college or greater	330 (44.1)	0.76 (0.93)	150 (60.2)	109 (43.8)	71 (28.4)
Body mass index (kg/m^2)					
<25.0	221 (30.1)	1.22 (1.72)	63 (26.0)	82 (33.5)	76 (30.8)
25.0–29.9	229 (31.2)	1.51 (1.55)	46 (19.0)	75 (30.6)	108 (43.7)
30.0	284 (38.7)	0.85 (1.61)	133 (55.0)	88 (35.9)	63 (25.5)
Missing	14		7	4	3
Smoking status					
Never	392 (52.4)	1.28 (1.83)	131 (52.6)	120 (48.2)	141 (56.4)
Former	183 (24.5)	0.93 (1.04)	63 (25.3)	62 (24.9)	58 (23.2)
Current	173 (23.1)	1.16 (1.74)	55 (22.1)	67 (26.9)	51 (20.4)
Parity/Lactation history					
Nulliparous	112 (15.0)	1.05 (1.49)	41 (16.5)	35 (14.1)	36 (14.4)
Parous/never lactated	387 (51.7)	1.11 (1.28)	115 (46.2)	134 (53.8)	138 (55.2)
Parous/ever lactated	249 (33.3)	1.30 (2.15)	93 (37.3)	80 (32.1)	76 (30.4)
Stage					
I/II	613 (88.2)	1.11 (1.63)	213 (92.2)	206 (88.4)	194 (84.0)
III/IV	82 (11.8)	1.57 (1.98)	18 (7.8)	27 (11.6)	37 (16.0)
Missing	53		18	16	19
Grade					
I/II	376 (57.7)	1.27 (1.94)	132 (60.6)	115 (54.5)	129 (51.9)
III	276 (42.3)	1.10 (1.34)	86 (39.4)	96 (45.5)	94 (42.1)
Missing	96		31	38	27
Tumor size (cm)					
2.0	396 (56.3)	1.14 (1.73)	130 (55.8)	143 (61.1)	123 (51.9)
>2.0	308 (43.8)	1.22 (1.60)	103 (44.2)	91 (38.9)	114 (48.1)
Missing	44		16	15	13
Node status					

Characteristic	n (%)	DDE	DDE Tertiles (µg/g lipid)		
		µg/g lipid Mean (SD)	0.36 n (%)	0.37–1.00 n (%)	1.01 n (%)
Negative	442 (62.3)	1.10 (1.64)	148 (62.7)	157 (66.5)	137 (57.6)
Positive	268 (37.7)	1.30 (1.73)	88 (37.3)	79 (33.5)	101 (42.4)
Missing	38		13	13	12
Estrogen receptor (ER) status					
ER ⁺	404 (58.7)	1.30 (1.98)	128 (55.4)	134 (59.8)	142 (60.9)
ER ⁻	284 (41.3)	1.00 (1.13)	103 (44.6)	90 (40.2)	91 (39.1)
Missing	60		18	25	17

Carolina Breast Cancer Study (CBCS) participants were diagnosed with invasive breast cancer from 1993–1996 (Phase I) and followed-up for vital status through December 31, 2016.

0.04	71	38	1.86 (1.32–2.61)	1.64 (1.10–2.44)	20	89	1.59 (0.91–2.78)	1.07 (0.56–2.01)
Ln(DDT)			1.19 (1.05–1.36)	1.19 (1.02–1.39)			1.26 (1.01–1.56)	1.17 (0.91–1.51)
Log ₂ (DDT)			1.13 (1.03–1.24)	1.13 (1.01–1.25)	0.03		1.17 (1.01–1.36)	1.12 (0.94–1.33)
								0.22

Carolina Breast Cancer Study (CBCS) participants were diagnosed with invasive breast cancer from 1993–1996 (Phase I) and followed-up for vital status through December 31, 2016. Conditional analyses are among women who survived >5 years.

^a Adjusted for age at diagnosis (continuous in years) and race (black vs. white).

^b Adjusted for age at diagnosis (continuous in years), race (black vs. white), smoking status (never, former, and current smoker), education (less than high school, high school, and college or greater), BMI (<25.0, 25.0–29.9, 30.0 kg/m²), parity/lactation history (nulliparous, parous/never lactated, parous/ever lactated), stage (III/IV vs. I/II), and ER status (ER⁺ vs. ER⁻).

^c Cox models based on 333 deaths and 313 censored observations due to missing covariate data.

^d Cox models based on 183 deaths and 463 censored observations due to missing covariate data.

Table 3.

Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between plasma levels of lipid-standardized DDE and DDT levels and 20-year conditional breast cancer-specific mortality in the CBCS Phase I women diagnosed with invasive breast cancer in 1993–1996 ($n=615$), stratified by race and ER status.

DDE ($\mu\text{g/g}$ lipid)	20-year Conditional Breast Cancer-Specific Mortality					20-year Conditional Breast Cancer-Specific Mortality						
	Median	Deaths ($n=97$)	Censored ($n=518$)	Model 1 ^a HR (95% CI)	Model 2 ^b HR (95% CI) ^c	HR (95% CI)	DDT ($\mu\text{g/g}$ lipid)	Deaths ($n=97$)	Censored ($n=518$)	Model 1 ^a HR (95% CI)	Model 2 ^b HR (95% CI) ^c	$P_{\text{Int.}}$ ^d
Overall												
0.58	0.284	40	273	1 (Reference)	1 (Reference)	<LOD	57	340	1 (Reference)	1 (Reference)		
>0.58	1.41	57	245	1.77 (1.15–2.72)	1.69 (1.06–2.68)	LOD	40	178	1.52 (0.98–2.36)	1.22 (0.75–1.98)		
Ln(DDE)				1.27 (1.04–1.56)	1.16 (0.94–1.43)	Ln(DDT)			1.26 (1.01–1.56)	1.17 (0.91–1.51)		
Log ₂ (DDE)				1.18 (1.03–1.36)	1.11 (0.96–1.28)	Log ₂ (DDT)			1.17 (1.01–1.36)	1.12 (0.94–1.33)		
Race												
0.42												
White												
0.58	0.254	32	222	1 (Reference)	1 (Reference)	<LOD	41	269	1 (Reference)	1 (Reference)		
>0.58	1.03	21	113	1.56 (0.89–2.74)	1.57 (0.86–2.89)	LOD	12	66	1.67 (0.87–3.21)	1.37 (0.66–2.83)		
Ln(DDE)				1.16 (0.87–1.55)	1.10 (0.81–1.51)	Ln(DDT)			1.42 (0.92–2.18)	1.33 (0.84–2.12)		
Log ₂ (DDE)				1.11 (0.91–1.35)	1.07 (0.86–1.33)	Log ₂ (DDT)			1.27 (0.94–1.71)	1.22 (0.88–1.68)		
Black												
0.58	0.366	8	51	1 (Reference)	1 (Reference)	<LOD	16	71	1 (Reference)	1 (Reference)		
>0.58	1.89	36	132	2.49 (1.12–5.51)	2.36 (1.03–5.42)	LOD	28	112	1.46 (0.77–2.77)	1.31 (0.62–2.73)		
Ln(DDE)				1.49 (1.08–2.06)	1.30 (0.93–1.82)	Ln(DDT)			1.24 (0.94–1.65)	1.20 (0.85–1.69)		
Log ₂ (DDE)				1.32 (1.06–1.65)	1.20 (0.95–1.51)	Log ₂ (DDT)			1.16 (0.96–1.41)	1.13 (0.89–1.44)		
ER Status												
0.03												
ER⁺												
0.58	0.284	29	144	1 (Reference)	1 (Reference)	<LOD	37	180	1 (Reference)	1 (Reference)		
>0.58	1.45	32	142	1.29 (0.75–2.21)	1.29 (0.73–2.28)	LOD	24	106	1.31 (0.74–2.32)	1.18 (0.62–2.26)		
Ln(DDE)				1.12 (0.87–1.45)	1.07 (0.83–1.38)	Ln(DDT)			1.26 (0.94–1.69)	1.11 (0.81–1.53)		
Log ₂ (DDE)				1.08 (0.91–1.29)	1.05 (0.88–1.25)	Log ₂ (DDT)			1.17 (0.96–1.44)	1.07 (0.86–1.34)		
ER⁻												

DDE (µg/g lipid)	20-year Conditional Breast Cancer-Specific Mortality					20-year Conditional Breast Cancer-Specific Mortality					
	Median	Deaths (n=97)	Censored (n=518)	Model 1 ^a HR (95% CI)	Model 2 ^b HR (95% CI) ^c	DDT (µg/g lipid)	Deaths (n=97)	Censored (n=518)	Model 1 ^a HR (95% CI)	Model 2 ^b HR (95% CI) ^c	P _{int.} ^d
0.58	0.287	9	110	1 (Reference)	1 (Reference)	<LOD	16	131	1 (Reference)	1 (Reference)	
>0.58	1.51	21	79	3.25 (1.43–7.38)	3.24 (1.38–7.58)	LOD	14	58	1.96 (0.91–4.18)	1.43 (0.64–3.19)	
Ln(DDE)				1.66 (1.16–2.39)	1.55 (1.04–2.30)	Ln(DDT)			1.30 (0.91–1.87)	1.30 (0.86–1.97)	
Log ₂ (DDE)				1.42 (1.11–1.83)	1.35 (1.03–1.78)	Log ₂ (DDT)			1.20 (0.94–1.54)	1.20 (0.90–1.60)	

Carolina Breast Cancer Study (CBCS) participants were diagnosed with invasive breast cancer from 1993–1996 (Phase I) and followed-up for vital status through December 31, 2016. Conditional analyses are among women who survived > 5 years.

^a Adjusted for age at diagnosis (continuous in years) and race (black vs. white), as appropriate.

^b Adjusted for age at diagnosis (continuous in years), race (black vs. white), smoking status (never, former, and current smoker), education (less than high school, high school, and college or greater), BMI (<25.0, 25.0–29.9, 30.0 kg/m²), parity/lactation history (nulliparous, parous/never lactated, parous/ever lactated), stage (III/IV vs. I/II), and ER status (ER⁺ vs. ER⁻), as appropriate.

^c Cox models based on 183 deaths and 463 censored observations due to missing covariate data.

^d P for multiplicative interaction from Cox regression models using continuous log₂-transformed lipid-standardized DDE/DDT levels.