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Organochlorine insecticides DDT and chlordane in relation to survival following breast cancer

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Abstract

Organochlorine insecticides have been studied extensively in relation to breast cancer incidence and results from two meta-analyses have been null for late-life residues, possibly due to measurement error. Whether these compounds influence survival remains to be fully explored. We examined associations between organochlorine insecticides (p,p'-DDT, its primary metabolite, p,p'-DDE, and chlordane) assessed shortly after diagnosis and survival among women with breast cancer. A population-based sample of women diagnosed with a first primary invasive or *in situ* breast cancer in 1996–1997 and with available organochlorine blood measures (n=633) were followed for vital status through 2011. After follow-up of 5 and 15 years, we identified 55 and 189 deaths, of which 36 and 74, respectively, were breast cancer-related. Using Cox regression models, we estimated the multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for lipid-adjusted organochlorine concentrations with all-cause and breast cancer-specific mortality. At 5 years after diagnosis, the highest tertile of DDT concentration was associated with all-cause (HR=2.19; 95%CI: 1.02, 4.67) and breast cancer-specific (HR=2.72; 95%CI: 1.04, 7.13) mortality. At 15 years, middle tertile concentrations of DDT (HR=1.42; CI 0.99, 2.06) and chlordane (HR=1.42; 95%CI: 0.94, 2.12) were modestly associated with all-cause and breast cancer-specific mortality. Third tertile DDE concentrations were inversely associated with 15-year all-cause mortality (HR=0.66; 95%CI: 0.44, 0.99). This is the first population-based study in the United States to show that DDT may adversely impact survival following breast cancer diagnosis. Further studies are warranted given the high breast cancer burden and the ubiquity of these chemicals.

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Keywords

Organochlorine compounds; pesticides; DDT; DDE; chlordane; breast cancer; survival

INTRODUCTION

In the United States (US), the organochlorine insecticide dichlorodiphenyltrichloroethane (DDT) was first used during World War II to combat malaria, typhus, and other diseases among military populations.[1] Widespread use began shortly after in 1945. DDT use increased until 1959 and declined steadily until its ban in 1972 because of growing environmental and wildlife concerns.[2,3] Other countries restricted its use several years earlier, including Canada in 1969, while others continued to use DDT until much later, including Mexico which halted the use of DDT in 2000.[2,4] Today, DDT production continues in China, India, and North Korea, as does indoor residual spraying for malaria control, which involves coating the walls and other surfaces of a house with a residual insecticide,[5] in countries such as India, Ethiopia, and South Africa.[6] Continued DDT use ensures continued direct and indirect exposure to DDT and its metabolites.[7] Another organochlorine insecticide, chlordane, was used agriculturally in the US from 1948 until 1983 and then restricted to use for termite control until its ban in 1988.[8]

DDT and its primary metabolite, dichlorodiphenyldichloroethylene (DDE), have been extensively studied in relation to breast cancer incidence because they are highly lipophilic and have long biological half-lives.[9,10] While DDT shows estrogenic activity in breast cells *in vitro*,[11] DDE is an anti-androgen.[11–13] Furthermore, organochlorine chemicals are stored in adipose tissue, including the breast.[14] Importantly, breast tissue levels can be estimated validly and less invasively with peripheral blood measures.[15] Additionally, it is important to consider weight and weight change since body mass index (BMI), a surrogate for adiposity, can alter tissue and blood concentrations and can cause slower elimination of organochlorine compounds and thus result in extended exposures in the body.[10] While several studies have found significant associations between DDT, DDE, and chlordane and breast cancer incidence,[16–21] results of most,[22–27] including two meta-analyses,[28,29] have largely been null, possibly because the measurements obtained may not correctly reflect the exposures during the etiologically relevant period(s). Although data on early life exposures are limited, results of a two-generation cohort studies found that blood measures of DDT ascertained prenatally or prior to a woman's reproductive years were associated with subsequent risk of developing breast cancer;[21,30,31] however, the role of early life exposures to DDT remains unresolved.[32]

Whether organochlorine pesticides impact breast cancer survival remains a largely unexplored topic, with only one research group in Denmark publishing a positive association between the organochlorine insecticide dieldrin and all-cause and breast cancer-specific mortality following a breast cancer diagnosis.[33–35] This potential association is particularly important given the high breast cancer incidence and mortality among women in the US and globally.[36,37]

The present study aimed to examine the associations of the organochlorine insecticides, DDT and chlordane, and the DDT metabolite DDE with survival among US women with breast cancer. We hypothesized that organochlorine compounds would be positively associated with mortality, particularly breast cancer-specific mortality. Additionally, we were interested in examining whether weight-related measures modified the relationships observed given the potential for adiposity to alter the elimination rate of organochlorine compounds.[10]

METHODS

Study design and study population

The Long Island Breast Cancer Study Project (LIBCSP) was a population-based study that was initiated as a case-control study to identify environmental factors associated with developing breast cancer, and then continued as a follow-up study to identify factors associated with survival. Details of the LIBCSP have been published previously.[24,38] Briefly, adult female residents of Nassau and Suffolk counties with a first diagnosis of invasive or *in situ* breast cancer between August 1, 1996, and July 31, 1997, confirmed by physicians and medical records, were identified for inclusion through daily/weekly contact of pathology departments of 31 hospitals on Long Island and New York City, NY.

At baseline, on average within three months of the participant's diagnosis, 1,508 women with breast cancer, with signed informed consent, completed an interviewer-administered questionnaire; 1,102 provided blood samples for laboratory analyses. The present study uses data from 633 women with breast cancer for whom blood levels of DDT (n=622), DDE (n=632), or chlordane (n=586) and lipids were available.[24] Participants with available organochlorine measures were primarily white (92%) with a mean age of 58 years (range=29–89 years), post-menopausal (66%), and diagnosed with a first primary invasive breast cancer (71%), as described in Table 1.

The LIBCSP study protocol was approved by the Institutional Review Board of all participating institutions and in accordance with an assurance filed with and approved by the US Department of Health and Human Services.

Laboratory assays

Blood sample collection, analytic methods, and QA/QC procedures in the LIBCSP have been previously published.[10,38] Briefly, approximately 73% of participants provided 40-mL non-fasting blood samples, of which 77% were collected prior to the initiation of chemotherapy. Samples for assaying were selected as follows: (1) randomly sampled from among women with invasive breast cancer (n=415); (2) all women with tumors initially categorized as *in situ* that were subsequently determined to be invasive (n=42); (3) all women with *in situ* tumors (n=184); and (4) all African-American participants who were not selected in the first three steps (n=5).

Gas chromatography/electron capture detection was conducted as outlined by Brock *et al.*[39] to estimate concentrations of p,p'-DDT (DDT), p,p'-DDE (DDE) and chlordane (the sum of oxychlordane and *trans*-nonachlor). Positive and zero values of individual organochlorine

levels below the detection limit (0.2ng/ml) were set to the lowest observed positive value for that compound, rather than being assigned a censored value. The proportions of observations that were below the detection limit were 8% for DDT, 1% for DDE, and 8% for chlordane.

Lipid profiles were determined for use in adjustment of DDT/DDE concentrations to account for non-fasting variations and to more closely approximate adipose tissue levels.[40,41] We also present results for models in which we include total lipids as a covariate (Table S1). In the main analyses, continuous concentrations of lipid-adjusted organochlorines were divided into tertiles using the following cut-points (in ng/g) for: p,p'-DDT, <56.82, ≥56.82–<91.22 and ≥91.22; p,p'-DDE, <467.86, ≥467.86–<1,058.20 and ≥1,058.20; and chlordane, <81.08, ≥81.08–<131.00, and ≥131.00.

Follow-up for mortality

The National Death Index (NDI), a centralized database of death record information maintained by the National Center for Health Statistics,[42] was used to ascertain date and cause of death. International Statistical Classification of Diseases codes 174.9 and C-50.9 listed anywhere on the death certificate were used to identify breast cancer-related deaths. Participants were followed from diagnosis in 1996–1997 until December 31, 2011. The maximum duration of follow-up was 15.42 years. Among our 633 participants after 5-years of follow-up, 55 (9%) deaths occurred, of which 36 were due to breast cancer; and, after 15 years, 189 (30%) deaths occurred, with 74 due to breast cancer.

Interview and medical record data

Prior to data collection, participants provided signed informed consent and permission for medical record release. Participants completed a 2-hour interviewer-administered questionnaire to assess demographic characteristics and potential and established risk/prognostic factors for breast cancer. Medical records were abstracted to obtain information on tumor hormone receptor status, primarily estrogen and progesterone receptor (ER and PR, respectively) status and first course of treatment.

Statistical analyses

Kaplan-Meier survival curves were used for preliminary examination of the unadjusted data (Figure 1). The proportional hazards assumption was assessed by testing interaction terms of the exposure variables with time and natural log of time and by Schoenfeld residuals for all covariates. No violations of the proportional hazards assumption were evident based on these tests; however, several of the p-values for the interaction terms of the exposure variables with time at 15 years were marginally significant for all-cause [log(time)*log(DDT) p=0.07] and breast cancer-specific [log(time)*log(DDT) p=0.09; log(time)*log(DDE) p=0.12] mortality. Multivariable Cox models[43] were fit to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for increasing tertiles of lipid-adjusted DDT, DDE, and chlordane concentrations in association with all-cause and breast cancer-specific mortality at 5 and 15 years after diagnosis. Models were re-run restricted to cases with invasive tumors. Tests for trend used continuous natural log-transformed lipid-adjusted concentrations in regression models.

To assess for effect modification interaction terms between continuous organochlorine concentrations and body size were included in Cox models. Additionally, models were stratified by: (1) body mass index (BMI; weight (kg)/height $(m)^2$), in the year prior to diagnosis, categorized as "BMI<25kg/m^2" and "BMI≥25kg/m^2;" and (2) percent weight-gain since age 20, categorized as "0–<20% weight-gain", "20–<40% weight-gain" and "≥40% weight-gain" [44]. Few women reported a decrease in adult weight change; therefore, associations within the strata of weight-loss were not examined. Also, at 5 years after diagnosis there were too few deaths to examine the associations stratified by body size; therefore, only 15-year associations are presented.

Possible confounders were selected based on previous studies of organochlorines and breast cancer incidence and survival[10,45] and directed acyclic graphs,[46] and included: age at diagnosis (5-year age groups), parity/lactation (nulliparous, parous/never lactated, and parous/ever lactated); menopausal status (premenopausal and postmenopausal), hormone replacement therapy use (continuous, number of months of use), BMI (continuous); annual household income (categorical); cigarette smoking (never, former, and current smokers).

Hormone receptor status was not included as a covariate in the models since ER/PR status may mediate the association between organochlorine compounds and breast cancer survival[47] precluding adjustment by stratification for receptor status.[48] Treatment undergone was also not included in our models as a covariate, given treatment is also a possible causal intermediate since ER/PR status is directly related to treatment.[49]

All statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

5-year all-cause and breast cancer-specific mortality

In the Kaplan-Meier survival curves, compared to tertile 1, tertiles 2 and 3 of DDT were associated with a higher probability of 5-year all-cause and breast cancer-specific mortality (Figure 1, **Panels A and D**). As shown in Table 2, multivariable-adjusted HRs for 5-year all-cause mortality were more than doubled for women with DDT concentrations in the middle (HR=2.55, 95%CI: 1.20, 5.45) and highest (HR=2.19, 95%CI: 1.02, 4.67)) tertiles, as compared to women with DDT concentrations in the lowest tertile (p-trend=0.02). The magnitude appeared modestly larger for the corresponding DDT estimates for 5-year breast cancer-specific mortality (HR=2.94; 95%CI: 1.12, 7.67; HR=2.72; 95%CI: 1.04, 7.13, respectively; p-trend=0.02). Estimates were slightly more pronounced when we restricted our analyses to women diagnosed with invasive breast cancer (Table S2) and post-menopausal women (Table S3). Additionally, these estimates were relatively unchanged when BMI was excluded from the adjustment set (Table S4).

In the Kaplan-Meier survival curves, the highest tertiles of DDE and chlordane did not appear to be associated with higher 5-year all-cause and breast cancer specific mortality (Figure 1, **Panels B, C, E, and F**). However, in the multivariable models associations with all-cause and breast cancer-specific mortality 5 years after breast cancer diagnosis were

positively associated with chlordane, and inversely associated with DDE, but the confidence intervals for the modest hazards included the null value.

15-year all-cause and breast cancer-specific mortality

In the Kaplan-Meier curves, the DDT survival curves for all-cause mortality appeared to converge after 8 years while the survival curves for chlordane after 5 years diverged. In the multivariable models, as shown in Table 2, 15-year all-cause mortality hazards were elevated for DDT (HR=1.42, 95%CI: 0.99, 2.06) and chlordane (HR=1.42, 95%CI: 0.94, 2.12) concentrations in the middle tertiles. The highest tertile of chlordane was elevated though closer to the null (HR=1.31; 95%CI 0.86, 2.00). Corresponding 15-year hazards for breast cancer-specific mortality were similarly elevated for DDT (HR=1.59, 95%CI: 0.90, 2.83) and chlordane (HR=1.47; 95%CI: 0.81, 2.67). In contrast, 15-year all-cause and breast cancer-specific mortality risk decreased with increasing DDE concentrations (p-trend=0.10). Most confidence intervals, however, included the null value. These inverse associations were not apparent for all-cause mortality in the Kaplan-Meier curves; however, the inverse association was apparent after 8 years for breast cancer-specific mortality (Figure 1, **Panels A and E**)

BMI-stratified 15-year all-cause mortality

As shown in Table 3, among women with BMI<25kg/m^2, but not among women with BMI≥25kg/m^2, hazards for all-cause mortality were increased in association with: DDT concentrations in the middle (HR=2.32; 95%CI: 1.23, 4.38) and highest (HR=1.43; 95%CI: 0.73, 2.79) tertiles (p-interaction=0.03; p-trend=0.19); and with chlordane concentrations in the middle (HR=1.79; 95%CI: 0.92, 3.47) and highest (HR=1.42; 95%CI: 0.69, 2.92) tertiles (p-interaction<0.01; p-trend=0.27). In contrast, within both strata of categorized BMI, increasing DDE concentrations were associated with decreasing hazard of all-cause mortality, but estimates were strongest among women with BMI<25kg/m^2 (p-interaction=0.09).

BMI-stratified 15-year breast cancer-specific mortality

As shown in Table 3, hazards for breast cancer-specific mortality 15 years after diagnosis were increased among women with BMI<25kg/m^2 for: DDT concentrations in the middle (HR=1.92; 95%CI: 0.76, 4.88) and highest (HR=1.46; 95%CI: 0.55, 3.89) tertiles (p-interaction<0.01; p-trend=0.56); and chlordane concentrations in the middle (HR=2.93; 95%CI: 1.10, 7.79) and highest (HR=1.72; 95%CI: 0.54, 5.48) tertiles (p-interaction=0.82; p-trend=0.57). In contrast, among women with BMI<25kg/m^2, but not among women with BMI≥25kg/m^2, breast cancer-specific mortality was reduced in association with the middle (HR=0.82; 95%CI: 0.34, 1.99) and highest (HR=0.23; 95%CI: 0.05, 1.09) DDE tertiles, but confidence intervals included the null value (p-interaction=0.14; p-trend=0.18).

Adult-lifetime percent weight gain-stratified 15-year all-cause mortality

As shown in Table 4, among women with 0–<20% lifetime weight-gain, 15-year all-cause mortality was positively associated with DDT concentrations in the middle tertile (HR=2.11; 95%CI: 1.03, 4.32). The DDT-mortality association decreased in magnitude with increasing

percent weight gain for concentrations in the middle tertile (20–<40% weight gain, HR=1.30; 95%CI: 0.67, 2.51; ≥40% weight gain, HR=1.11; 95%CI: 0.54, 2.25; p-interaction=0.25).

A similar pattern was observed for chlordane concentrations, where 15-year all-cause mortality was positively associated with middle tertile levels among women with 0–<20% lifetime weight-gain (HR=1.55; 95%CI: 0.70, 3.41) and a decrease in magnitude with increasing percent weight gain was observed (20–<40% weight gain HR=1.34; 95%CI: 0.69, 2.60; ≥40% weight-gain HR=1.17; 95%CI: 0.50, 2.75; p-interaction=0.65).

In contrast, DDE concentrations were inversely associated with 15-year all-cause mortality among women with 20–<40% adult-lifetime percent weight-gain (HR=0.71; 95%CI: 0.37, 1.38; HR=0.49; 95%CI: 0.24, 0.99; p-interaction=0.84).

DISCUSSION

In this first US population-based study to examine the association between blood levels of organochlorine compounds and survival following breast cancer, we observed a greater than two-fold increase in all-cause and breast cancer-specific mortality after 5 years of follow-up in association with DDT concentrations measured within a few month of diagnosis. Estimates were more pronounced when we restricted our analysis to women with invasive breast cancer only. Slightly attenuated DDT HRs remained elevated after 15 years of follow-up, but CIs were imprecise. The more pronounced association 5 years after breast cancer diagnosis, rather than after 15, may reflect susceptible women dying within 5 years. The risk of death from breast cancer within 5 years of diagnosis, while low (10%), decreases after 6–8 years during which death from other causes increases.[50]

To date, only one research group in Denmark has published on the association between organochlorine compounds and breast cancer mortality.[33–35] In their initial report [33], among the compounds examined in 195 Danish women only dieldrin was associated with increased all-cause and breast cancer-specific mortality. In the present study, we were unable to examine dieldrin due to insufficient number of cases with levels above detectable limits;[24] however, we were able to examine DDT, DDE and chlordane. In the Danish study, there was a suggestion of elevated mortality following breast cancer for p,p'-DDT, which is consistent with the results reported here. In contrast to the Danish study, we also observed an increased risk of all-cause mortality 15 years after a breast cancer diagnosis for chlordane, but a decreased risk for DDE despite the much lower concentrations of organochlorine compounds observed in this study. In the US, one study has examined whether organochlorine levels were associated with recurrence among women of Long Island, NY.[51] In their study, the highest tertiles of total PCBs and the middle tertiles of DDE were positively associated with recurrence. However, their study was limited by the small case-control (n=224 women, 30 of which were diagnosed with a recurrence), hospital-based study design.

Although endocrine disrupting chemicals may act through multiple, complex, and unknown pathways, several biological mechanisms related to the estrogenic and hormone-antagonistic

potential of these compounds may explain the associations observed here. The first is that organochlorine compounds may directly affect tumor cell proliferation by interacting with important receptors.[52] The second proposed mechanism is that estrogenic organochlorine compounds stored in breast adipose tissue adjacent to the breast carcinoma may affect the tumor microenvironment making it more estrogenic favoring cell proliferation among hormone receptor positive neoplasms.[47] Our positive findings between the estrogenic compounds DDT and chlordane and mortality support these mechanisms. We also observed an inverse association between DDE, a known anti-androgen, and mortality.[13]

Our stratified results that women with lower BMI and less adult-lifetime weight gain had the highest HRs of all-cause mortality, may reflect the competing estrogenic effects associated with high BMI. Our observation may be analogous to the situation where the positive association between breast cancer incidence and hormone replacement is only evident among non-obese women.[53] Third, organochlorines compounds with known endocrine disruption effects may also result in metabolic disruption[54] leading to pre- and post-diagnosis weight changes which may influence survival.[44,55]

At least two studies[21,31] have shown that timing of exposure, especially during critical developmental windows, may be important for breast cancer etiology. Failure to account for exposure windows may partially explain the lack of association observed for breast cancer incidence. In contrast, for survival following breast cancer, the relevant windows of exposure to environmental contaminants, including continued endogenous exposure from the release of stored toxins, may extend from as early as 5 years before diagnosis[56] through death.[55] Thus, a possible explanation for our observation of stronger associations with 5-year mortality, rather than 15-year mortality, may be that biomarker concentrations assessed at baseline are more likely to reflect the relevant exposure period influencing mortality closer to diagnosis, rather than the exposures that are likely to have changed over the 15-year period of follow-up; although we were not able to assess how organochlorine levels changed over time as a result of ongoing low-level dietary exposure.[57] However, it is also possible that exposures in early life may influence the characteristics of the tumor (e.g. receptor status, grade, lymph node involvement, and stage at diagnosis),[34,47,58,59] which are known impact the effectiveness of chemotherapy, aggression of the cancer, and probability of survival. Approximately one-third (212 of 633) of the women included in our study were born in or after 1945 when DDT was widely introduced in the US. These women could have been potentially exposed to technical DDT *in utero*, a window of exposure that has been shown to be associated with breast cancer incidence.[31] Additionally, almost half (295 of 633) of the women in our study were of younger reproductive age, between the ages of 14 and 25, during the years of DDT peak use in the US, from 1955 through 1962.

Our study has several strengths including biomarker assessments of organochlorine compounds in blood samples that were collected from a population-based sample of American women within a few months following diagnosis of their first primary breast cancers, who were then subsequently followed using the NDI, which provides high quality ascertainment of vital status. Nonetheless, this study has several limitations. While the largest HR of mortality was observed 5 years after breast cancer diagnosis, the low frequency of deaths at 5 years in our study population precluded us from examining whether

these associations varied by *a priori* covariates of interest or by other potentially important characteristics such as birth cohort, although even with larger numbers we would be unable to say with certainty that birth cohort directly corresponds to age of exposure.

Another potential study concern is that we adjusted for BMI, which may have resulted in model misspecification. A recent study suggests that organochlorines may influence the metabolic system, including weight.[60] Given that weight is a strong predictor of breast cancer survival,[44,55] BMI is a possible causal intermediate for the organochlorine-breast cancer survival association. Thus, we also fit Cox models excluding BMI as a covariate. However, removal of BMI from the model did not appreciably alter our HR estimates; any potential bias of our results due to inclusion of BMI in our models is likely to be low.

Our study included only one organochlorine measurement. While concentrations measured at baseline are likely to be more temporally relevant to the outcomes, we were unable to account for changes in exposure to organochlorine compounds. Additionally, the biomarker assessment does not provide any information about the source of exposure and whether women were exposed to technical DDT and chlordane or whether they were exposed through other sources such as diet. Although we considered associations stratified by weight gain, we were not able to fully account for changes in organochlorine concentrations over time due to BMI changes, which may result in changes in the amount of chemicals stored in fatty breast tissue.[10]

Finally, determination of breast cancer-related deaths may have resulted in outcome misclassification. However, this misclassification is likely to be non-differential with respect to organochlorine levels. This non-differential misclassification would attenuate the risk estimates for breast cancer-specific mortality.[61]

Results of this first US population-based study indicate that exposure to organochlorine insecticides, especially those with known estrogenic properties, may negatively impact survival following breast cancer. In our study, DDT was associated with a more than two-fold increase in 5-year all-cause and breast-cancer specific mortality; and the mortality hazards, while attenuated, remained elevated 15 years after the first primary breast cancer diagnosis. Our finding that DDE was inversely associated with mortality may be suggestive of an anti-androgenic pathway that requires further investigation. Given the limited research on breast cancer survival conducted to date, our findings require replication in future studies, which should explore additional organochlorine compounds. Our study findings, which are consistent with the results from Denmark,[35] emphasize the importance of environmental exposures in cancer survival and have important policy implications since further restriction of the use of these and other similar chemicals may be warranted due to the high burden of breast cancer worldwide.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	Body Mass Index
CI	Confidence Interval
DDE	dichlorodiphenyldichloroethylene
DDT	dichlorodiphenyltrichloroethane
ER	Estrogen Receptor
ERR	Estrogen-Related Receptor
HR	Hazard Ratio
ICD	International Statistical Classification of Diseases
LIBCSP	Long Island Breast Cancer Study Project
NDI	National Death Index
PR	Progesterone Receptor
US	United States

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Novelty and Impact

While organochlorine compounds have been extensively studied in relation to breast cancer incidence, only one research group to date has examined whether these compounds are associated with survival. In this first population-based study in the United States, we show that DDT may adversely impact survival following breast cancer diagnosis. These results emphasize the importance of environmental exposures in cancer survival.

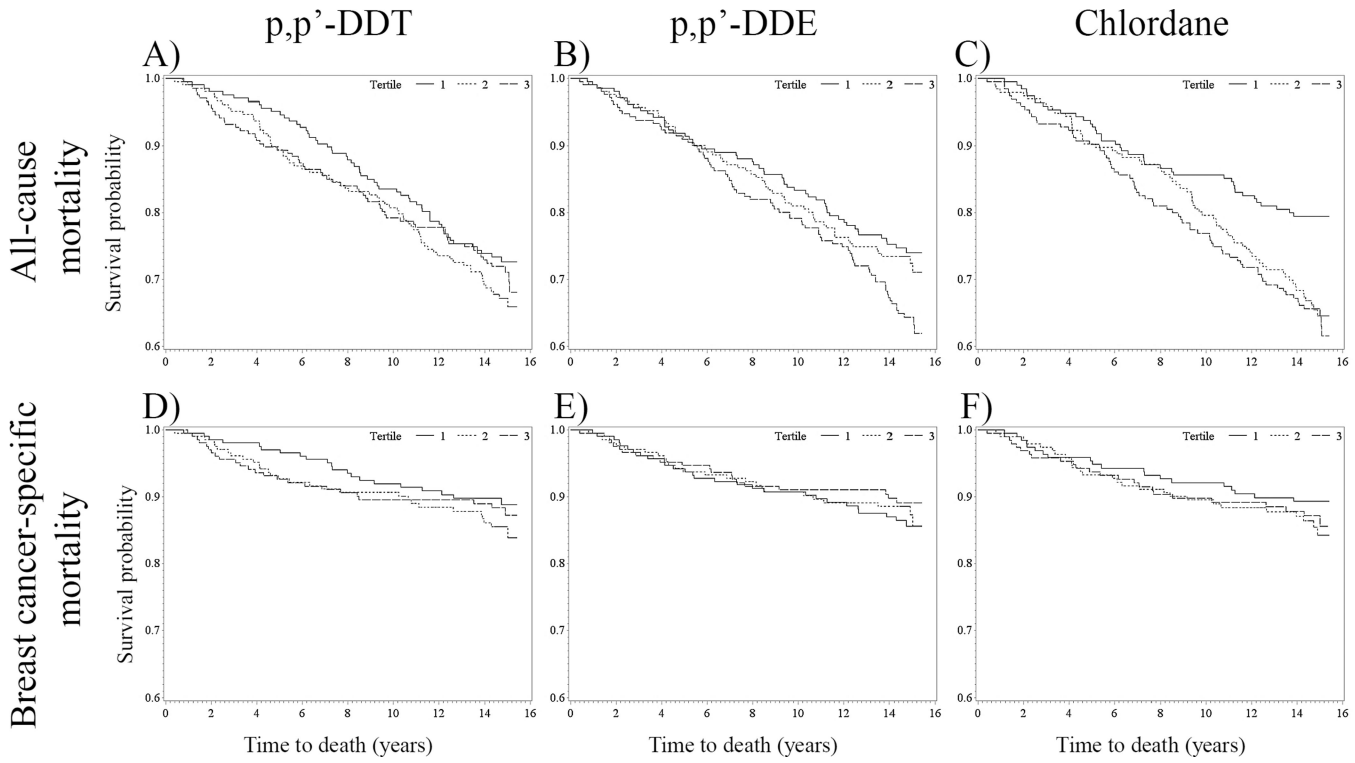

Figure 1.

Kaplan-Meier survival curves for all-cause mortality for (A) p,p'-DDT, (B) p,p'-DDE, and (C) chlordane and for breast cancer-specific mortality for (D) p,p'-DDT, (E) p,p'-DDE, and (F) chlordane stratified by organochlorine concentration tertiles 1 (solid line), 2 (dotted line), and 3 (dashed line) among LIBCSP women diagnosed with breast cancer in 1996–1997 (n=633). The x-axis shows times to death in years; the y-axis shows proportion of participants alive.

Table 1

Distribution of the selected baseline characteristics of the LIBCSP women diagnosed with breast cancer in 1996–1997 (n=633).

		p,p'-DDT[a] (n=622)		
	Total (n=633)	**Tertile 1 (n=207)**	**Tertile 2 (n=208)**	**Tertile 3 (n=207)**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Age				
<35	14 (2%)	5 (2%)	5 (2%)	11 (5%)
35–44	90 (14%)	27 (13%)	32 (15%)	42 (20%)
45–54	160 (25%)	59 (29%)	55 (26%)	44 (21%)
55–64	163 (26%)	55 (27%)	60 (29%)	64 (31%)
65–74	155 (24%)	51 (25%)	40 (19%)	39 (19%)
75+	51 (8%)	10 (5%)	16 (8%)	7 (3%)
BMI				
<25kg/m^2	283 (45%)	94 (46%)	100 (49%)	85 (42%)
25–30kg/m^2	206 (33%)	78 (38%)	53 (26%)	74 (36%)
30+kg/m^2	136 (22%)	34 (17%)	50 (25%)	46 (22%)
Missing	8	1	5	2
Income				
<$15,000–$24,999	125 (20%)	28 (14%)	40 (19%)	54 (26%)
$25,000–$49,999	188 (30%)	66 (32%)	60 (29%)	59 (29%)
$50,000-$90,000+	318 (50%)	113 (55%)	107 (52%)	93 (45%)
Missing	2	0	1	1
Education				
<HS-HS graduate	277 (44%)	89 (43%)	85 (41%)	99 (48%)
Some college/-College graduate	253 (40%)	82 (40%)	93 (45%)	73 (36%)
Post college	100 (16%)	36 (17%)	29 (14%)	33 (16%)
Missing	3	0	1	2
Parity/Lactation history				
Nulliparous	67 (11%)	27 (13%)	17 (8%)	22 (11%)
Parous/never lactated	350 (55%)	115 (56%)	108 (52%)	121 (58%)
Parous/ever lactated	216 (34%)	65 (31%)	83 (40%)	64 (31%)
Menopausal status				
Premenopausal	212 (34%)	71 (35%)	78 (38%)	60 (30%)
Postmenopausal	409 (66%)	133 (65%)	128 (62%)	140 (70%)
Missing	12	3	2	7

Long Island Breast Cancer Study Project (LIBCSP) participants diagnosed with breast cancer between August 1, 1996 and July 31, 1997 and followed-up through December 31, 2011.

[a] Lipid-adjusted p,p'-DDT concentration cut-points: Tertile 1 (<56.8ng/g), Tertile 2 (≥56.8–<91.2ng/g), Tertile 3 (≥91.2ng/g)

Table 2

Cox regression hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between blood levels of organochlorines and mortality in the LIBCSP women diagnosed with breast cancer in 1996–1997 (n=633).

	5-Year All-Cause Mortality					5-Year Breast Cancer Specific-Mortality				
			Age-Adjusted[a]	Multivariable-Adjusted[b]				Age-Adjusted[a]	Multivariable-Adjusted[b]	
	Deaths	**Censored**	**HR (95% CI)**	**HR (95% CI)**	**p-trend**	**Deaths**	**Censored**	**HR (95% CI)**	**HR (95% CI)**	**p-trend**
p,p'-DDT[c]										
Tertile 1	10	197	1 (Reference)	1 (Reference)		6	201	1 (Reference)	1 (Reference)	
Tertile 2	22	186	2.24 (1.06, 4.73)	2.55 (1.20, 5.45)		15	193	2.53 (0.98, 6.51)	2.94 (1.12, 7.67)	
Tertile 3	22	185	2.19 (1.03, 4.64)	2.19 (1.02, 4.67)	0.02	15	192	2.65 (1.03, 6.86)	2.72 (1.04, 7.13)	0.02
p,p'-DDE[d]										
Tertile 1	17	193	1 (Reference)	1 (Reference)		12	198	1 (Reference)	1 (Reference)	
Tertile 2	19	192	0.98 (0.50, 1.92)	0.95 (0.48, 1.89)		13	198	1.14 (0.51, 2.54)	1.10 (0.48, 2.52)	
Tertile 3	19	192	0.85 (0.41, 1.78)	0.72 (0.33, 1.56)	0.78	11	200	1.04 (0.42, 2.61)	0.85 (0.32, 2.23)	0.38
Chlordane[e]										
Tertile 1	13	182	1 (Reference)	1 (Reference)		9	186	1 (Reference)	1 (Reference)	
Tertile 2	19	177	1.40 (0.69, 2.87)	1.26 (0.61, 2.61)		13	183	1.59 (0.67, 3.76)	1.53 (0.63, 3.69)	
Tertile 3	19	176	1.34 (0.63, 2.86)	1.26 (0.58, 2.71)	0.13	12	183	1.70 (0.67, 4.33)	1.68 (0.65, 4.35)	0.13
	15-Year All-Cause Mortality					15-Year Breast Cancer Specific-Mortality				
			Age-Adjusted[a]	Multivariable-Adjusted[b]				Age-Adjusted[a]	Multivariable-Adjusted[b]	
	Deaths	Censored	HR (95% CI)	HR (95% CI)	p-trend	Deaths	Censored	HR (95% CI)	HR (95% CI)	p-trend
p,p'-DDT[c]										
Tertile 1	56	151	1 (Reference)	1 (Reference)		21	186	1 (Reference)	1 (Reference)	
Tertile 2	69	139	1.28 (0.90, 1.82)	1.42 (0.99, 2.06)		29	179	1.43 (0.81, 2.50)	1.59 (0.90, 2.83)	
Tertile 3	61	146	0.98 (0.68, 1.41)	0.99 (0.68, 1.44)	0.70	24	183	1.20 (0.67, 2.15)	1.23 (0.68, 2.24)	0.30
p,p'-DDE[d]										
Tertile 1	54	156	1 (Reference)	1 (Reference)		28	182	1 (Reference)	1 (Reference)	

	5-Year All-Cause Mortality					5-Year Breast Cancer Specific-Mortality				
			Age-Adjusted[a]	Multivariable-Adjusted[b]				Age-Adjusted[a]	Multivariable-Adjusted[b]	
	Deaths	**Censored**	**HR (95% CI)**	**HR (95% CI)**	**p-trend**	**Deaths**	**Censored**	**HR (95% CI)**	**HR (95% CI)**	**p-trend**
Tertile 2	58	153	0.84 (0.57, 1.22)	0.81 (0.56, 1.19)		25	186	0.90 (0.52, 1.57)	0.92 (0.53, 1.62)	
Tertile 3	77	134	0.79 (0.54, 1.18)	0.66 (0.44, 0.99)	0.10	21	190	0.78 (0.41, 1.47)	0.70 (0.36, 1.37)	0.43
Chlordane[e]										
Tertile 1	40	155	1 (Reference)	1 (Reference)		20	175	1 (Reference)	1 (Reference)	
Tertile 2	68	128	1.48 (1.00, 2.20)	1.42 (0.94, 2.12)		27	169	1.46 (0.81, 2.62)	1.47 (0.81, 2.67)	
Tertile 3	70	125	1.23 (0.81, 1.87)	1.31 (0.86, 2.00)	0.07	24	171	1.43 (0.75, 2.72)	1.45 (0.76, 2.75)	0.35

Long Island Breast Cancer Study Project (LIBCSP) participants diagnosed with breast cancer between August 1, 1996 and July 31, 1997 and followed-up through December 31, 2011.

[a] Adjusted for age at diagnosis

[b] Adjusted for age at diagnosis, smoking status, income, body mass index, and parity/lactation history

[c] Lipid-adjusted p,p'-DDT concentration cut-points: Tertile 1 (<56.8ng/g), Tertile 2 (≥56.8–<91.2ng/g), Tertile 3 (≥91.2ng/g)

[d] Lipid-adjusted p,p'-DDE concentration cut-points: Tertile 1 (<467.1ng/g), Tertile 2 (≥467.1–<1,058.2ng/g), Tertile 3 (≥1,058.2ng/g)

[e] Lipid-adjusted chlordane (Σoxychlordane and *trans*-nonachlor) concentration cut-points: Tertile 1 (<81.1ng/g), Tertile 2 (≥81.1–<131.0ng/g), Tertile 3 (≥131.0ng/g)

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Table 3

Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between blood levels of organochlorines and mortality in the LIBCSP women diagnosed with breast cancer in 1996–1997 (n=625), stratified by BMI.

BMI <25kg/m²	**15-Year All-Cause Mortality**				**15-Year Breast Cancer Specific-Mortality**			
	Multivariable-Adjusted[a]				**Multivariable-Adjusted[a]**			
	Deaths	**Censored**	**HR (95% CI)**	**p-trend**	**Deaths**	**Censored**	**HR (95% CI)**	**p-trend**
p,p'-DDT[b]								
Tertile 1	16	78	1 (Reference)		8	86	1 (Reference)	
Tertile 2	29	71	2.32 (1.23, 4.38)		12	88	1.92 (0.76, 4.88)	
Tertile 3	20	65	1.43 (0.73, 2.79)	0.19	9	76	1.46 (0.55, 3.89)	0.56
p,p'-DDE[c]								
Tertile 1	25	96	1 (Reference)		15	106	1 (Reference)	
Tertile 2	23	73	0.72 (0.39, 1.33)		11	85	0.82 (0.34, 1.99)	
Tertile 3	18	48	0.53 (0.24, 1.14)	0.26	3	63	0.23 (0.05, 1.09)	0.18
Chlordane[d]								
Tertile 1	15	84	1 (Reference)		6	93	1 (Reference)	
Tertile 2	26	65	1.79 (0.92, 3.47)		15	76	2.93 (1.10, 7.79)	
Tertile 3	20	51	1.42 (0.69, 2.92)	0.27	17	64	1.72 (0.54, 5.48)	0.57
BMI ≥25kg/m²	15-Year All-Cause Mortality				15-Year Breast Cancer Specific-Mortality			
	Multivariable-Adjusted[a]				Multivariable-Adjusted[a]			
	Deaths	Censored	HR (95% CI)	p-trend	Deaths	Censored	HR (95% CI)	p-trend
p,p'-DDT[b]								
Tertile 1	39	73	1 (Reference)		13	99	1 (Reference)	
Tertile 2	40	63	1.10 (0.69, 1.75)		17	86	1.51 (0.71, 3.19)	
Tertile 3	40	80	0.73 (0.46, 1.17)	0.47	15	105	1.11 (0.51, 2.41)	0.37
p,p'-DDE[c]								
Tertile 1	29	59	1 (Reference)		13	75	1 (Reference)	

BMI <25kg/m^2	15-Year All-Cause Mortality				15-Year Breast Cancer Specific-Mortality			
	Multivariable-Adjusted[a]				Multivariable-Adjusted[a]			
	Deaths	Censored	HR (95% CI)	p-trend	Deaths	Censored	HR (95% CI)	p-trend
Tertile 2	35	77	0.77 (0.46, 1.29)		14	98	0.98 (0.45, 2.14)	
Tertile 3	57	84	0.67 (0.40, 1.11)	0.14	18	123	0.93 (0.42, 2.08)	0.98
Chlordane[d]								
Tertile 1	25	71	1 (Reference)		14	82	1 (Reference)	
Tertile 2	40	62	1.13 (0.66, 1.94)		12	90	0.94 (0.41, 2.14)	
Tertile 3	50	70	1.09 (0.63, 1.89)	0.24	17	103	1.36 (0.60, 3.08)	0.47

Long Island Breast Cancer Study Project (LIBCSP) participants diagnosed with breast cancer between August 1, 1996 and July 31, 1997 and followed-up through December 31, 2011.

[a] Adjusted for age at diagnosis, smoking status, income and parity/lactation history

[b] Adjusted for age at diagnosis, smoking status, income, body mass index, and parity/lactation history

[c] Lipid-adjusted p,p'-DDT concentration cut-points: Tertile 1 (<56.8ng/g), Tertile 2 (≥56.8–<91.2ng/g), Tertile 3 (≥91.2ng/g)

[d] Lipid-adjusted p,p'-DDE concentration cut-points: Tertile 1 (<467.1ng/g), Tertile 2 (≥467.1–<1,058.2ng/g), Tertile 3 (≥1,058.2ng/g)

[e] Lipid-adjusted chlordane (Σoxychlordane and *trans*-nonachlor) concentration cut-points: Tertile 1 (<81.1ng/g), Tertile 2 (≥81.1–<131.0ng/g), Tertile 3 (≥131.0ng/g)

Table 4

Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between blood levels of organochlorines and mortality in the LIBCSP women diagnosed with breast cancer in 1996–1997 (n=558), stratified by adult-lifetime weight-gain.

0-<20% gain	**15-Year All-Cause Mortality**			
			Multivariable-Adjusted[a]	
	Deaths	**Censored**	**HR (95% CI)**	**p-trend**
p,p'-DDT[b]				
Tertile 1	15	47	1 (Reference)	
Tertile 2	21	53	2.11 (1.03, 4.32)	
Tertile 3	15	53	0.81 (0.37, 1.75)	0.56
p,p'-DDE[c]				
Tertile 1	15	57	1 (Reference)	
Tertile 2	18	54	0.91 (0.43, 1.94)	
Tertile 3	18	45	0.92 (0.39, 2.16)	0.86
Chlordane[d]				
Tertile 1	12	56	1 (Reference)	
Tertile 2	17	39	1.55 (0.70, 3.41)	
Tertile 3	19	44	1.30 (0.58, 2.93)	0.22
20-<40% gain	15-Year All-Cause Mortality			
			Multivariable-Adjusted[a]	
	Deaths	Censored	HR (95% CI)	p-trend
p,p'-DDT[b]				
Tertile 1	19	48	1 (Reference)	
Tertile 2	21	31	1.30 (0.67, 2.51)	
Tertile 3	25	45	0.98 (0.50, 1.90)	0.82
p,p'-DDE[c]				
Tertile 1	21	44	1 (Reference)	
Tertile 2	19	40	0.71 (0.37, 1.38)	
Tertile 3	26	40	0.49 (0.24, 0.99)	0.09
Chlordane[d]				
Tertile 1	15	39	1 (Reference)	
Tertile 2	28	40	1.34 (0.69, 2.60)	
Tertile 3	20	39	0.72 (0.34, 1.52)	0.23
≥40% gain	15-Year All-Cause Mortality			
			Multivariable-Adjusted[a]	
	Deaths	Censored	HR (95% CI)	p-trend

0-<20% gain	15-Year All-Cause Mortality			
			Multivariable-Adjusted[a]	
	Deaths	Censored	HR (95% CI)	p-trend
p,p'-DDT[b]				
Tertile 1	17	41	1 (Reference)	
Tertile 2	20	32	1.11 (0.54, 2.25)	
Tertile 3	13	33	0.63 (0.28, 1.41)	0.68
p,p'-DDE[c]				
Tertile 1	11	32	1 (Reference)	
Tertile 2	16	42	0.95 (0.42, 2.15)	
Tertile 3	23	36	0.93 (0.40, 2.14)	0.40
Chlordane[d]				
Tertile 1	11	38	1 (Reference)	
Tertile 2	16	34	1.17 (0.50, 2.75)	
Tertile 3	19	32	1.01 (0.41, 2.50)	0.51

Long Island Breast Cancer Study Project (LIBCSP) participants diagnosed with breast cancer between August 1, 1996 and July 31, 1997 and followed-up through December 31, 2011.

[a] Adjusted for age at diagnosis, smoking status, income, body mass index and parity/lactation history

[b] Lipid-adjusted p,p'-DDT concentration cut-points: Tertile 1 (<56.8ng/g), Tertile 2 (≥56.8–<91.2ng/g), Tertile 3 (≥91.2ng/g)

[c] Lipid-adjusted p,p'-DDE concentration cut-points: Tertile 1 (<467.1ng/g), Tertile 2 (≥467.1–<1,058.2ng/g), Tertile 3 (≥1,058.2ng/g)

[d] Lipid-adjusted chlordane (Σoxychlordane and *trans*-nonachlor) concentration cut-points: Tertile 1 (<81.1ng/g), Tertile 2 (≥81.1–<131.0ng/g), Tertile 3 (≥131.0ng/g)