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Correlation of body mass index with serum DDTs predicts lower risk of breast cancer before age 50: Prospective evidence in the Child Health and Development Studies

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Abstract

Many suspected breast cancer risk factors, including the pesticide dichlorodiphenyltrichloroethane (DDT) and its metabolite dichlorodiphenyldichloroethylene (DDE), are stored in fat where they could influence carcinogenesis. We tested the hypothesis that the relationship of DDT and DDE (DDTs) with adiposity is modified by disposition to develop breast cancer. We predicted that concentrations of serum DDTs would be inversely correlated with body mass index (BMI) during active exposure when DDTs move into the larger fat pool. We described this correlation an average of 17 years before breast cancer was diagnosed, in a prospective nested case-control study in the Child Health and Development Studies. Women entered the study during pregnancy from 1959-1966 when DDT was in active use. 133 breast cancer cases were diagnosed under age 50 as of 1998. Mean time to diagnosis was 17 years. 133 controls were matched to cases on birth year. We observed the expected inverse correlation of serum DDTs with BMI only in women who remained cancer-free and not in women who ultimately developed breast cancer (p for interaction <0.05). Findings suggest that vulnerability to breast cancer before age 50 may be associated with an uncoupling of the inverse correlation between BMI and serum DDTs. Investigation into mechanisms may eventually reveal early biomarkers of breast cancer risk.

Keywords

breast cancer; DDT; DDE; body mass index; adipose; prospective; Child Health and Development Studies

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CONFLICT OF INTEREST

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INTRODUCTION

Previous Research on DDT and Breast Cancer in the Child Health and Development Studies

The Child Health and Development Studies (CHDS) is a large pregnancy cohort that began in 1959 [1-3] with long-term follow-up for cancer in two generations including fathers, mothers and their now-adult children.[4-9] Commercial "DDT" (dichlorodiphenyltrichloroethane, *p,p'-DDT)* is a pesticide that was used heavily in the United States beginning in 1945, peaking in 1959 and finally banned in the U.S. in 1972.[8, 10] The compound *p,p*'-DDT is the highest concentration ingredient of commercial "DDT" and the component responsible for its insecticidal properties. (https://www.atsdr.cdc.gov/toxprofiles/tp35-c4.pdf, accessed 5/17/18). In a previous prospective study in the CHDS we reported that *p,p'*-DDT assayed in early postpartum serum samples was associated with breast cancer diagnosed before age 50, an average of 17 years after blood collection. The *p,p'*-DDT association was strongest in birth cohorts that were initially exposed to DDT prior to age 14 (Odds Ratio = 5.4, 95 percent Confidence Interval=1.7,17.1, p-value for interaction with age at exposure=0.02 (see Table 4 in Cohn et al.).[5]

Lipophilic carcinogens, body fat function and breast cancer

In 2015, the International Agency for Research on Cancer classified DDT as 'Probably carcinogenic in humans (Group 2A) citing sufficient evidence that DDT causes cancer in experimental animals and limited evidence in humans".[11] Both *p,p'*-DDT and its primary metabolite *dichlorodiphenyldichloroethylene (p,p'-DDE)* are lipophillic and are persistently stored in human adipose tissue, including in the breast.[12, 13] It is notable that adipose tissue also surrounds breast epithelial cells, the primary cell type in which breast cancer develops, and has been implicated in extensive paracrine effects on breast carcinogenesis. We posit that the dual roles of adipose tissue in paracrine carcinogenesis and in storing lipophilic contaminants may not be independent, and that adipose tissue may also respond to lipophilic exposures in ways that are further permissive of carcinogenesis.[14] Several lines of evidence support this notion. For example, DDTs have experimentally produced at least two key characteristics of carcinogens in adipose: inflammation (e.g. macrophage infiltration) and altered nutrient supply (e.g. perturbed nutrient processing and increased adipose mass).[15-18] Additionally, predisposition to mammary cancer appears to make mice more susceptible to adipose tissue abnormalities (e.g. increased adipose mass) that are viewed as mammary cancer risk factors.[19] These observations raise the possibility that predisposition to breast cancer somehow influences adjacent adipose tissue function with respect to lipophilic chemical storage and carcinogenic processes; raising the possibility that adipose tissue function is an early marker for breast cancer risk.

Objective and Rationale for the Present Study.

As adipose tissue accumulates, given concentrations of DDTs are accumulated into a larger fat pool causing their dilution on a lipid basis. During active exposure to DDTs it is thus expected that DDTs would be sequestered in fat leading to an inverse correlation of serum and adipose levels of DDTs with body fat mass.[20] We indirectly explore here whether predisposition to breast cancer alters adipose tissue properties in women who develop early

breast cancer. Thus we predicted that women who went on to develop breast cancer by age 50 over an average follow-up of 17 years would not show the expected negative correlation of body mass index (BMI) with lipophilic DDTs at baseline.

CHDS blood samples were collected from 1959-1967, prior to the ban on DDT in the United States.[8] Therefore the null hypothesis in the present study is that there would be an inverse correlation of body mass index (BMI) with serum *p,p'*-DDT and serum *p,p'*-DDE in all CHDS subjects at baseline, regardless of their future breast cancer status. The present study tests this hypothesis in an effort to help discover whether higher adipose levels of DDTs, beyond what is explained by toxicokinetics, are a possible mechanism for the DDT – breast cancer associations we have previously observed in the CHDS.

MATERIALS AND METHODS

Design

In this prospective, nested case-control study we investigated correlations of serum DDT compounds with body mass index for peripartum women who subsequently developed breast cancer compared with women who remained cancer-free.

Subjects.

The study population is a subset of the Child Health and Development Studies (CHDS) pregnancy cohort that was the basis of our previous prospective study on postpartum serum DDT and subsequent breast cancer.[5] The sample size for the current study was based on the study sample for our previous report in order to further discover possible mechanisms that explained our finding that postpartum serum DDT predicted risk of breast cancer. Briefly, pregnant women entered the study at an average age of 26 years, during pregnancies occurring from 1959-1966 (with deliveries extending through 1967) and have been followed for place of residence, vital status, and cancer incidence since that time.[5] Archived pregnancy serum samples were collected from 1959-1967 during peak DDT exposure in the U.S., and were assayed for *p,p'*-DDT, *p,p'*-DDE and *o,p'*-DDT in non-fasting early postpartum samples drawn between 1-3 days after delivery. The laboratory that measured serum DDT compounds was blind to case status. Cases and their matched control were assayed in the same batch with order randomized within batch and case-control strata were randomized across batches. Details are given in our previous report.[5] For the present study we report on 133 women diagnosed with breast cancer before age 50 as of 1998. Cases were diagnosed an average of 17 years after entry into the study. One control subject, who remained free of breast cancer as of the age of the case, was matched to each case on year of birth. This study population is the basis of our previous report on postpartum DDT and subsequent breast cancer in the CHDS where details are given.[5]

Statistical Methods

Height measured in early pregnancy and weight measured closest to the time the blood sample was drawn was used to calculate maternal body mass index (weight in kg/ height in m^2) (BMI). In order to address the role of blood lipids in analyses we compared and report results of models for two alternative approaches: 1) DDT outcomes based on wet weight

(ng/mL) adjusted for serum triglycerides and cholesterol within the model and 2) DDT outcomes standardized for serum cholesterol and triglycerides (ug/g lipid)[21], which we refer to as lipid standardized DDTs throughout the manuscript. This strategy was based on a report by Schisterman et al. which demonstrated reduced bias of estimates over several causal scenarios using adjustment for lipids within the model.[22] However, we also provide results for lipid standardized DDTs for the purposes of comparison with other reports prevalent in the literature.[22] We estimated the linear association of BMI with natural log-transformed (ln) *p,p'*-DDE, and ln *p,p'*-DDT for cases compared to controls, using Proc Mixed in SAS 9.3 to account for matching. The model contained an indicator variable for case status (yes vs. no), BMI, and a product term between case status and BMI to test whether the association of BMI with serum DDT compounds differed for women who subsequently developed breast cancer compared to women who did not. Models were adjusted for African American race/ethnicity (yes versus no), age, and number of previous births (parity). Models were based on 129 controls and 130 cases after excluding 2 controls and three cases due to missing data on BMI and 2 controls with insufficient serum for lipid assays. We tested equality of variance using the Brown-Forsythe test which was not significant for case control comparisons of *p,p'*-DDE or *p,p'*-DDT. *p,p'*-DDT and *p,p'*-DDE distributions were highly skewed. Natural log transformation did not result in perfect normality, but was superior to square and cube root transformations. We conducted additional sensitivity analyses. First we conducted an additional non-parametric analysis by calculating partial Spearman correlation coefficients (Proc Corr in SAS 9.3) to determine whether results would be consistent with regression results. We examined outliers using box plots to identify observations that were > 1.5 x the interquartile range for the DDT compounds to investigate whether these outliers showed patterns suggesting laboratory error. We excluded case-control strata from Proc Mixed regression models where Cooks Distance exceeded 0.03 (4/130 strata) and compared estimates of BMI slopes with those based on the full sample to determine the impact of influential observations on regression models. Subjects voluntarily participated in the CHDS, giving oral informed consent. This study was approved by the Institutional Review Board for the Protection of Human Subjects at the Public Health Institute. Code Availability: Computer code used in this study can be obtained from the authors. Analyses were completed using Statistical Analysis System (SAS) 9.3. All statistical tests were two sided.

RESULTS

Blood samples for this study were collected at a time when DDT use was active and widespread in the U.S. Therefore all CHDS women were exposed and DDTs were detected in 100% of serum samples. Characteristics of cases and controls are shown in Table 1. Figure 1 presents correlations of BMI with lipid standardized DDT compounds for breast cancer cases an average of 17 years prior to diagnosis compared to controls. We observed an inverse correlation between BMI and early postpartum serum *p,p'*-DDE or serum *p,p'*-DDT among women who remained free of breast cancer before age 50 (Figure 1). In contrast, we did not observe an inverse correlation between BMI and early postpartum DDTs among women who subsequently developed breast cancer before age 50 (Figure 1). The patterns shown in Figure 1 were also observed for DDTs measured as wet weight concentrations

unadjusted for serum lipids (Supplemental Figure A). After adjustment for parity, race, and age, the case-control differences in BMI correlations with *p,p'*-DDE and *p,p'*-DDT (interactions) were statistically significant in regression models (Table 2). The inverse correlation of BMI with DDT compounds was statistically significant for controls (Table 2). In contrast, there was no evidence of a statistically significant BMI correlation with DDT compounds for cases either before (Figure 1 and Supplemental Figure A) or after adjustment for age, race, and parity (Table 2). These findings are consistent with results from Spearman partial correlation analysis which does not require normal distribution of the dependent variable (Table 3). Significant negative Spearman partial correlations of BMI with DDT compounds were observed for controls with no significant correlations observed among cases (Table 3). Examination of outliers (> 1.5 x interquartile range) revealed that most outliers were on the lower end of the DDT and DDE distributions for controls. These outliers were women with high BMIs, an observation consistent with the hypothesis that BMI would be inversely correlated with DDTs.. The outliers did not cluster by sample batch and did not occur within case-control pairs which were analyzed in the same batch. We had no basis for excluding these outliers as bad data points. When we used Cooks Distance > 0.03 to exclude influential observations from regression analyses reported in Table 2, whether for lipid standardized or wet weight DDT models, we still observed statistically significant interactions of BMI by case status, significant inverse BMI slopes for controls, and no significant association of BMI with DDT compounds among cases (for example see Supplemental Table A). When we excluded these outliers from graphs shown in Figure 1, the graphs remain consistent with results of multivariate models (see Supplemental Figure B). Thus we found little evidence that outliers drove study observations and no evidence to warrant excluding them.

DISCUSSION

It is well understood that a larger mass of fat will dilute a given amount of lipophilic chemical, e.g. DDTs, stored in the fat. As expected,[14, 23] in a cross-sectional assessment of BMI and DDT during an active DDT exposure period (1960s), we found an inverse correlation between BMI and serum DDTs in women who remained cancer-free. We were surprised that this correlation was only observed in women who remained cancer-free, but was absent in women who subsequently developed breast cancer.

Why would the inverse relationship between serum DDTs and BMI be uncoupled in women who subsequently developed breast cancer before age 50? This difference between cases and controls is not likely to be due to the presence of occult breast cancer because these subjects were an average age of 26 years at the time of blood sampling, and an average of 17 years prior to diagnosis. The difference in the BMI – DDTs relationship in cases vs. controls is unlikely to be a cohort effect [23] given case and control samples are from the same actively exposed cohort and cases and controls are matched on birth year. Further, we found no evidence that year of blood draw, which varied only from 1959-1967, explained our findings or influenced results.

The absence of an inverse correlation between BMI and serum DDTs in women who went on to develop breast cancer before age 50 appears to result from altered metabolism of

DDTs in their fat tissue. A given tissue concentration of DDTs can be altered by a difference in exposure, or in the amount of DDTs entering or leaving the tissue. Determining the mechanism of this interplay between DDTs, obesity, and later breast cancer may help identify biomarkers of breast cancer risk among women exposed to DDTs.

Host factors, particularly excess body fat, could increase the toxicity of lipophilic xenobiotic chemicals by enhancing their accumulation and carcinogenic characteristics in body fat adjacent to breast epithelium. Siiteri and colleagues previously suggested that the interplay of environmental factors and host tissue characteristics could help explain why only some women with higher estrogen exposure, such as those with high body fat in the menopause, develop estrogen-related cancer while others do not.[24]

Advantages

The prospective design of this study, with an average follow-up of 17 years, minimizes the likelihood of reverse causation. The timing of blood collection was during active DDT exposure. It was therefore possible to observe pre-existing differences in BMI-DDT correlations during active exposure for women who developed breast cancer before age 50 compared to women who did not. By examining breast cancers diagnosed before age 50, we reduced heterogeneity in the diagnosis group.

Limitations

Our study does not address the majority of breast cancers which occur in women older than age 50 and also does not address tumor subtypes. Our study is also limited because it considers only DDTs. It is possible that other environmental chemicals or other factors correlated with DDTs account for our findings. We could not determine when DDT exposure occurred in our study participants. Therefore we do not know whether case-control differences reflect long-term storage differences or shorter-term response to recent exposure. We measured DDT in non-fasting serum samples and it is possible that the DDT-BMI associations we observed do not reflect a steady state. Since this same condition applies to both cases and controls we do not expect this limitation to directionally bias our findings, though it could contribute to greater variance of our estimates of association. We addressed possible case/control differences in fasting state by directly adjusting for serum levels of cholesterol and also triglycerides which increase and bind DDT following high fat ingestion, at least in rats.[25] Our results apply primarily to the DDT-BMI associations proximal to pregnancy and the early postpartum which might not reflect equilibrium or the relationship of BMI and DDTs at other points in the life-course. However the pregnancy and the postpartum windows are considered to be critical windows of susceptibility for breast cancer.[26] This study did not identify levels of DDTs in adipose tissue directly. Perhaps animal studies can make additional contributions to measure DDTs in both serum and adipose to better evaluate DDT-related risk for breast cancer. This would be an important contribution as birth cohorts who were DDT-exposed are now at the age of breast cancer risk and might benefit.

CONCLUSIONS

Since many potential environmental chemicals are nearly ubiquitous exposures, research strategies that characterize differential response may eventually identify susceptible individuals, mechanisms and also prevention strategies. There may be a number of opportunities to provide mechanistic clues by querying response to exposure based on other plausible biological mechanisms. Adipose may be one of many modifiers of exposure effects. The role of adipose in risk modification appears to vary early, prior to diagnosis, in susceptible women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

BMI	body mass index
DDE	dichlorodiphenyldichloroethylene
DDT	dichlorodiphenyltrichloroethane
CHDS	Child Health and Development Studies
ln	natural log

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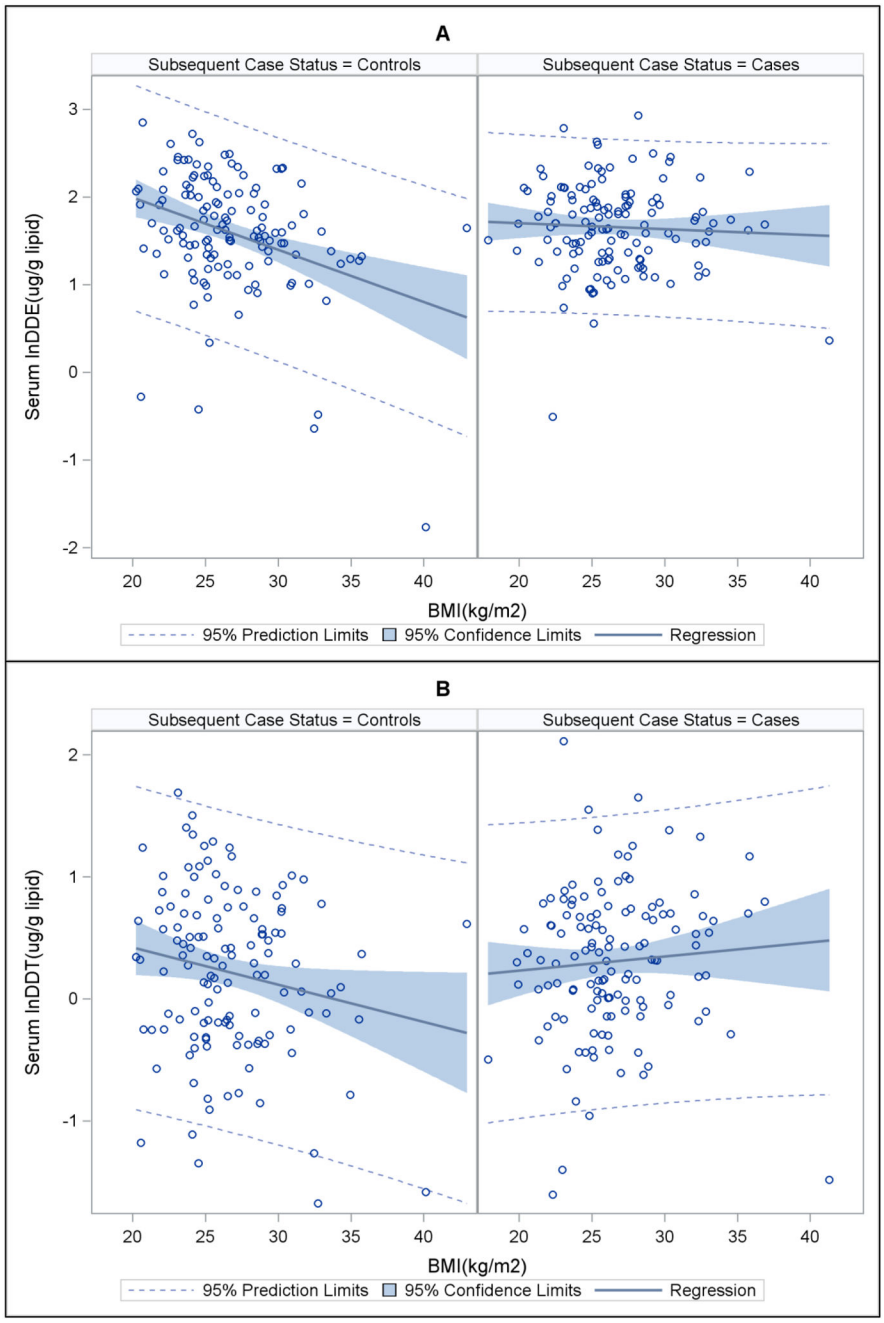

Figure 1.

Correlation of body mass index with lipid standardized serum DDTs an average of 17 years before diagnosis with breast cancer (cases) compared to women who remained cancer-free (controls). Regression lines shown are unadjusted for any other covariables. Panel A: *p,p'* DDE. Panel B: *p,p'*-DDT.

Table 1.

Characteristics of controls and cases an average of 17 years before diagnosis

	Controls (N=129)			Cases (N=130)		
	Percentile			Percentile		
	25th	50th	75th	25th	50th	75th
Serum *p,p'*-DDT (ng/mL)	6.9	11.8	16.1	8.3	11.6	17.8
Serum *p,p'*-DDE (ng/mL)	31.0	43.3	63.5	34.2	46.8	62.2
Serum *p,p'*-DDT (ug/g lipid)	0.8	1.3	2.0	0.9	1.4	2.0
Serum *p,p'*-DDE (ug/g lipid)	3.7	5.0	7.7	3.9	5.4	7.2
BMI closest to blood draw (kg/m^2)	24.1	25.9	28.9	23.9	25.9	28.5
Age at blood draw (years)	22	26	31	21	26	31
Cholesterol (mg/dL)	201	254	321	216	256	308
Triglycerides (mg/dL)	144	191	256	147	194	260
Number of previous births	0	1	2	0	1	2
	Controls (N=129)			Cases (N=130)		
	Percent (n)			Percent (n)		
African-American	26 (33)			21 (27)		

Abbreviation: BMI, body mass index

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Table 2.

Association of BMI with serum DDTs according to subsequent breast cancer diagnosis an average of 17 years later

A. Models using wet weight concentrations of DDTs as outcomes and also adjusted for triglycerides and cholesterol within the model				
Outcome		**Estimated change[a] in ng/mL per kg/m^2**	**(95%CI)**	**P$_{interaction}$[b]**
ln *p,p′*DDT (ng/mL)				
	Controls	**−0.04** *	(−0.07,−0.01)	
	Cases	0.01	(−0.02, 0.03)	
ln *p,p′*-DDE (ng/mL)				0.01
	Controls	**−0.06** **	(−0.09,−0.04)	
	Cases	−0.01	(−0.03, 0.02)	
				0.004
B. Models using lipid standardized DDTs as outcomes				
Outcome		**Estimated change[a] in ug/g lipid per kg/m^2**	**(95%CI)**	**P$_{interaction}$[b]**
ln *p,p′*DDT (ug/g lipid)				
	Controls	**−0.04** *	(−0.07,−0.01)	
	Cases	0.00	(−0.02, 0.03)	
ln *p,p′*-DDE (ug/g lipid)				0.03
	Controls	**−0.06** **	(−0.09,−0.04)	
	Cases	−0.01	(−0.04, 0.02)	
				0.04

Abbreviations:BMI, Body Mass Index(kg/m^2); ln, natural log; ug, microgram; g, gram; ng, nanogram; mL, mililiter

[a]Estimated Body Mass Index (BMI) slopes significantly different from zero are shown in bold. Slopes were estimated by linear regression in a model containing a dichotomous variable for breast cancer diagnosed as of 1998, body mass index (BMI) nearest to DDT sampling, a product term between case status and BMI, and adjusted for age, race and parity. Models based on DDT wet weight concentrations as outcomes were additionally adjusted for triglycerides and cholesterol. Serum samples were collected between 1959 and 1967, an average of 17 years prior to diagnosis for breast cancer cases. Cases were diagnosed before age 50 and were matched, retrospectively, to one control exactly on year of birth. This analysis included 130 cases (3 cases excluded due to missing data on BMI) and 129 controls (2 controls excluded due to missing data on BMI and 2 controls excluded due to insufficient serum for lipid assays).

[b]P$_{interaction}$ is the significance probability for difference in BMI slope for breast cancer cases compared to controls.

*p≤0.01

**p<0.0001

Table 3.

Spearman partial correlation coefficients for BMI with DDT compounds

	Controls (N=129	Cases (N=130)
ln *p,p'*-DDE (ng/mL)	-0.3^{a**}	0.04^{a}
ln *p,p'*- DDT (ng/mL)	-0.2^{a*}	0.14^{a}
ln *p,p'*-DDE (ug/g lipid)	-0.3^{b***}	-0.02^{b}
ln *p,p'*- DDT (ug/g lipid)	-0.2^{b*}	0.11^{b}

[a]Adjusted for age, race, parity, triglycerides and cholesterol

[b]Adjusted for age, race, and parity

*p<0.03

**p<0.0005

***p<0.0001