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DDT and Breast Cancer in Young Women: New Data on the Significance of Age at Exposure

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Abbreviations:

CI	Confidence Interval
p,p'-DDE	bis(4chlorophenyl)-1,1-dichloroethene
p,p'-DDT	bis(4chlorophenyl)-1,1,1-trichloroethane
o,p'-DDT	2-(2-chlorophenyl)-2(4-chlorophenyl)-1,1,1-trichloroethane
OR	Odds Ratio
P	Significance probability

Abstract

Background: Prior studies of DDT and breast cancer assessed exposure later in life when the breast may not have been vulnerable, after most DDT had been eliminated, and after DDT had been banned.

Objectives: Investigate whether DDT exposure in young women during peak DDT use predicts breast cancer.

Methods: We conducted a prospective, nested case-control study with a median time to diagnosis of 17 years using blood samples obtained from young women from 1959-1967. Subjects were members of the Child Health and Development Studies, Oakland, California, who provided blood samples 1 to 3 days after giving birth (mean age 26 years). Cases (n=129) developed breast cancer before age 50 years. Controls (n=129) were matched to cases on birth year. Serum was assayed for *p,p'*-DDT, the active ingredient of DDT, *o,p'*-DDT a low concentration contaminant, and *p,p'*-DDE, the most abundant *p,p'*-DDT metabolite.

Results: High levels of serum *p,p'*-DDT predicted a statistically significant five-fold increased risk of breast cancer among women who were born after 1931. These women were under age 14 in 1945, when DDT came into widespread use and mostly under age 20 as DDT use peaked. Women who were not exposed to *p,p'*-DDT before age 14 showed no association between *p,p'*-DDT and breast cancer (p=0.02 for difference by age).

Conclusions: Exposure to *p,p'*-DDT early in life may increase breast cancer risk. Many U.S. women heavily exposed to DDT in childhood have not yet reached age 50. The public health significance of DDT exposure in early life may be large.

Introduction

Most prior studies do not support the hypothesis that exposure to DDT is an important risk factor for breast cancer (Lopez-Cervantes et al. 2004). However, prior studies were limited by inability to measure exposure in young women, during periods of heaviest DDT use. Consequently most prior studies observed very low levels of *p,p'*-DDT and *o,p'*-DDT, the primary constituents of commercial DDT (Table 1). The conclusions of prior reviews apply to the effects of *p,p'*-DDE, the primary metabolite of *p,p'*-DDT (Lopez-Cervantes et al. 2004). *p,p'*-DDE is more persistent in the environment and in biological systems and could therefore be measured years after DDT use had declined (Stehr-Green 1989).

The present study investigates whether serum *p,p'*-DDT and *o,p'*-DDT are associated with breast cancer using blood samples obtained before DDT was banned, when use of this pesticide was very high (1960's). The median year of blood sampling in the present study was 1963, very close to the peak use of DDT in the United States in 1959 (U. S. Environmental Protection Agency 1975) and near the peak dietary content of DDT estimated around 1965 (Wolff et al. 2005). Exposure declined considerably thereafter, even prior to the DDT ban in 1972 (Kutz et al. 1991).

This is the first study to measure blood levels in young adulthood (mean age of 26 years). Prior studies collected blood when women were of middle age or much older (Table 1).

This is also the first study specifically designed, *a priori,* to consider whether age at exposure may modify DDT effects on breast cancer. Since DDT was first widely introduced in the United States beginning in 1945 (U. S. Environmental Protection Agency 1975), a woman's age in 1945 is a proxy for the youngest possible age at exposure to DDT and for her age when DDT use was peaking. A range of ages in 1945 is represented among women in the Child Health and Development Studies. Moreover these women could be observed prospectively. These data permit a unique design that tests the hypothesis that DDT associations with breast cancer are larger for birth cohorts where women could have been most heavily exposed in early life.

Materials and Methods

Subjects. Subjects were participants in the Child Health and Development Studies (CHDS), residents of the Oakland, California area and members of the Kaiser Permanente Health Plan who sought obstetric care between 1959 and 1967 (van den Berg et al. 1988). Subjects voluntarily participated in the CHDS, giving an oral informed consent for an in-person interview, collection of blood specimens at several points in pregnancy and the early postpartum, and permission for medical record access. The present study was reviewed and approved by The Institutional Review Board of the Public Health Institute and we have complied with all federal guidelines governing use of human participants.

Breast cancer cases were identified by linkage to the California Cancer Registry, and the California Vital Status Records (Cohn et al. 2001). All names for each CHDS subject are submitted for cancer linkages using fixed (i.e. birth date, sex, race and name) and changeable (i.e. address and patient record number) identifiers. A rigorous protocol is used to verify cases, comparing fixed versus changeable identifiers by manual review. The California Cancer Registry is reported to be >99 percent complete after a lag time of about 2 years (Kwong et al. 2001).

Cases were defined as women with incident invasive or non-invasive breast cancer diagnosed before age 50, or deaths due to breast cancer before age 50, obtained from linkage conducted in early 1998. There were 133 cases who met study criteria.

All members of the CHDS cohort are additionally linked to the California Department of Motor Vehicles (DMV) files on a regular basis to determine residence history allowing us to assess their control status and to update any name changes. All names registered with the DMV are used in establishing a match. Simultaneous linkage of multiple family members enhances matching. The regular DMV matching provides a history of location for each subject which is used to determine the population at risk for cancer, corresponding with geographic surveillance by California's cancer registries. Subjects who cannot be located are considered lost to follow-up at the date of their last definitive classification as a California resident. One control, matched exactly on birth year, was selected at random for each case from those who were under cancer surveillance and known to be free of breast cancer at the age of diagnosis for the matching case. The median time to diagnosis for cases was 17 years. The mean age at diagnosis was 44 years.

Serum Assays. In 2000-2001, we measured DDT-related compounds in serum samples that had been collected from 1959 through 1967. The mean age of subjects when blood was drawn was 26 years. Samples collected within one to three days of delivery were used for 82% of the cases and 86% of controls, while serum drawn during the third trimester was used for the remainder. Prior work has established correspondence of organochlorine levels assayed across all trimesters of pregnancy and soon after delivery (Longnecker et al. 1999). Serum samples had been stored at –20 degrees centigrade, and were first thawed to prepare an aliquot of 1.5 mL for organochlorine assays. The aliquots were shipped frozen to the laboratory. *p,p'*-DDE, *o,p'*-DDT and *p,p'*-DDT were assayed in the laboratory of Dr. Mary Wolff, using methods developed previously (Gammon et al. 2002). Sample order was randomly assigned within and across batches. Case-control pairs were analyzed in the same batches to minimize differences due to laboratory drift. The laboratory was blind as to case or control status of the samples. As described previously (Berkowitz et al. 2003), we used all observed positive values of *o,p'*-DDT in analyses, even those reported to be below the limit of detection; seven *o,p'*-DDT measurements with reported negative values were recoded as the lowest measured value (i.e., 0.01 ug/L). Inter-batch and intra-batch coefficients of variation were 16% and 5% respectively for *p,p'*-DDT, 11% and 4% for *p,p'*-DDE and 26% and 5% for *o,p'*-DDT. Total cholesterol and total triglycerides were measured enzymatically on the Hitachi 911 analyzer (Roche Diagnostics, Indianapolis, IN) in a lab certified by the Centers for Disease Control and Prevention and the National Heart Lung and Blood Institute Lipid Standardization Program.

Statistical Analysis. This report is based on 129 case-control pairs, matched on year of birth, after excluding 2 pairs with insufficient serum for lipid assays and 2 pairs with missing data on body mass index. We imputed *o,p'*-DDT for individuals within 15 pairs where the laboratory did not report data for *o,p'*-DDT using analysis of covariance based on year of blood draw, number of prior pregnancies, breast feeding , race, *p,p'*-DDT and *p,p'*-DDE. Findings were similar when the 15 pairs with imputed *o,p'*-DDT were excluded from analyses (details available on request from authors). We report results where these 15 pairs are included.

p,p'-DDT was considered the primary analysis variable as it is the main constituent of commercial grade DDT. Initial analyses examined the effect of mutual adjustment for the three DDT-related compounds: *p,p'*-

DDT, *o,p'*-DDT and *p,p'*-DDE where each compound was categorized in tertiles based on the control population and represented as two nominal variables: tertile 2 and tertile 3 where tertile 1 was the reference category. Data analyses were performed using age-matched, conditional logistic regression. Breast cancer associations were compared for the following models: 1) All three DDT-related compounds entered into the model simultaneously, 2) Compounds entered two at a time 3) Each compound entered alone. Based on the likelihood ratio test, we chose the best model for further examination of study hypotheses. Trend across tertiles of *p,p'*-DDT was tested using a continuous variable.

We examined whether age in 1945 (for the case-control pair) modified *p,p'*-DDT associations with breast cancer. This is a test of our *a priori* hypothesis that exposure to DDT in childhood and adolescence could increase susceptibility of the breast to DDT effects. Since DDT was first used widely in 1945 in the United States (U. S. Environmental Protection Agency 1975), age in 1945 is a proxy for the youngest age when a woman could have been exposed. For example, women born before 1930 were not exposed during early adolescence, being over age 15 when DDT was first introduced. By 1959, the first year of CHDS study enrollment, when DDT use was at its highest, these women would be age 29 years.

Age in 1945 was coded as a four category ordinal variable, defined by quartiles of age in 1945 represented in the study sample (< 4 years, 4-7 years, 8-13 years and >13 years). We estimated odds ratios for *p,p'*-DDT tertiles within quartiles of age in 1945, adjusted for year of blood draw and for *o,p'*-DDT, coded as an ordinal variable representing tertiles of *o,p'*-DDT, coded at the median values in the control population (Greenland 1995) (0.22 ug/L, 0.57 ug/L and 0.98 ug/L for tertiles 1, 2, and 3 respectively). *o,p'*-DDT was included in the model as it proved to be a confounder of the *p,p'*-DDT association.

In order to evaluate confounding by other measured breast cancer risk factors, we fit a series of models that entered one risk variable domain at a time to avoid adding a large number of variables to the model. Risk variable domains were: race/ethnicity (African American, Asian, mixed race with Caucasian as the reference category), number of prior pregnancies, blood lipids (total cholesterol and total triglycerides) (Longnecker et al. 2001), age at first pregnancy of 7 months or more, menarche before age 12 years (yes versus no), body mass index (BMI, weight/height^2 (kg/m^2), measured at the first interview in early pregnancy, coded as two nominal

variables: below the 33rd percentile and above the 66th percentile of the control distribution, versus the 33rd -66th percentiles), and whether the woman breast fed following the observed pregnancy (yes versus no).

Results

All subjects had detectable levels of *p,p'*-DDE and *p,p'*-DDT ($\geq$ 0.8 ug/L). Sixty-five percent of subjects had measurements of *o,p'*-DDT above the minimum detectable level of 0.4 ug/L.

Serum levels of *p,p'*-DDT and *p,p'*-DDE were considerably higher in the Child Health and Development Studies (CHDS) population than in populations where blood was sampled one to four decades later (Table 1 and Figure 1).

At the time of blood draw (median year of 1963), all birth cohorts in the CHDS sample had been potentially exposed to DDT for roughly the same number of years (1945-1963). However age at first possible exposure and age at blood sampling differs considerably among these women (Table 2). The age in 1945 quartiles represented in the CHDS population were: <4 years, 4-7 years, 8-13 years, >13 years (Table 2). Median age at blood sampling also differed for these four groups. Blood samples were drawn at a median age of 19 years for women who were youngest in 1945, compared to a median age of 36 years among women who were oldest in 1945 (Table 2). As noted in the discussion, both difference in age at exposure and age at blood sampling helps inform interpretation of findings for these four groups of women.

Table 3 presents estimates of breast cancer associations for DDT-related compounds for women of all ages in 1945. *p,p'*-DDT was associated with increased risk of breast cancer, while *o,p'*-DDT was associated with decreased risk of breast cancer. Adjustment for *o,p'*-DDT increased the *p,p'*-DDT association with breast cancer, but adjustment for *p,p'*-DDE made little contribution to association estimates for *p,p'*-DDT or *o,p'*-DDT, nor was *p,p'*-DDE significantly, independently associated with breast cancer.

Table 4 presents estimates of breast cancer associations for *p,p'*-DDT according to age in 1945, adjusted for *o,p'*-DDT and year of blood draw. There was an excess of *p,p'*-DDT in the serum of breast cancer cases a median of 17 years prior to diagnosis ($p<0.01$ for linear trend, Table 4), but only among women potentially exposed before age 14 years ($p=0.02$ for DDT by age interaction, Table 4). Body mass index did not account

for differences in *p,p'*-DDT associations by age in 1945 and there was no evidence that age in 1945 modified *o,p'*-DDT or *p,p'*-DDE associations with breast cancer (data not shown).

Table 5 is provided to compare associations for DDT-related compounds for women <14 years of age in 1945 with similar models for women of all ages previously shown in Table 3. Associations for *p,p'*-DDT were stronger in women <14 years of age in 1945.

Table 6 presents a series of models that adjust *p,p'*-DDT and *o,p'*-DDT associations for other measured breast cancer risk factors in women <14 years of age in 1945. There was little evidence of substantial confounding by any risk variables considered.

Discussion

High levels of serum *p,p'*-DDT, a median of 17 years before diagnosis, predicted a five-fold increased risk of breast cancer among women who were born after 1931. These women were under age 14 years in 1945, the year when DDT came into widespread use in the United States. These women would have mostly been under age 20 years as DDT use rose to its peak. Women who were not exposed to *p,p'*-DDT before age 14 (born in 1931 or earlier) and who would have been older than age 27 when DDT use peaked, showed no increased risk of breast cancer according to serum levels of *p,p*'-DDT. There was no evidence that any adjustment variables examined, including body mass index, explained the stronger *p,p'*-DDT association in women exposed at a young age.

Serum *o,p'*-DDT is one of the least persistent DDT-related compounds and is an indicator of recent, active exposure to DDT (Morgan and Roan 1975). Serum *o,p'*-DDT has usually not been studied in relation to breast cancer (Table 1). In this study, serum *o,p'*-DDT was inversely associated with breast cancer. This inverse association may be an indication that exposure to *p,p'*-DDT that occurred at a younger age, earlier in time, was the more important risk factor for breast cancer in this study population. On average, within *o,p'*-DDT tertiles, cases had higher levels of *p,p'*-DDT than their matched controls as evidenced by the significant *p,p'*-DDT associations in models adjusted for *o,p'*-DDT (Tables 3 and 5). There was no evidence that case-control differences in body mass could explain these findings (Table 6). Alternatively, the opposing direction

of breast cancer associations for *p,p'*-DDT and *o,p'*-DDT could be explained by different metabolic pathways and hence varying exposures to intermediate products of metabolism. Metabolic studies have shown that the rate of metabolism of these two compounds differs, with *o,p'*-DDT eliminated more quickly (Morgan and Roan 1975).

Our results are consistent with the hypothesis that *p,p'*-DDT retained longer, possibly due to slower metabolism, is the underlying risk factor for breast cancer in this study. However, it is impossible to rule out an alternative explanation, that women at greatest risk were simply more heavily exposed at a critical age; some years before their blood was sampled or during their pregnancy.

Birth cohorts which did not show a *p,p'*-DDT association in this study were older when first exposed and also older when their blood was sampled (Table 2). We cannot distinguish between the significance of these two factors: 1) perhaps the earlier birth cohorts were not exposed at a vulnerable age or 2) perhaps we would have detected a *p,p'*-DDT effect in the earlier birth cohorts if we could have measured their exposure at a younger age. Thus our findings do not rule out a *p,p'*-DDT association for earlier birth cohorts.

Possible mechanisms. Direct toxicity of *p,p'*-DDT, induction of enzymes that produce other genotoxic intermediates and DNA adducts, or covariance with another as yet unknown factor are possible explanations of the associations we observed. Studies of polychlorinated biphenyls suggest that genetic differences in metabolism may interact with body burden to predict breast cancer risk (Moysich et al. 1999).

Genotoxicity is one possible mechanism for the *p,p'*-DDT association that we observed. However, modern, highly sensitive molecular methods have only very recently been used to examine the genotoxicity of DDT in humans (Yanez et al. 2004).

Direct DNA damage to human blood cells, possibly with effects on immune surveillance has received recent attention in studies of DDT exposure in Mexico, where DDT use was not banned until 2000 (Perez-Maldonado et al. 2006; Perez-Maldonado et al. 2005; Yanez et al. 2004). This research group has paired *in vitro* investigations based on human blood cells with *in vivo* investigations of toxicity in blood samples collected from women and children in Mexico (Perez-Maldonado et al. 2006; Perez-Maldonado et al. 2005; Yanez et al. 2004). Doses tested *in vitro* exceeded levels of DDT-related compounds observed *in vivo*.

Nevertheless, *p,p'*-DDT and *p,p'*-DDE were associated with DNA damage *in vivo* for women (Yanez et al. 2004) and children (Perez-Maldonado et al. 2006) as well as *in vitro* (Yanez et al. 2004). The authors suggest that *in vitro* studies do not accurately simulate *in vivo* conditions because humans are exposed chronically over a long period to mixtures of *p,p'*-DDT and its metabolites, including toxic metabolites other than *p,p'*-DDE (Perez-Maldonado et al. 2005). We note that the median blood levels of DDT-related compounds in the present study were higher than average levels in women living in Mexico (Yanez et al. 2004). At this time, the biological significance of DNA damage associated with DDT-related compounds is not clear (Yanez et al. 2004). Further consideration of these exposures in experimental settings and in human populations could lead to better understanding of mechanisms for the associations we observed in the present study.

Comparison with other studies. The contrast between findings in the present study compared with largely negative results of prior studies can be explained by differences in study design. Below we discuss reasons for discrepancies between the present study and most others.

p,p'-DDE may not be an adequate proxy for exposure to DDT. Commercial grade DDT consists primarily of *p,p'*-DDT, as well as a low concentration contaminant, *o,p'*-DDT. Neither of these compounds are as persistent as *p,p'*-DDE, a highly lipophilic metabolite formed from *p,p'*-DDT (Morgan and Roan 1975; Stehr-Green 1989). Humans form *p,p'*-DDE from *p,p'*-DDT particularly during periods of active exposure to commercial DDT (Morgan and Roan 1975). However, humans also ingest *p,p'*-DDE directly, as it is present in foods containing animal fat and is more persistent than its parent compound (Longnecker et al. 1997). Thus, *p,p'*-DDE levels in human serum may not accurately reflect past exposure to *p,p'*-DDT, particularly when blood samples are obtained decades after exposure to *p,p'*-DDT. Moreover, individual differences in metabolism and body fatness may further complicate the interpretation of serum levels of *p,p'*-DDE in serum samples obtained long after direct exposure to DDT (Perry et al. 2005; Wolff and Anderson 1999; Wolff et al. 2005). There is prior empirical evidence that *p,p'*-DDT exposure may not be meaningfully approximated by *p,p'*-DDE in human serum. The ratio of these compounds in human serum is variable, and a higher level of *p,p'*-DDT for a given level of *p,p'*-DDE has been reported to be associated with adverse outcomes, including longer time to pregnancy in daughters exposed in utero (Cohn et al. 2003) and primary liver cancer (McGlynn et al. 2006).

Various DDT-related compounds do not have the same biologic activity. The compound *p,p'*-DDE acts as an anti-androgen, but not as an estrogen; *o,p'*-DDT acts as an extremely weak estrogen; and *p,p'*-DDT shows little or no androgenic or estrogenic activity (Kelce et al. 1995). Thus it is not likely that the *p,p'*-DDT association that we observed is due to estrogenic or androgenic activity. Moreover, it is reasonable to expect that the effects of these three compounds differ. Few prior studies measured all three compounds, or considered all three compounds simultaneously (Table 1).

Prior human studies have not measured exposure during critical periods of susceptibility (Birnbaum and Fenton 2003). For the human breast, the critical periods appear to be during fetal life, adolescence, and early reproductive life, particularly before the first full term pregnancy. Radiation, an established environmental risk factor for breast cancer, increases breast cancer risk most strongly when exposures occur early in life (Howe and McLaughlin 1996). Atomic bomb survivors under age 20 years had the greatest excess risk of breast cancer (Tokunaga et al. 1994). These findings are consistent with rodent studies which show that effects of environmental exposures depend on whether the exposure occurs during critical periods of mammary development (*in utero*, during puberty, or during pregnancy)(Fenton 2006).

The year of blood sampling may influence the strength of DDT associations with breast cancer. In nearly all prior studies, blood samples were collected in the mid-1970's and mostly much later, well after exposure to *p,p'*-DDT or *o,p'*-DDT could be directly observed for most women (Table 1 and Figure 1). Only one prior study was based on samples collected during years of heavier DDT use, in the 1960's, but *p,p'*-DDT and *o,p'*-DDT were not measured (Krieger et al. 1994). That study reported no overall association between *p,p'*-DDE and breast cancer (Table 1), consistent with the present study.

The United States Environmental Protection Agency estimated that the maximum use of DDT occurred in 1959 (U. S. Environmental Protection Agency 1975) and dietary DDT is estimated to have peaked around 1965 (Wolff et al. 2005). In the Second National Health and Nutrition Examination Survey, conducted between 1976 and 1980, *o,p'*-DDT was detectable in only 0.4% of human serum samples, while *p,p'*-DDT was detectable in 37.5% of human serum samples (Stehr-Green 1989). In contrast, *p,p'*-DDE was detectable in 99.5% of human samples. These survey data are consistent with early metabolic studies which reported that the rates of

elimination for DDT-related compounds differ considerably. Humans eliminate *o,p'*-DDT most rapidly, followed by *p,p'*-DDT and then *p,p'*-DDE (Morgan and Roan 1975).

Age at diagnosis. Most prior studies have included both pre-menopausal and postmenopausal cases (Table 1), but even studies that did stratify findings by age at diagnosis did not find significant breast cancer associations for *p,p'*-DDT or *p,p'*-DDE in younger or pre-menopausal women (Gammon et al. 2002; Lopez-Carillo et al. 1997; Romieu et al. 2000). We speculate that these studies share a common limitation, namely that reported levels of *p,p'*- DDT observed were much lower than those found in the present study (Table 1, Figure 1). Studies conducted with blood samples drawn in the 1970s and later could be more subject to misclassification of early life exposure, due to sampling well after peak DDT exposure (Figure 1).

Age at blood sampling. Most prior studies were based on blood samples that were obtained from middle aged or older women (Table 1), whereas blood samples were obtained at a mean age of 26 years in the present study. Accordingly, the failure to observe increased risk in earlier studies where *p,p'*-DDT was measured, may be explained if the breast is vulnerable to the cancer-promoting effects of DDT only during early breast growth and development.

Age at exposure. We found that serum *p,p'*-DDT was associated with breast cancer only for women potentially exposed at a young age (before age 14). These women would also have been mostly under the age of 20 when DDT use peaked. This finding is consistent with results obtained in studies of exposure to atomic bomb radiation where excess risk of breast cancer was observed primarily in women who were young at the time of exposure (Tokunaga et al. 1994).

Limitations of the present study. We were unable to sample serum serially by age to determine more precisely when the body burden of DDT-related compounds was acquired. However, our findings support the hypothesis that initial exposure to *p,p'*-DDT, during a critical period in early life, is more important for breast cancer development than chronic exposure to its metabolite, *p,p'*-DDE. As found in numerous prior studies (Lopez-Cervantes et al. 2004), *p,p'*-DDE was not related to breast cancer in this study population.

We could not determine how women acquired their exposure to DDT. However, we had information on farm residence in early life for 70% of our subjects as this question was added to a later revision of the intake

interview. Among those with available information, 78 percent of cases and 74 percent of controls reported no residence on a farm, suggesting that most DDT exposure occurred in the context of urban life, probably through diet and direct contact for insect control.

We lack information on risk factors between the time of the pregnancy we observed and the subsequent development of breast cancer. Thus we were not able to fully adjust for completed parity, lifetime lactation, or fluctuations in weight before or after the blood draw. However, we were able to adjust for body mass in early pregnancy, breast feeding following the observed pregnancy and age at first pregnancy, one of the strongest reproductive risk factors for breast cancer.

Lactation following the observed pregnancy, which we could measure, may have helped clear lipophilic DDT-related compounds acquired in early life, and may be more relevant to our hypothesis. Lactation was not a risk factor for breast cancer and any clearance of *p,p'*-DDT due to lactation after the observed pregnancy did not appear to confound the *p,p'*-DDT association with breast cancer (Table 6). However, breastfeeding was rare and short-term among women in this study. Only 34 percent of women breast fed and among those who did, 60 percent breast fed for less than 4 months. In a prior study of postmenopausal breast cancer, Moysich et.al. found evidence supporting a stronger association for body burden of organochlorines among parous women who had never lactated, suggesting that lactation could help protect the breast (Moysich et al. 1998). We did not see this interaction. The difference could be that our study measured exposure at a much younger age in relation to pre-menopausal breast cancer, which may have been initiated earlier in life.

It is possible that our method for adjusting for serum lipids may be imperfect and could also result in some residual confounding. Unmeasured and unknown confounders remain an alternative explanation of our findings.

We have suggested that the higher serum levels of DDT-related compounds observed in the present study (Figure 1) are due to blood collection during peak, active DDT exposure. We supported this interpretation by citing reports of declines in DDT-related compounds in human samples as DDT use declined. However it is possible that population differences in lactation history, or other factors could contribute to the differences seen in Figure 1.

Our study is limited by a relatively small sample size, and replication will be difficult because populations with samples obtained from young women during active DDT use are scarce. Follow-up of populations in countries with more recent and heavy use of DDT could provide new information. Timely sample collection during active exposure, in a population with a wide range of exposure, may increase power to detect effects even in small studies. For example, a prior study of dioxin exposure based on 15 cases in a cohort of 981 women accidentally exposed in Seveso, Italy, reported a significant dioxin effect on breast cancer (Warner et al. 2002).

The sample size for the present study might be considered a possible explanation of negative findings. However, the strong and statistically significant effect observed for *p,p'*-DDT (OR =5.4. $p<0.01$) is of more interest given the sample size. Although the effect estimate was not precise (95% CI=1.7-17.1) (Table 4, last column), the public health significance of DDT exposure is potentially large, even if the effect is actually closer to the lower limit of the 95% CI. This is because of the ubiquitous nature of DDT exposure.

Conclusion. It is too soon to decide that DDT exposure has little public health significance for breast cancer risk. We base this conclusion on 1) the long latency of possible effects on breast cancer, 2) the large numbers of women exposed world-wide, and 3) the evidence that we provide here which suggests that women exposed when young may be most strongly affected. Women born in the late 1950's and 1960's, who were heavily exposed when young, have not yet reached age 50, let alone the age of greatest breast cancer risk.

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Table 1. Studies of blood levels of DDT-related compounds and breast cancer

Year of Blood Draw	Place	Design	Age at blood draw (yrs)	Age at diagnosis or percent pre-menopausal	Cases:Controls	*p,p'*-DDE Association	*p,p'*-DDT association	*o,p'*-DDT association	*p,p'*-DDE [μg/g]	*p,p'*-DDT [μg/g]	*o,p'*-DDT [μg/g]
1963	N.California (CHDS)	Prospective, median follow-up 17 yrs	26	100% <50 yrs.	129:129	None	↑	↓	5.1	1.4	0·06 65% >LOD
1967	N.California (Krieger et al. 1994)	Prospective, mean follow-up 14 yrs.	45	20%	150:150	None	NR	NR	NR[a]	NR	NR
1974 or 1989	Maryland (Helzlsouer et al. 1999)	Prospective follow-up ≥10 yrs. for 70%	20% ≤ 40 (1974); 2.9% ≤ 40 (1989)	Not given	340:340	↓	NR	NR	" DDE" [b] 1.7 (1974) 1.2 (1989)	NR	NR
1979	Norway (Ward et al. 2000)	Prospective, mean follow-up 9 yrs	41	60% < 50 yrs.	150:150	None	None	NR	1.9 (1974) 1.6 (1976) 1.0 (1980) 0.44 (1988)	0.23 (1974) 0.16 (1976) 0.10 (1980) 0.02 (1988)	NR
1977 or 1982	Copenhagen (Hoyer et al. 1998; Hoyer et al. 2000)	Prospective, mean follow-up 8 yrs. (1977) and 5 yrs (1982)	55 (1977) 60 (1982)	32% 16%	240:477 155: 274	None	None (1977);(Hoyer et al. 1998) ↑ (for average of 1977 & 1982)(Hoyer et al. 2000)	NR	1.2 (1977) 1.2 (1982)	0.14 (1977) 0.05 (1982)	20% > LOD (1977)(Hoyer et al. 1998)
1982	Missouri (Dorgan et al. 1999)	Prospective follow-up ≤3 yrs for half, > 3 < 12 yrs. for half	57	21%	105:208	None	None	NR	2.4	0.3	4% > LOD
1986	NYC 1986 (Wolff et al. 2000b)	Prospective, follow-up 3 to 9 years	54	44%	148:295	None	NR	NR	1.10	NR	NR
1989	W. NY (Moysich et al. 1998)	Retrospective	41-85	0%	154:192	None	NR	NR	1.15(Laden et al. 2001)	NR	NR

Year of Blood Draw	Place	Design	Age at blood draw (yrs)	Age at diagnosis or percent pre-menopausal	Cases:Controls	*p,p'*-DDE Association	*p,p'*-DDT association	*o,p'*-DDT association	*p,p'*-DDE [μg/g]	*p,p'*-DDT [μg/g]	*o,p'*-DDT [μg/g]
1990	U.S. Nurses (Hunter et al. 1997)	Prospective, maximum follow-up 3 yrs(Hunter et al. 1997); extended to 5 yrs. (Laden et al. 2001)	59	18%(Laden et al. 2001)	372:372	↓, NS(Hunter et al. 1997); None (Laden et al. 2001)	NR	NR	0.82	NR	NR
1993	Mexico City (Romieu et al. 2000)	Retrospective	48	47%	120:126	↑, more so for postmenopausal women	None	NR	2.51	0·23	NR
1995	NYC 1995 (Wolff et al. 2000a)	Retrospective	54	37%	175:181	None	None	NR	0.66	0.03	NR
1995	Mexico City (Lopez-Carillo et al. 1997)	Retrospective	~50	50%	141:141	↓ , NS	None	NR	0.51	0.08	3% >LOD
1995	N. Carolina, African Americans (Millikan et al. 2000)	Retrospective	50 (both races)	51% (both races)	292:270	None; ↑among thinnest, NS	NR	NR	1.69	40% >LOD	1% > LOD
1995	N. Carolina, whites (Millikan et al. 2000)	Retrospective	50 (both races)	51% (both races)	456:389	↓, NS	NR	NR	0.76	40% >LOD	1% >LOD
1996	Connecticut(Zheng et al. 2000)	Retrospective	30-80	17% $\leq$ 45 yrs.	475:502	None	NR	NR	0.46	NR	NR
1996	Quebec (Demers et al. 2000)	Retrospective	53	Not given	315:219 or 307	None	None		0.48	0.01	NR
1996	L.I., NY (Gammon et al. 2002)	Retrospective	24-96	41%	633:418	None	None	NR	0.65	0.07	NR
1997	LA, CA, African Americans (Gatto et al. 2007)	Retrospective	49.7	35-64	381:335	None	NR	NR	1.25	NR	NR

Abbreviations: CHDS, Child Health and Development Studies which is the present study; LA, Los Angeles; L.I., Long Island; LOD, limit of detection; N, Northern; NR, not reported; NS, not statistically significant; NY,NewYork; ↓ indicates that risk declines as DDT compound increases; ↑ indicates that risk increases as DDT compound increases; Includes studies where exposure was measured in blood. With the exception of the second study in the table, which is the only other study conducted with bloods drawn in the 1960's, this table includes only studies where lipid-adjusted organochlorines are given. Lipid-adjusted organochlorine levels are presented to account for differences in lipid levels for study populations. If available, we report median levels or geometric means for controls. If these are not available, we report arithmetic means. Note that organochlorine

levels are not age-adjusted, so that some differences by study population could be due to age differences. Most studies reported that organochlorines are higher for older women. For *o,p'*-DDT, most studies only report percent above limit of detection (LOD). The present study is the exception. Year of blood draw is median or mean year and sometimes represents a single year. For the Quebec study, two sets of controls were given, the first set is hospital-based controls, and the second set is population-based controls. Mean or median age at blood draw given as reported for cases, if not given or could not be estimated then range is given.

[a]Lipid adjusted levels of *p,p'*-DDE not available, and *p,p'*-DDT and *o,p'*-DDT were not measured in this study. The arithmetic mean concentration of *p,p'*-DDE was 43 ug/L (Krieger et al. 1994) compared to median of 46 ug/L in the CHDS study. Both studies were based on blood samples drawn in the 1960's from N. California women enrolled in the Kaiser Permanente Health Plan, and are therefore highly comparable.

[b]In the Maryland Study, "DDE" was defined as *p,p'*-DDT + *o,p'*-DDT + p,*p'*-DDE for the 1974 cohort. For the 1989 cohort "DDE" was defined as *p,p'*-DDT + *p,p'*-DDE (Helzlsouer et al. 1999)

Table 2. Characteristics of study subjects (N=129 case-control pairs matched on year of birth) (page1 of 2)

Variable and Age in 1945[a]		Characteristics of Controls and Cases						Difference within matched pairs (Case-Control)	
		33rd percentile		50th percentile		66th percentile			
		Controls	Cases	Controls	Cases	Controls	Cases	Mean	Standard Error
p,p'-DDT (ug/L)									
< 4 yrs.		6.3	9.2	10.9	10.8	13.4	13.1	0.1	1.6
4-7 yrs.		6.9	7.7	8.4	10.0	13.5	15.8	3.1	2.1
8-13 yrs.		7.0	8.3	9.4	10.6	12.0	17.4	3.2	2.2
	<=13 yrs	7.0	8.7	9.1	10.6	12.9	14.8	2.1*	1.1
	> 13 yrs	11.9	9.5	14.0	13.6	18.2	15.4	-2.0	3.2
p,p'-DDE (ug/L)									
< 4 yrs.		33.4	37.9	39.2	44.4	54.3	53.4	2.5	6.5
4-7 yrs.		34.2	36.3	47.7	48.2	62.5	56.4	2.4	7.1
8-13 yrs.		29.4	33.8	38.7	40.3	51.4	55.0	4.5	7.2
	<=13 yrs	32.7	36.4	40.7	44.7	54.3	55.0	3.1	4.0
	> 13 yrs	42.4	36.9	52.8	48.9	61.9	55.7	-5.2	6.6
o,p'-DDT (ug/L)									
< 4 yrs.		0.42	0.47	0.57	0.54	0.73	0.70	0.07	0.15
4-7 yrs.		0.45	0.39	0.66	0.52	0.79	0.67	-0.07	0.19
8-13 yrs.		0.42	0.36	0.56	0.50	0.69	0.66	0.05	0.14
	<=13 yrs	0.42	0.39	0.57	0.52	0.74	0.67	0.02	0.09
	> 13 yrs	0.51	0.39	0.67	0.51	0.84	0.74	-0.23	0.15
Year of blood draw									
< 4 yrs.		1963	1963	1964	1964	1965	1965	0.0	0.4
4-7 yrs.		1962	1961	1964	1962	1965	1964	-0.9	0.6
8-13 yrs.		1961	1961	1962	1962	1963	1964	0.1	0.5
	<=13 yrs	1962	1962	1963	1963	1965	1964	-0.2	0.3
	> 13 yrs	1961	1960	1962	1961	1963	1962	-0.4	0.4
Age at blood draw									
< 4 yrs.		19	19	19	20	20	21	0.0	0.4
4-7 yrs.		23	22	24	23	25	24	-0.9	0.6
8-13 yrs.		27	28	29	28	29	29	0.1	0.5
	<=13 yrs	21	21	24	23	26	25	-0.2	0.3
	> 13 yrs	35	33	36	35	37	36	-0.4	0.4

		33rd percentile		50th percentile		66th percentile			
		Controls	Cases	Controls	Cases	Controls	Cases	Mean	Standard Error
Age at first pregnancy (yrs)									
< 4 yrs.		18	18	19	19	20	20	0.1	0.5
4-7 yrs.		21	20	21	21	24	22	-0.7	0.7
8-13 yrs.		21	24	23	25	24	27	2.0**	1.0
	<=13 yrs	20	20	21	21	23	23	0.5	0.4
	> 13 yrs	22	23	26	26	29	27	-0.3	1.4
Body mass index (kg/m2)[b]									
< 4 yrs.		21	21	22	22	25	24	-1.0	1.1
4-7 yrs.		21	21	22	23	23	24	0.6	0.7
8-13 yrs.		21	21	24	23	25	24	0.7	1.0
	<=13 yrs	21	20	22	22	24	23	-0.1	0.6
	> 13 yrs	21	22	23	23	25	24	-0.2	1.0
Number of prior pregnancies									
< 4 yrs.		0	0	0	0	0	1	0.1	0.1
4-7 yrs.		0	0	0	1	1	1	-0.1	0.2
8-13 yrs.		0	0	1	1	2	1	-0.6**	0.2
	<=13 yrs	0	0	0	0	1	1	-0.2*	0.1
	> 13 yrs	2	2	2	2	3	2	-0.3	0.4

[a]Age in 1945 corresponds to earliest possible age of exposure to DDT. Age in 1945 categories (< 4yrs., 4-7 yrs., 8-13 yrs., and >13 yrs.) correspond to quartiles represented in the study sample.

[b]Body mass index is based on measured weight and height obtained at an interview conducted in early pregnancy.

*p<0.10 for paired t-test for the hypothesis that the within pair difference = 0

**p<0.05 for paired t-test for the hypothesis that the within pair difference = 0

Table 3. Associations between DDT-related compounds and breast cancer with and without mutual adjustment: Women of all ages in 1945 (N=258, 129 case-control pairs matched on year of birth)

Model and Variables		OR [a]	95% CI	p
Model with all compounds				
p,p′-DDT	tertile 1	1.0	–	–
	tertile 2	1.9	0.9–4.1	0.09
	tertile 3	2.9	1.1–8.0	0.04
p,p′-DDE	tertile 1	1.0	–	–
	tertile 2	1.3	0.6–2.7	0.48
	tertile 3	1.0	0.4–2.4	0.92
o,p′-DDT	tertile 1	1.0	–	–
	tertile 2	0.5	0.3–1.0	0.06
	tertile 3	0.4	0.2–0.8	0.02
Models with two compounds				
Model 1				
p,p′-DDT	tertile 1	1.0	–	–
	tertile 2	2.0	0.9–4.2	0.07
	tertile 3	3.0	1.3–6.8	0.01
o,p′-DDT	tertile 1	1.0	–	–
	tertile 2	0.5	0.3–1.0	0.05
	tertile 3	0.4	0.2–0.8	0.01
Model 2				
p,p′-DDT	tertile 1	1.0	–	–
	tertile 2	1.5	0.7–3.0	0.26
	tertile 3	2.0	0.8–5.0	0.14
p,p′-DDE	tertile 1	1.0	–	–
	tertile 2	1.1	0.6–2.3	0.72
	tertile 3	0.7	0.3–1.7	0.40
Model 3				
p,p′-DDE	tertile 1	1.0	–	–
	tertile 2	1.8	1.0–3.4	0.06
	tertile 3	1.6	0.8–3.4	0.22
o,p′-DDT	tertile 1	1.0	–	–
	tertile 2	0.6	0.3–1.1	0.11
	tertile 3	0.5	0.3–1.0	0.06
Unadjusted Models				
p,p′-DDT only	tertile 1	1.0	–	–
	tertile 2	1.4	0.7–2.7	0.33
	tertile 3	1.6	0.8–3.0	0.18
p,p′-DDE only	tertile 1	1.0	–	–
	tertile 2	1.5	0.8–2.6	0.19
	tertile 3	1.1	0.6–2.0	0.85
o,p′-DDT only	tertile 1	1.0	–	–
	tertile 2	0.7	0.4–1.3	0.22
	tertile 3	0.6	0.4–1.1	0.12

Abbreviations: 95% CI, 95 percent confidence interval;OR,odds ratio; p, significance probability

[a]Odds ratios were estimated by conditional logistic regression. *p,p'*-DDT was represented as two indicator variables, tertile 2 and tertile 3 where tertile 1 was the reference category: tertile 1, <8.09 ug/L; tertile 2, 8.09-13.90 ug/L; tertile 3, >13.90 ug/L. *o,p'*-DDT was represented as two indicator variables, tertile 2 and tertile 3 where tertile 1 was the reference category: tertile 1, <=0.42 ug/L; tertile 2, 0.43-0.72 ug/L; tertile 3, >0.72 ug/L. *p,p'*-DDE was represented as two indicator variables, tertile 2 and tertile 3 where tertile 1 was the reference category: tertile 1, <=35.23 ug/L; tertile 2, >35.23-58.49 ug/L; tertile 3, >58.49 ug/L. No additional variables are in the models, other than those specified in the table.

Table 4. *p,p'*-DDT association with breast cancer stratified by the age of each case-control pair in 1945, the year DDT became widely used in the United States

	Age in 1945											
p,p'-DDT Level	All ages[a]		Age Quartile 1[a] <4 years		Age Quartile 2[a] 4-7 years		Age Quartile 3[a] 8-13 years		Age Quartile 4[a] ≥14 years		Age Quartiles 1-3[a] <14 years	
	OR[b]	*(95% CI)*	*OR*[b]	*(95% CI)*	*OR*[b]	*(95% CI)*	*OR*[b]	*(95% CI)*	*OR*[b]	*(95% CI)*	*OR*[b]	*(95% CI)*
Tertile1	1.0	–	1.0	–	1.0	–	1.0	–	1.0	–	1.0	–
Tertile 2	1.9*	(0.9–4.0)	7.0*	(0.9–55.5)	4.1	(0.6–29.3)	1.4	(0.4–5.4)	0.7	(0.1–3.3)	2.8**	(1.1–6.8)
Tertile 3	2.8**	(1.2–6.7)	11.5*	(1.0–138.9)	9.6	(0.7–137.2)	3.9	(0.8–19.2)	0.6	(0.1–3.2)	5.4#	(1.7–17.1)
P-value for trend[c]											0.01	
P-value for interaction between *p,p'* DDT and Age in 1945[d]											0.02	

Abbreviations: 95% CI, 95% Confidence Interval; OR,Odds ratio for *p,p'*-DDT

[a]All ages sample includes 258 subjects or 129 case-control pairs matched on year of birth. Categories of age in 1945 correspond to age quartiles in this sample. Quartile 1 consists of 34 case-control pairs, quartile 2 consists of 29 case-control pairs, quartile 3 consists of 33 case-control pairs and quartile 4 consists of 33 case-control pairs. Uneven numbers by quartile result from the age distribution in the sample.

[b]Odds ratios were estimated by conditional logistic regression models within subsets shown, matched on year of birth. Models included year of blood draw, *p,p'*-DDT represented as two indicator variables, tertile 2 and tertile 3 where tertile 1 was the reference category based on the distribution in the control population: tertile 1: <8.09 ug/L; tertile 2: 8.09-13.90 ug/L; tertile 3: >13.90 ug/L, and, *o,p'*-DDT was represented as a three category ordinal variable based on tertiles of the control population and coded at tertile medians of the control population: 0.22 ug/L, 0.57 ug/L and 0.98 ug/L for tertiles 1, 2, and 3 respectively.

[c]Test for trend was based on *p,p'*-DDT coded as a continuous variable in a conditional logistic model, adjusted as described in note *b* above.

[d]Estimated by a product term between a dichotomous variable for age in 1945 (< 14 years vs. ≥ 14 years) and *p,p'* DDT (continuous variable) in conditional logistic model adjusted as described in note *b* above.

*p<0.10

**p<0.05

# p<0.01

Table 5. Associations between DDT-related compounds and breast cancer with and without mutual adjustment: Women <14 years of age in 1945 (N=192, 96 case-control pairs matched on year of birth)

Model and Variables		OR [a]	95% CI	p
Model with all compounds				
p,p′-DDT	tertile 1	1.0	–	–
	tertile 2	2.5	1.0–6.3	0.05
	tertile 3	5.2	1.4–19.1	0.01
p,p′-DDE	tertile 1	1.0	–	–
	tertile 2	1.5	0.6–3.4	0.34
	tertile 3	0.9	0.3–3.0	0.90
o,p′-DDT	tertile 1	1.0	–	–
	tertile 2	0.5	0.2–1.2	0.13
	tertile 3	0.3	0.1–0.7	0.01
Models with two compounds				
Model 1				
p,p′-DDT	tertile 1	1.0	–	–
	tertile 2	2.6	1.1–6.4	0.04
	tertile 3	5.0	1.7–14.8	0.00
o,p′-DDT	tertile 1	1.0	–	–
	tertile 2	0.5	0.2–1.2	0.12
	tertile 3	0.3	0.1–0.7	0.01
Model 2				
p,p′-DDT	tertile 1	1.0	–	–
	tertile 2	1.7	0.8–3.8	0.18
	tertile 3	2.9	0.9–9.1	0.06
p,p′-DDE	tertile 1	1.0	–	–
	tertile 2	1.3	0.6–2.7	0.56
	tertile 3	0.6	0.2–1.7	0.32
Model 3				
p,p′-DDE	tertile 1	1.0	–	–
	tertile 2	2.2	1.0–4.8	0.04
	tertile 3	2.1	0.8–5.2	0.12
o,p′-DDT	tertile 1	1.0	–	–
	tertile 2	0.6	0.3–1.4	0.21
	tertile 3	0.4	0.2–1.0	0.06
Unadjusted Models				
p,p′-DDT only	tertile 1	1.0	–	–
	tertile 2	1.5	0.7–3.2	0.25
	tertile 3	1.9	0.9–4.2	0.09
p,p′-DDE only	tertile 1	1.0	–	–
	tertile 2	1.7	0.9–3.5	0.12
	tertile 3	1.2	0.6–2.4	0.62
o,p′-DDT only	tertile 1	1.0	–	–
	tertile 2	0.8	0.4–1.7	0.59
	tertile 3	0.6	0.3–1.2	0.18

Abbreviations: 95% CI, 95 percent confidence interval; OR,odds ratio; p, significance probability

[a]Odds ratios were estimated by conditional logistic regression. *p,p'*-DDT was represented as two indicator variables; tertile 2 and tertile 3 where tertile 1 was the reference category: tertile 1, <8.09 ug/L; tertile 2, 8.09-13.90 ug/L; tertile 3, >13.90 ug/L . *o,p'*-DDT was represented as two indicator variables, tertile 2 and tertile 3 where tertile 1 was the reference category: tertile 1, <=0.42 ug/L; tertile 2, 0.43-0.72 ug/L; tertile 3, >0.72 ug/L. *p,p'*-DDE was represented as two indicator variables, tertile 2 and tertile 3 where tertile 1 was the reference category: tertile 1, <=35.23 ug/L; tertile 2, >35.23-58.49 ug/L; tertile 3, >58.49 ug/L. No additional variables are in the models other than those specified in the table.

Table 6. *p,p'*-DDT association with breast cancer before and after adjustment for other risk factors: Women <14 years of age in 1945[a]

	OR	95% CI	p
Model 1			
p,p'-DDT tertile 1	1.0	–	–
p,p'-DDT tertile 2	2.8	1.1–6.8	0.03
p,p'-DDT tertile 3	5.4	1.7–17.2	0.00
o,p'-DDT (tertile 3 versus tertile 1)	0.3	0.1–0.7	0.00
Year of blood draw	1.0	0.8–1.2	0.97
Model 2			
p,p'-DDT tertile 1	1.0	–	–
p,p'-DDT tertile 2	2.7	1.1–6.8	0.03
p,p'-DDT tertile 3	5.4	1.7–17.3	0.00
o,p'-DDT (tertile 3 versus tertile 1)	0.3	0.1–0.7	0.01
Year of blood draw	1.0	0.9–1.2	0.88
Number of previous pregnancies	0.8	0.5–1.2	0.23
Model 3			
p,p'-DDT tertile 1	1.0	–	–
p,p'-DDT tertile 2	3.0	1.2–7.4	0.02
p,p'-DDT tertile 3	6.7	1.9–24.1	0.00
o,p'-DDT (tertile 3 versus tertile 1)	0.3	0.1–0.6	0.00
Year of blood draw	1.0	0.9–1.2	0.88
Total cholesterol (mg/dl)	1.0	1.0–1.0	0.53
Total triglycerides (mg/dl)	1.0	1.0–1.0	0.95
Model 4			
p,p'-DDT tertile 1	1.0	–	–
p,p'-DDT tertile 2	2.8	1.1–7.0	0.02
p,p'-DDT tertile 3	5.8	1.8–19.0	0.00
o,p'-DDT (tertile 3 versus tertile 1)	0.3	0.1–0.7	0.00
Year of blood draw	1.0	0.8–1.2	1.00
BMI tertile 1[b]	1.3	0.6–2.8	0.58
BMI tertile 3[b]	1.2	0.5–2.5	0.70
Model 5			
p,p'-DDT tertile 1	1.0	–	–
p,p'-DDT tertile 2	2.7	1.1–6.6	0.04
p,p'-DDT tertile 3	5.4	1.7–17.7	0.01
o,p'-DDT (tertile 3 versus tertile 1)	0.3	0.1–0.7	0.01
Year of blood draw	0.9	0.8–1.1	0.50
Age at first pregnancy (yrs.)	1.1	1.0–1.2	0.18

Model 6			
p,p'-DDT tertile 1	1.0	–	–
p,p'-DDT tertile 2	2.8	1.1–7.1	0.03
p,p'-DDT tertile 3	5.4	1.7–17.1	0.00
o,p'-DDT (tertile 3 versus tertile 1)	0.3	0.1–0.7	0.00
Year of blood draw	1.0	0.8–1.2	0.92
Menarche before age 12	1.1	0.6–2.3	0.74
Model 7			
p,p'-DDT tertile 1	1.0	–	–
p,p'-DDT tertile 2	3.1	1.2–8.2	0.02
p,p'-DDT tertile 3	7.3	2.1–26.0	0.00
o,p'-DDT (tertile 3 versus tertile 1)	0.2	0.1–0.6	0.00
Year of blood draw	1.0	0.9–1.2	0.61
African American[c]	0.9	0.4–2.0	0.75
Asian[c]	0.1	0.0–1.3	0.08
Mixed-race[c]	1.7	0.6–5.3	0.35
Model 8			
p,p'-DDT tertile 1	1.0	–	–
p,p'-DDT tertile 2	3.0	1.2–7.7	0.02
p,p'-DDT tertile 3	6.4	1.9–21.5	0.00
o,p'-DDT (tertile 3 versus tertile 1)	0.3	0.1–0.7	0.00
Year of blood draw	1.0	0.8–1.2	0.96
Breastfeeding in observed pregnancy (yes versus no)	1.4	0.8–2.8	0.27

Abbreviations: OR, Odds Rato; 95% CI, 95 percent confidence interval; p, significance probability.

[a]Odds ratios were estimated by conditional logistic regression. Each model is based on 192 subjects representing 96 case-control pairs matched on year of birth. *p,p'*-DDT was represented as two indicator variables, tertile 2 and tertile 3 where tertile 1 was the reference category. Tertiles of *p,p'*-DDT were based on the distribution in the control population: tertile 1, <8.09 ug/L; tertile 2, 8.09-13.90 ug/L; tertile 3, >13.90 ug/L. *o,p'*-DDT was represented as a three-category ordinal variable based on tertiles in the control population: tertile 1, $\leq$0.42 ug/L; tertile 2, 0.43-0.72 ug/L; tertile 3, >0.72 ug/L; and coded at the median value within each tertile: 0.22 ug/L, 0.57 ug/L and 0.98 ug/L for tertiles 1, 2, and 3 respectively. Odds ratios for *o,p'*-DDT are given for difference between the median in the third tertile and the median in the first tertile which is 0.76 ug/L. Model 1 is the same model shown in the last column of Table 4 and is provided here to allow comparison with estimates after adjustment for other breast cancer risk factors.

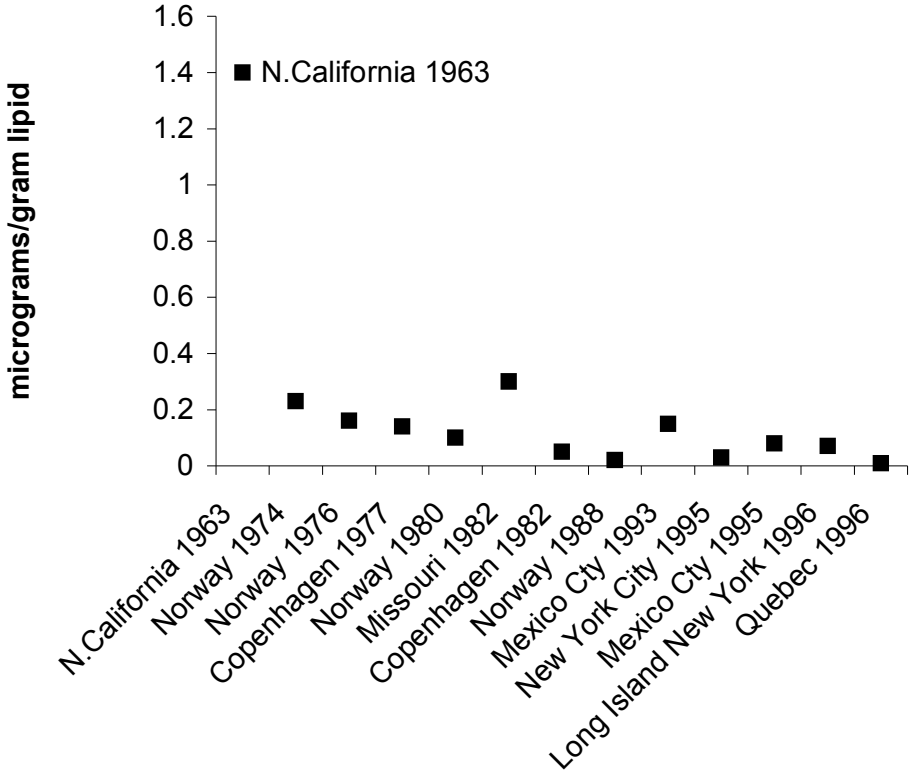
[b]Reference category is 33rd-66th percentiles of body mass index (kg/m^2). Percentiles are based on distribution of body mass in controls. The 33rd percentile was defined as $\leq$21.23 kg/m^2; the 66th percentile was defined as >23.71 kg/m^2

[c]Reference category is Caucasian.

***FIGURE LEGEND**

Figure 1. Reported *p,p'*-DDT and *p,p'*-DDE levels in blood observed in epidemiological studies of breast cancer by year and place of blood draw. **A** *p,p'*-DDT **B** *p,p'*-DDE Note difference in scale for A and B. The median that was reported for the control group is pictured whenever given in the original paper. If the median was not available, then geometric or arithmetic mean is shown, depending on what was given in the original paper. Only prior studies that reported lipid-adjusted levels in blood samples are shown because lipids confound observed levels. One other study, based on 1960's blood samples, but without lipid adjustment (Krieger et al. 1994) is shown in Table 1. That study reported high levels of *p,p'*-DDE consistent with present study, but did not measure *p,p'*-DDT. References alphabetically by location: N.California, 1963 (present study), Connecticut 1996 (Zheng et al. 2000), Copenhagen 1977(Hoyer et al. 1998), Copenhagen 1982 (Hoyer et al. 2000), Long Island, New York 1996 (Gammon et al. 2002), Los Angeles 1997 (Gatto et al. 2007), Maryland 1974 (Helzlsouer et al. 1999), Mexico City 1993 (Romieu et al. 2000), Mexico City 1995 (Lopez-Carillo et al. 1997), Missouri 1982 (Dorgan et al. 1999), New York City 1986 (Wolff et al. 2000b), New York City 1995 (Wolff et al. 2000a), North Carolina, African Americans 1995 (Millikan et al. 2000), North Carolina, whites (Millikan et al. 2000), Norway 1974, 1976 and 1988 (Ward et al. 2000), Quebec 1996 (Demers et al. 2000), U.S. Nurses 1990 (Hunter et al. 1997), Western New York 1989 (Moysich et al. 1998)

A *p,p'*-DDT



B *p,p'*-DDE