Improving Organochlorine Biomarker Models for Cancer Research

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Abstract

Multivariate methods were used to predict levels of dichlorodiphenyldichloroethene (DDE) and polychlorinated biphenyl (PCB) concentrations in plasma from characteristics that included age, diet, race, reproductive history, socioeconomic status, and reported body mass index (BMI) at several decades of life before blood collection. Measurements were available for organochlorine compound (organochlorines), cholesterol, and triglycerides in plasma from 1,008 women participants in a population-based case-control study of breast cancer undertaken in 1996 to 1997 on Long Island, NY. Organochlorine compound levels were associated with age, race, lactation history, body size characteristics, and plasma lipids. PCB predictors also included fish consumption. DDE was correlated with current BMI, BMI at every decade of age from ages 20 to 60 years, and BMI-gain (from ages 20 or 30 years to 1997). In contrast, PCBs were correlated inversely with both BMI (fifth to seventh decades of age) and BMI-gain. After adjusting for covariates, DDE and PCB were both positively associated with BMI and inversely with BMI-gain; they were lowest with low BMI, high BMI-gain, and longer lactation. This pattern is consistent with a pharmacokinetic model that predicts higher body burdens during windows of highest uptake, faster elimination of organochlorine compounds in leaner women, and lowered levels accompanying BMI-gain. As a result, lifetime intake for specific organochlorine compound may lead to different plasma levels dependent on changes in body size, absolute intensity of intake, and whether exposure is ongoing (i.e., PCB) or long discontinued (i.e., DDE). (Cancer Epidemiol Biomarkers Prev 2005;14(9):2224–36)

Introduction

Dichlorodiphenyltrichloroethane (DDT), its metabolite dichlorodiphenyldichloroethene (DDE), polychlorinated biphenyls (PCB), dieldrin, and chlordane are persistent organochlorine compounds that were distributed widely in North America by 1950. They have subsequently been banned in the United States, DDT in 1972 and PCBs in 1977. However, because levels in the environment declined slowly, human exposure only gradually tapered off. By 1990, dietary intakes of DDE and DDT were negligible according to Food and Drug Administration reports (1). PCBs in the environment were also relatively low by 2000, but exposure still exists, especially in freshwater fish (2). For example, in 1992, striped bass from the New York Harbor Estuary had average PCB levels of 1,560 ng/g wet weight, whereas average DDT levels were 174 ng/g wet weight (3). In the population, most neutral organochlorine compounds (but not tetrachlorodibenzodioxin and PCBs) have shown a parallel decline, with elimination half-lives in the range of 7 to 15 years (4, 5).

Organochlorine compound biomarker measurements have been done in numerous studies of cancer etiology, including the Long Island Breast Cancer Study Project (LIBCSP; ref. 6). Their use as biomarkers has been based on their presumed reflection of long-term exposure, an inference based on their strong correlations with age and relatively long half-lives. In the body, organochlorine compounds reside mainly in adipose (80%), with rapid, passive distribution to blood and other tissues proportional to their neutral lipid content. Yet, body mass index (BMI; weight in kg divided by height in meters squared), a surrogate for adiposity, exhibits both positive and negative correlations with organochlorine compound levels in cross-sectional studies (6-19). On the other hand, reported relationships between BMI and elimination rate (expressed as rate constants or half-life) are consistently positive, such that a higher BMI results in a longer half-life (13, 15, 20-27). In addition, weight loss leads to more rapid elimination of organochlorine compounds (28-31), as does lactation; that is, breast-feeding can reduce a woman's body burden rapidly [half-life, 0.5-2 years (32-35)].

Among nonoccupationally exposed persons, age is the strongest predictor of organochlorine compounds measured in adipose tissue or blood. Some studies have also noted associations with dietary intake (11), geography (36), lactation (37), and BMI (11, 36). In both general (11, 36, 38, 39) and special (40, 41) populations, fish consumption is commonly (42), but not always (43), associated with PCB levels.

Together, these observations suggest that the temporal sequence of organochlorine compound exposure and related pharmacokinetic factors might influence organochlorine compound levels. Besides the reported associations of organochlorine compound with BMI (6-19), relationships with reproductive history are also inconsistent, and all explanatory variables typically explain <30% of the variance. Therefore, this relatively unexplored area of environmental epidemiology invites further study. Better models to predict organochlorine compound biomarker exposure may improve

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study of cancer risk as well as other health-related outcomes. To address this question, we undertook an analysis of organochlorine compound predictors in a population-based study of women on Long Island, NY.

Materials and Methods

Study Overview. The LIBCSP population has been described (6). In brief, a population-based case-control study was conducted. Eligible women included residents of Nassau and Suffolk counties, ages ≥20 years, who spoke English. Cases (n = 1,508) were newly diagnosed with *in situ* or invasive breast cancer between August 1, 1996 and July 31, 1997. Controls (n = 1,556), randomly selected through random-digit dialing (women ages <65 years) and Health Care Financing Administration Rosters (women ages ≥65 years), were frequency matched by the 5-year age group to the expected age distribution of the cases. The in-person interview included an interviewer-administered questionnaire and a self-administered modified Block Food Frequency Questionnaire, and a nonfasting blood sample was taken. A similar percentage (>70%) of cases (n = 1,102) and controls (n = 1,141) donated blood.

Assessment of Predictors. Factors considered as potential predictors of organochlorine compound levels were assessed as part of the 2-hour case-control interview (6). Information was collected on sociodemographic characteristics (age, race, and education). Women were queried about their weight by decade of adult life, starting at age 20 years until the year before diagnosis (44). Lifestyle characteristics included a smoking history and alcohol intake patterns for each decade of life. Detailed reproductive information was collected for each pregnancy, including the calendar year of the pregnancy and the duration of breast-feeding. Calendar year and total years of residence on Long Island were assessed using a lifetime recall of home addresses.

Laboratory Assays. Organochlorine compounds were determined as reported previously (6). DDE was detected (>0.1 μg/L) in >99% of women and PCBs in >98% (PCB 138) and 100% (PCB 153). Due to the high assay cost, a random subset of the study population (646 cases and 429 controls) was selected for the organochlorine compound laboratory analyses (details of sample selection provided in ref. 6). The current study was restricted to women who identified themselves as either White or African American. Thus, of the 1,075 women with organochlorine compound measurements, those with missing lipid values (n = 7), with incomplete DDE or PCB values (n = 3), or whose race could not be classified as non-Black or non-White (n = 22) were excluded. Women missing information on BMI at age 30 years (BMI30) or at reference date (current BMI; n = 35) were excluded because these factors were among the strongest pharmacokinetic predictors of organochlorine compound levels in our study population. An additional two women who were missing BMI at age 20 years (BMI20) were retained in final analyses. Final analyses were conducted on 1,008 women, specifically 1,007 with DDE and 998 with PCB values and covariates.

Statistical Analyses. We used continuous values of DDE and PCBs, as described previously in detail (6), with the PCB variable defined as the sum of the four major PCB congeners (IUPAC nos. 118, 153, 138, and 180). This sum constituted ~50% of the total PCBs in the LIBCSP population. Organochlorine compound levels were $\log_e$ (ln) transformed to achieve normality. No differences in organochlorine compounds were seen between cases and controls (6), including models stratified by reproductive factors, BMI, tumor estrogen receptor/progesterone receptor positivity, and stage of disease. In addition, the strongest organochlorine compound predictors in control-only models were similar to those in case-control models, and predictors in the final models adjusted or stratified by case-control status were identical for DDE and were not materially different for PCBs (data not shown). Therefore, to increase the stability of estimates, cases and controls were combined for all data analyses. Statistical analyses were done using SAS-PC version 9.0 (SAS, Inc., Cary, NC).

To compare our results with historical studies, Spearman correlations and age-partial Spearman correlations were computed for organochlorine compound-BMI correlations. Additionally, Spearman correlations (r_S) were computed to examine the relationship between lipid-corrected organochlorine compound levels and potential continuous predictors. Median levels of continuous characteristics were compared across organochlorine compound tertiles using the Kruskal-Wallis test (45). Finally, the Mantel-Haenszel χ^2 test was used to determine whether categorical variables were associated with organochlorine compound levels (46).

To be consistent with the usual practice, we first modeled organochlorine compound values that were corrected for total plasma lipid levels using the algorithm derived by Akins et al. (47) as recommended by Phillips et al. [ref. 48; total lipids (g/L) = triglycerides + 2.27 × cholesterol + 0.623]. In the resulting models, a portion of the variability in lipid-corrected organochlorine compound levels was due to the underlying correlation between plasma lipids and some of the independent variables (e.g., age, BMI, or race). The Akins algorithm may have limitations for certain populations; for example, it was derived from a small sample that included both men and women. Therefore, models for log-transformed, non-lipid-corrected DDE and PCBs were fit with the characteristics of interest using the SAS general linear models procedure. Cholesterol and triglycerides were included as independent predictors of non-lipid-corrected organochlorine compound levels. In these models, cholesterol was a statistically significant predictor for both DDE and PCBs, whereas triglycerides was statistically significant only for PCB levels. This further suggests that the Akins equation may not adequately correct for total lipids. A further justification for presenting models based on non-lipid-corrected organochlorine compound values is that not all previously published findings were lipid corrected. Furthermore, almost identical estimates for the pharmacokinetic variables were found using lipid-corrected organochlorine compounds. However, bivariate comparisons are based on lipid-corrected values to reduce the variability introduced by lipids to some of these relationships.

We investigated models of organochlorine compounds with predictors of primary interest, including age at reference date, body size characteristics, and breast-feeding history. Weight and BMI were available for each decade from ages 20 to 70 years as well as for age at reference date. The predictive value of BMI was similar to the predictive values of weight, considered independently or adjusted for height; therefore, only BMI was used in the models. Variables representing the change in BMI from age 20 years to reference age (BMI20-gain), change in BMI from age 30 years to reference age (BMI30-gain), BMI at reference date (current BMI), average adult BMI (mean of BMIs reported at each decade), and BMI at various calendar time points or intervals pertaining to organochlorine compound exposure opportunities (e.g., BMI and BMI-gain before 1945, in windows from 1945 to 1975 and afterward, years when widespread commercial use of DDT or PCBs did or did not exist or after they were banned). Rate of change of weight

and BMI were also examined. Variables were also derived to represent duration of lactation as well as the temporality of lactation before, during, and after widespread commercial use of DDE and PCBs. Body fat was estimated using published equations for women (49).

Based on the literature as well as on our unique study population characteristics (e.g., total years of residence on Long Island), other (secondary) predictors of organochlorine compounds were investigated. Secondary organochlorine compound predictors and their optimal definitions included case/control status, race (Black/White), education (high school or less/more than high school), marital status (ever/never), having been breast-fed as an infant (ever/never), parity (ever/never), age at first birth, menopausal status (premenopausal/postmenopausal), alcohol intake during the year before reference date (0, 1.0-42.2, or >42.2 gm/d), cigarette smoking (current/former/never), total years of residence on Long Island, age first moved to Long Island, and weekly servings of vegetables (green, yellow vegetables, tomatoes, and potatoes), meat (beef, pork, liver, and prepared meats), fish, and dairy products (cream, milk, cheese, and yogurt). Eggs, poultry, nuts, fruits, total meat (fish + poultry + meat), and various combinations of grains were also considered.

Model building proceeded in a forward stepwise fashion conducted manually. First, the main effects of all predictors were independently explored in the base model, which adjusted for reference age in years, cholesterol, and triglycerides. Model components were included to maximize the R^2, the mutual influence of variables in the model, and a characteristic's own β and statistical significance. Each added variable was examined to obtain the fewest categories needed to retain the underlying interrelationships and to maximize the stability of the estimates (e.g., tertiles, quartiles, and quintiles of both BMI and BMI-gain). Multiplicative interaction was evaluated by a test of differences in the −2 log likelihoods of models with and without the interaction term included (50), including interactions for BMI × age, BMI × lactation, BMI-gain × lactation, age × lactation, and BMI or lactation within calendar windows related to exposure. The resulting variables and their definitions are those presented in the final models, which may be useful to include as confounders in study of organochlorine compounds and cancer risk. Secondary characteristics were then added one at a time to the best-fitting primary predictor models.

Finally, to be complete, best-fitting models were determined in subgroup-specific analyses, where the predictive ability of other characteristics under consideration might be more clearly observed. These included women who never-lactated, women with stable adulthood BMI, and women in 5- and 10-year age groups. Older women should have had greater variance in, and higher exposures to, organochlorine compounds than younger women, which could increase power to detect an association.

Pharmacokinetic models were generated using Microsoft Excel. Dietary exposure data of DDT and DDE (daily intake) for the models were obtained from surveys conducted by Food and Drug Administration and other agencies reported for 1965 to 1996 (1, 51-56). A first-order kinetic model was constructed by estimating adipose concentration at available time points from dietary intake in each of the available years (i.e., [adipose concentration] = [added DDE during the interval dt] + [DDE before the interval] × $e^{-k \times dt}$, where k for lean persons is −0.13, the elimination rate constant corresponding to a half-life of 5.3 years; dt is years from [DDE before] to [added DDE]). The [added DDE] is the dietary intake (μg/d) over the interval dt derived from references above for 1965 to 1996 multiplied by 1.9. Brackets (e.g., [added DDE]) denote ''concentration''. For obese persons, [added DDE] was divided by 2 to account for lipid dilution, and the rate constant was increased from −0.13 to −0.065, corresponding to a half-life of 10.7 years. Values of DDE daily intake (μg/d) were deduced for years before reported values (<1965) to obtain nonzero initial values. PCB models similar to those for DDE could be created using imputed and available PCB dietary intakes with the same rate constants as for DDE. However, the models are very speculative because we did not find data on PCBs in the diet before 1977 when highest exposure occurred. For comparison, ''actual'' plasma DDE levels were compared with the pharmacokinetic predictions, by computing running averages for 5-year intervals, obtained from various published values (including refs. 5–15, 57, 58). When only adipose data or lipid-based plasma data were available, they were converted to whole basis by dividing by 140, which gave values most consistent with the non-lipid-corrected data.

Results

In our study, DDE levels showed a positive correlation with current BMI, whereas PCBs had a negative correlation (Table 1). In the LIBCSP study, DDE and PCB levels were correlated (r_S = 0.62), but as seen in Table 2, DDE levels were higher than PCBs [medians (interquartile ranges), 4.2 (2.2-8.3) versus 2.4 (1.7-3.4) μg/L, respectively, and 663 (375-1,246) versus 372 (277-534) ng/g lipid, respectively]. Both DDE and PCB increased with age, Black race, having been breast-fed as an infant, longer residence on Long Island, and less education. Parity (>4 births) was positively associated with DDE; parity was not associated with PCB levels. Parous women who lactated had lower organochlorine compound levels, although the lactation influence was much weaker for PCBs than DDE. Triglycerides increased with lipid-corrected DDE levels, whereas all lipid variables were inversely correlated with lipid-corrected PCBs. Neither alcohol intake nor smoking history was associated with organochlorine compounds. Fish intake was positively correlated with PCB levels, and dairy consumption was inversely associated with both DDE and PCB. Dietary intakes of vegetables, meat, dairy products, and other foods were not related to organochlorine compounds (data not shown).

BMI at every decade as well as BMI20-gain and BMI30-gain increased with DDE levels (lipid corrected; Table 2). Less than 10% of women had negative BMI-gain [i.e., they reported a weight loss from age 20 years (n = 70) or age 30 years (n = 49) until reference date (44)]. PCBs showed an inverse correlation with both BMI (at ages 50, 60, and 70 years and at reference date) and BMI-gain but had a positive correlation with BMI20. Age adjustment marginally changed the correlation of DDE with BMI variables and reduced the correlation with BMI-gain, whereas correlation of PCBs with BMI and BMI-gain were improved with the age-partial. The Spearman correlation (r_S) of current BMI with DDE went from 0.20 to 0.15 after partialing on age, and the correlation with BMI30-gain became statistically nonsignificant (from 0.11 to 0.01 after age-partial). The PCB correlation with current BMI changed from −0.048 (nonstatistically significant) to −0.11 ($P < 0.001$) when adjusted for age. The correlation of PCBs with BMI30-gain changed from −0.11 to −0.21 (both statistically significant) with age adjustment.

Relationships of BMI30-gain with age and organochlorine compound levels are shown in Table 3. The median current BMI increased >50% from the lowest to highest quintile of BMI-gain along with ~30 kg increase in weight and 22 kg increase in estimated body fat. Median DDE levels increased 25%, whereas median PCB levels decreased ~20%, between the lowest and the highest quintiles of

Table 1. Reported correlations between organochlorine compound levels and BMI at time of biological sample collection relative to 1972 (the year that DDT use was banned in the United States) from selected reports, including recent breast cancer studies and earlier studies with reported correlations

No. years between 1972 and year of sample collection	Correlation coefficient of BMI with		Biological* sample	Study design
	DDE	PCB		
−7	(Negative)	(Negative)	Blood serum	James et al. (16): Cohort study of pregnant women; PCBs were sum of nine penta-heptaCBs
4	−0.11		Adipose	Wolff and Anderson (15)†: Cross-sectional, females, all ages, Michigan farm residents seen in 1976; ''higher PCBs'' measured by sum-of-area comparison to Aroclor 1254 for penta-heptaCBs (not congener specific)
4	0.18		Adipose	Wolff and Anderson (15)†; Cross-sectional, males, all ages, Michigan farm residents 1976; PCBs as in ref. 15
6	−0.014	−0.2	Blood serum	Wolff et al. (19)†; Cross-sectional, all ages, Michigan general population; PCBs as in ref. 15
8	−0.20	−0.23	Adipose	Wolff and Anderson (15)†; Cross-sectional, females, all ages, Michigan farm residents seen in 1980; PCBs as in ref. 15
8	0.34	0.22	Adipose	Wolff and Anderson (15)†; Cross-sectional, males, all ages, Michigan farm residents seen in 1980; PCBs as in ref. 15
10	(Positive)	(Negative)	Blood serum	Dorgan et al. (14); Breast cancer nested case-control study; PCBs were sum of 27 tri-octaCBs
15	0	−0.29	Blood serum	Wolff et al. (13); Breast cancer case-control study; PCBs were sum of 16 penta-heptaCBs
18	(Positive)‡	0	Blood serum	Laden et al. (12); Breast cancer cohort study; PCBs were sum of 16 penta-heptaCBs
24	0.03	−0.23	Blood serum	Moysich et al. (11); Breast cancer case-control study
20	(Positive)‡		Adipose	van't Veer et al. (10); Breast cancer case-control study
21	0.12‡	−0.17	Blood serum	Millikan et al. (9); Breast cancer case-control study, blacks; PCBs were sum of 35 tetra-octaCBs
21	0.09‡	−0.08	Blood serum	Millikan et al. (9); Breast cancer case-control study, Whites
23	0.35‡	0.10	Blood serum	Stellman et al. (8); Breast cancer case-control study; PCBs were sum of 14 tri-heptaCBs
24	0.21	−0.15	Blood serum	Wolff et al. (7); Breast cancer case-control study; PCBs were sum of 16 penta-heptaCBs
25	0.20	−0.11	Blood serum	Gammon et al. (6) (This study); Breast cancer case-control study; PCBs were sum of four highest PCBs (nos. 118, 138, 153, and 180)

*Organochlorine compound values were lipid based or lipid adjusted in correlations and analyses, with the exception of ref. 19.
†Additional unpublished data from the study population in refs. 15 and 19 as indicated.
‡These correlations were not age adjusted. The correlations were age-adjusted Spearman, Pearson, or multiple regression coefficients.

BMI30-gain. Among other characteristics that influence organochlorine compound levels, median current age increased with BMI30-gain, leveling off in the upper two quintiles. Never-lactators were more likely to have higher BMI30-gain, and women who had lactated >56 weeks had less BMI30-gain.

DDE and PCB Models for Age and Lactation. The effect of previous lactation on organochlorine compound levels, including various combinations of parity and duration of lifetime lactation in quartiles, was explored in detail. For example, median DDE levels in nulliparae were 710 ng/g lipid (n = 124), in never-lactators were 731 ng/g (n = 532), and in the first three quartiles of lactation were 638 (<9 weeks; n = 85), 566 (<26 weeks; n = 94), and 636 ng/g (<56 weeks; n = 84). Three categories then used for multivariate analyses were nulliparous and parous women who never-lactated, parous women who lactated from 1 to 56 weeks, and parous women who lactated >56 weeks (median DDE 340 ng/g lipid; n = 89). Variables representing temporality of lactation (i.e., before, during, after widespread commercial use of organochlorine compounds) did not improve the models (data not shown).

The interplay between age, lactation history, and organochlorine compound levels is depicted in Fig. 1. For DDE, women ages between 30 and 69 years who had ever breast-fed had lower levels than women who had not breast-fed; differences were most pronounced for women ages 40 to 69 years and those with longest lactation (data not shown). Among the oldest women (ages >70 years), lactation reductions were small for DDE and reversed for PCB, perhaps because older women would have breast-fed their children before being exposed to organochlorine compound. However, the age × lactation interactions were nonstatistically significant for either DDE or PCB, when tested in multivariate analyses (discussed below), so that factors other than lactation may be responsible for these patterns. Within various age strata, DDE levels were lower by 6 to 220 ng/g lipid (or up to 1.5 μg/L without lipid-correction) among women who lactated versus those who had not (Fig. 1). For PCBs, the influence of lactation was weaker, but lactators had marginally lower levels than never-lactators in the 40- to 69-year age groups (by 12-28 ng/g lipid).

DDE and PCB Models for Age and BMI Characteristics. We focused on BMI at ages 20 and 30 years and at reference age (current BMI) for several reasons: this information was available for most of the women; previous studies have most frequently reported on BMI at age 20 years and at reference age, and compared with BMI20, BMI30 was more strongly correlated with BMI at other decades in the adult life span (data not shown). BMI and BMI-gain variables were created using various quantile definitions (i.e., tertiles, quartiles, and quintiles) and added as categorical indicator variables to the base model. The association between organochlorine compound levels and BMI at various ages was most efficiently

described using tertile categories. Tertile cut points shifted upward as age increased [15.0 (minimum), 19.5, 21.4, and 53.3 (maximum) for BMI20; 16.1, 20.8, 23.0, and 49.9 for BMI30; and 16.6, 23.6, 27.8, and 62.6 for current BMI]. For BMI-gain, quintiles were necessary to adequately capture underlying relationships with BMI, organochlorine compounds, and covariates. BMI20-gain and BMI30-gain cut points were similar: −9.8 (minimum), 1.7, 3.9, 6.0, 9.4, and 32.9 (maximum) and −6.6, 0.7, 2.5, 4.4, 7.3, and 27.6, respectively. BMI and lactation required joint consideration as described below. Average adulthood BMI as well as BMI at various organochlorine compound exposure-opportunity periods were weaker organochlorine compound predictors than BMI and BMI-gain (data not shown) and were not considered further.

Graphical displays of organochlorine compound distributions by reference age and selected body size characteristics are presented in Fig. 2. The figures illustrate the correlations observed for organochlorine compound with current BMI and BMI30-gain. Thus, when organochlorine compound were measured (at current or reference age), the leanest women (lowest tertile of current BMI) had lower DDE levels but higher PCB levels across age strata than obese women (Fig. 2A). In contrast, at age <70 years, women with the least weight gain (lowest quintile of BMI30-gain) had lower DDE levels than women whose BMI increased the most (upper quintile of BMI30-gain; Fig. 2B). For PCBs, women with the smallest BMI-gain since age 30 years (bottom quintile) had higher levels across age strata than women with the greatest BMI-gain (top, or fifth quintile). For both DDE and PCBs, the differences between the lowest and the highest quintile strata of BMI30-gain were ~100 ng/g lipid. Both DDE and PCB levels by age were higher in the third than the first tertile of BMI30 (data not shown). As it turned out, these different directions of the BMI effect on DDE and PCBs have proven misleading because body size and weight change required simultaneous consideration.

Multivariate Models for Organochlorine Compound Predictors. The best predictive models for DDE and PCB accounted for 33% of the variance in DDE levels and 30% of the PCB levels (Table 4). The strongest predictor, older age at reference date, accounts for ~20% of the explained variance in both organochlorine compound models. Plasma triglycerides and cholesterol were both positive predictors of organochlorine compound levels, yet multivariate adjustment did not notably alter the β estimates of the other characteristics in the model and contributed <5% to the variance. Of the other demographic characteristics considered, only race was a statistically significant predictor. Black women had higher organochlorine compound levels than White women. In general, all the characteristics examined were stronger predictors of DDE than PCB levels.

Simultaneous consideration of lactation and the BMI characteristics required evaluation of whether these variables interacted or confounded one another as well as which model explained the most variance. BMI at ages 20 and 30 years and at current age were each considered in conjunction with BMI-gain; this combination was less collinear than including BMI at two ages in the same model, and it fit well with existing knowledge about the influence of weight gain on organochlorine compound levels (59). Predicted increments in organochlorine compound levels for each unit change in a body size predictor (e.g., current BMI tertile) were similar for models that included the predictor as a categorical indicator variable or as an ordered categorical variable [e.g., either 0, 1, 2, or the quantile midpoints of each category as suggested by Greenland (60)]. Therefore, all BMI-related characteristics were incorporated simply as ordered categorical variables in the final models.

DDE models were straightforward as there were no statistically significant interactions between lactation and other characteristics. A strong, inverse association was seen between lactation and DDE levels. Relative to nulliparous women and parous women who never-lactated, women who lactated 1 to 56 and >56 weeks had 14% and 37% lower DDE levels, respectively. These figures are derived from the adjusted ln DDE levels as predicted from the coefficients in Table 4 (i.e., for >56 weeks versus never-lactators, a difference of −0.46 ln DDE, $e^{-0.46}$ = 0.63, indicating 37% reduction in levels). When considered individually in the DDE base model, BMI20, BMI30, and current BMI were each statistically significant predictors. However, BMI-gain was statistically significant only if current BMI (but not BMI20 or BMI30) was included in the model (data not shown). When mutually adjusted, BMI-gain reduced DDE levels; higher current BMI increased DDE levels. No BMI × lactation interaction was evident; thus, similar BMI effects were obtained within lactation strata (never, ≤56 weeks, or >56 weeks). Therefore, final DDE prediction models were adjusted for lactation history, current BMI, and BMI30-gain (Table 4).

For PCBs, a BMI30-gain × lactation interaction was observed (P = 0.006; Table 4). Lowest PCB levels were predicted for women who lactated longest and who experienced the greatest BMI-gains (i.e., the upper three quintiles of BMI30-gain). In models built within lactation strata, current BMI was a stronger PCB predictor among never-lactators, but BMI30 or BMI20 was stronger among ever-lactators. PCB models had almost identical R^2 (0.30) whether current BMI or BMI30 was included in the model, and the predicted PCB levels were practically the same. Thus, for simplicity and compatibility with the DDE model, the PCB model with current BMI rather than BMI30 is presented.

To summarize our results, predicted differences in organochlorine compound levels were substantial for different strata of BMI-gain, BMI, and lactation (Fig. 3). In the final models, higher levels of DDE and PCB were associated with higher BMI, lower BMI-gain, and no lactation. For DDE, an increase of 0.5 log units (antilog = 1.65, indicating 65% higher levels) was predicted for any of the following: a 14-year age increase, lowest compared with highest BMI-gain quintile, highest compared with lowest tertile of current BMI, or never compared with long lactation (>56 weeks). In combination, the extreme subgroupings [first tertile of current BMI within the fifth quintile of BMI-gain plus >56 weeks lactation versus the opposite extreme (third, first, or no lactation)] differ by 1.5 log units or a 4-fold difference (Fig. 3A).

Predicting PCB levels was more complex because of the interaction of BMI-gain with lactation and the inverse association of PCBs with BMI-gain and with BMI at older ages. A resulting prediction of lower PCB levels from lactation was seen only among women with high BMI30-gain such that in the highest BMI30-gain quintile longest lactators had 38% lower levels than never-lactators (Fig. 3B). Thus, the predicted effect of BMI30-gain in the lowest compared with highest quintile (i.e., the least BMI-gain adjusted for current BMI) was an increase of 0.27 log units (30%; 0.066 × 4 = 0.26; $e^{0.26}$ = 1.30 where 0.066 = β for BMI30-gain in Table 4 and 4 is the value for the fifth quintile) in adjusted PCB levels in never-lactators and 0.56 log units (76%) in the longest lactators.

To ensure that the final model included all important covariates, the secondary predictor variables were reintroduced into each of the models presented in Table 4. All of the secondary predictors with the exception of fish consumption were nonstatistically significant and did not alter the βs of the primary predictors. Fish consumption was the only dietary

Table 2. Association between personal characteristics and plasma concentrations of DDE and PCBs among women in the LIBCSP, 1996-1997

Tertiles of DDE serum concentration, lipid corrected (ng/g lipid)

Characteristics	Lower third 8.4-455 (n = 335)	Middle third 458-1,005 (n = 336)	Upper third 1,006-11,819 (n = 336)	r_S*	P†
Median age (y)	50.0	55.0	66.0	0.46***	<0.001
Blacks, n (%)	15 (4.5)	18 (5.4)	54 (16)		<0.001
Breast-fed as an infant,‡ n (%)	93 (31)	150 (44)	176 (62)		<0.001
Parity, n (%)					0.014 (Kruskal-Wallis test)
0	41 (12)	41 (12)	42 (13)	0	0.0055 (Mantel-Haenszel χ^2 test)
1	41 (12)	33 (9.8)	36 (11)		
2-3	207 (62)	190 (57)	178 (53)		
≥4	46 (14)	72 (21)	80 (24)		
Ever lactated,§ n (%)	148 (44)	99 (29)	109 (32)		0.0015
Median length of lactation§ (mo)	8.2	4.9	4.5	−0.17***	<0.001
Median (n) BMI‖ (kg/m^2)					
Age 20 y	20.0 (335)	20.5 (333)	20.8 (336)	0.16***	<0.001
Age 30 y	21.1 (335)	21.6 (336)	21.9 (336)	0.18***	<0.001
Age 40 y	22.5 (282)	22.5 (320)	23.0 (334)	0.16***	0.0010
Age 50 y	23.9 (172)	24.0 (244)	24.2 (297)	0.11***	0.069
Age 60 y	24.9 (65)	23.8 (132)	25.1 (226)	0.11****	0.032
Age 70 y	27.4 (16)	24.3 (46)	24.6 (104)		0.221
Current¶	24.2 (335)	25.0 (336)	26.6 (336)	0.20***	0.001
Median BMI-gain** (kg/m^2)					
Age 20 y-current	4.3	5.0	5.7	0.097***	<0.001
Age 30 y-current	2.7	3.5	4.3	0.11***	<0.001
Median length of residence on Long Island (y)	31.0	33.0	33.0	0.082****	0.186
High school education or less, n (%)	99 (30)	141 (42)	177 (53)		<0.001
Never used alcohol, n (%)	152 (46)	152 (46)	178 (54)		0.043
Never smoked cigarettes, n (%)	158 (46)	148 (43)	170 (49)		0.359
Median dairy consumption, weekly servings	12.7 (262)	10.47 (253)	8.7 (259)	−0.17***	<0.016
Median fish consumption, weekly servings	0.9 (269)	0.99 (268)	0.8 (266)		0.820
Median cholesterol (g/L)	1.95	1.98	1.98		0.861
Median triglycerides (g/L)	1.14	1.18	1.28	0.086***	0.004
Median total serum lipids (g/L)	6.20	6.35	6.52		0.058
Median (range) DDE, uncorrected for lipids (μg/L)	1.6 (0.06-4.7)	4.2 (1.5-10.1)	10.6 (3.9-66.4)		

Tertiles of PCB†† serum concentration, lipid corrected (ng/g lipid)

Characteristics	Lower third 34-302 (n = 333)	Middle third 303-476 (n = 333)	Upper third 477-3,287 (n = 333)	r_S*	P†
Median age (y)	51.0	56.0	64.0	0.39***	<0.001
Blacks, n (%)	21 (6)	21 (6)	45 (14)		<0.001
Breast-fed as an infant,‡ n (%)	104 (35)	128 (45)	164 (58)		<0.001
Parity, n (%)					0.718 (Kruskal-Wallis test)
0	41 (12)	34 (10)	48 (14)		
1	36 (11)	40 (12)	33 (9.9)		0.230 (Mantel-Haenszel χ^2 test)
2-3	197 (59)	201 (62)	173 (52)		
≥4	59 (18)	58 (17)	79 (24)		
Ever lactated,§ n (%)	124 (37)	118 (35)	110 (33)		0.256
Median length of lactation§ (mo)	6.0	6.0	5.7	−0.11****	0.161
Median (n) BMI‖ (kg/m^2)					
Age 20 y	20.2 (333)	20.4 (332)	20.6 (331)	0.072****	0.149
Age 30 y	21.6 (333)	21.5 (333)	21.6 (333)		0.381
Age 40 y	22.8 (275)	22.7 (323)	22.6 (327)		0.844
Age 50 y	24.6 (164)	24.1 (250)	23.8 (287)	−0.083****	0.245
Age 60 y	25.4 (56)	25.0 (139)	24.3 (214)	−0.12****	0.038
Age 70 y	26.5 (16)	26.5 (48)	23.9 (98)	−0.17****	0.017
Current¶	25.7 (333)	25.0 (333)	25.4 (333)		0.655
Median BMI-gain** (kg/m^2)					
Age 20 y-current	5.4	4.8	4.4	−0.11***	0.017
Age 30 y-current	3.9	3.8	2.9	−0.11***	0.038
Median length of residence on Long Island (y)	30.0	32.0	35.0	0.13***	0.001
High school education or less, n (%)	127 (38)	138 (41)	151 (45)		0.059

(*Continued on the following page*)

Table 2. Association between personal characteristics and plasma concentrations of DDE and PCBs among women in the LIBCSP, 1996-1997 (Cont'd)

Tertiles of PCB†† serum concentration, lipid corrected (ng/g lipid)					
Characteristics	Lower third 34-302 (n = 333)	Middle third 303-476 (n = 333)	Upper third 477-3,287 (n = 333)	r_S*	P †
Never used alcohol, n (%)	145 (45)	167 (51)	166 (50)		0.136
Never smoked cigarettes, n (%)	148 (43)	151 (44)	174 (51)	−0.071****	0.046
Median dairy consumption, weekly servings	12.6	10.0	9.1	−0.11***	<0.001
Median fish consumption, weekly servings	0.7	0.8	1.0	0.089****	0.059
Median cholesterol (g/L)	2.01	1.98	1.91	−0.15***	<0.001
Median triglycerides (g/L)	1.27	1.17	1.14	−0.11***	0.094
Median total serum lipids (g/L)	6.56	6.33	6.16	−0.14***	<0.001
Median (range) PCB, uncorrected for lipids (μg/L)	1.5 (0.27-3.2)	2.4 (1.1-5.9)	4.0 (1.3-21.9)		

*Spearman correlations, r_S, reported if statistically significant: ***, $P < 0.01$; ****, $P < 0.05$.
†P for trend: Mantel-Haenszel χ^2 test for categorical variables and Kruskal-Wallis test for continuous variables.
‡Information available on only 874 women.
§Among parous women only. Mantel-Haenszel χ^2 test statistics is for ever lactated versus never lactated by organochlorine compound tertiles.
‖BMI = weight (kg) / height squared (m^2).
¶Current = reference date.
**Change in BMI from age 20 years to age at reference date or from age 30 years to age at reference date (e.g., current BMI-BMI20).
††PCB defined as sum of PCB nos. 118,138,153, and 180.

variable that predicted organochlorine compound levels at statistical significance in final models, and its association was limited to PCBs. Fish intake, available for 80% of the population, ranged from none to ~30 servings weekly (servings of fish weekly by quartile: <0.4, 0.4-0.8, 0.9-1.6, and >1.6 servings weekly). The highest fish consumption (top quartile) would increase PCB levels by 14% (change in logs of 0.135), and the r^2 increased by 0.009 [i.e., the R^2 for the PCB model with the statistically significant predictors listed in Table 4 was 0.298 when fish intake was added to the model versus 0.288 without fish among women with fish information available (n = 796)].

Pharmacokinetic Models. To better understand temporal changes of organochlorine compound in relation to BMI, we constructed a simple pharmacokinetic model for DDE (Fig. 4A). This model differs from a previous report (61) by incorporating actual reported dietary intake of DDT/DDE (see Materials and Methods) and by comparing the predicted values of DDE to the reported DDE levels in various populations since 1950 (see Materials and Methods). The model's values for a lean BMI body size are quite similar to those reported. Although only longitudinal data can quantify pharmacokinetics by using individual changes in exposure levels over time to compute elimination rate or half-life, cross-sectional data can provide

Table 3. Distribution of selected characteristics within quintiles of BMI-gain from age 30 years to reference age (n= 1,008), LIBCSP, 1996-1997

Characteristic (median or %)	Quintile of BMI change from age 30 y to reference age (range in kg/m^2)				
	1 (−6.5 to 0.7)	2 (0.7-2.5)	3 (2.5-4.4)	4 (4.4-7.3)	5 (7.4-27.6)
Reference age (y)	50	55	56	58	59
BMI20-gain (kg/m^2)	0.6	2.6	4.8	7.1	12.1
BMI30-gain (kg/m^2)	0	1.7	3.4	5.7	10.2
% Increase ([current BMI − BMI30] / BMI30)	0	7.8	15.4	25.9	45.3
Current BMI (kg/m^2; reference age)	21.5	22.8	25.1	27.4	33.3
Current weight (kg)	56.7	61.2	68.0	72.6	88.0
Current body fat (kg)*	15.9	18.8	23.3	27.2	38.2
% Current body fat*	28	31	34	37	43
Organochlorine compound levels in serum					
DDE (ng/g lipid)	578	581	696	746	730
PCB (ng/g lipid)	414	388	195	374	322
DDE (μg/L)	3.3	3.5	4.4	4.9	4.9
PCB (μg/L)	2.4	2.3	2.5	2.4	2.2
Total lipids (g/L†)	5.89	6.01	6.51	6.47	6.80
Lactation history (% in quintile)					
Never (n = 651)	19	19	20	20	22
1-56 wk (n = 268)	21	21	18	23	17
>56 wk (n = 89)	24	27	25	11	13
n	201	203	201	202	201

*Estimated using data and equations from Frankenfield et al. (49).
†Computed using the equation of Akins et al. (47).

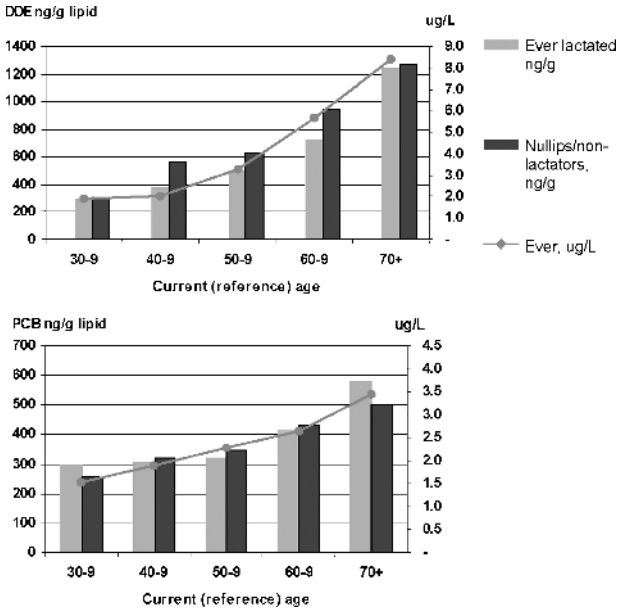

Figure 1. Medians of DDE and PCB in serum (ng/g lipid) by age and lactation history. There were 651 never-lactators and 357 ever-lactators, the latter including 89 women whose lifetime lactation was >56 weeks. For comparison, non-lipid-corrected values (μg/L) are shown for ever-lactators.

a good approximation. Thus, DDT/DDE levels in various cross-sectional data sets from 1950 to 2000 (Fig. 4A) show a downward trend that corresponds to the elimination rates we used in the models, which were those observed in the few existing longitudinal studies (4, 13). Similarly, dietary intakes of DDT, as measured in market-basket surveys, show a trend comparable with that of the biomarker data for the corresponding time period (see Materials and Methods for references).

The model in Fig. 4 applies two principles. (*a*) Obese persons have a lower organochlorine compound concentration during uptake given an equivalent absorbed amount (as in Fig. 4A). In other words, compared with women with low BMI, organochlorine compound concentrations are lower in women with high BMI, who also have larger adipose lipid depots during a time of uptake (e.g., ppm-DDE = mg-DDE / kg body lipids). (*b*) Obesity, and higher body fat, means a longer organochlorine compound half-life (13, 15, 20-27). In the model, the result is that from 1950 to 1975, during the time of sizeable DDE absorption, DDE levels are lower in heavier than lean persons, and at any single time point before crossover, there would exist an inverse correlation with BMI (Fig. 4B). Crossover of the elimination curves for lean and obese persons occurs at some point after exposure declines (i.e., 1975 in Fig. 4A, 12 years in Fig. 4B). As noted previously, after crossover, BMI is positively associated with organochlorine concentrations at any time point, explaining why in cross-sectional data heavier persons may show higher organochlorine compound levels than leaner persons many years after the exposure has occurred (61). Hypothetical PCB pharmacokinetic models, based on limited and imputed data, gave similar results with a maximum PCB level of ~6 μg/L around 1980 (data not shown). Models for PCBs exhibited a later crossover of obese and lean curves (e.g., after 1980-1990 or not at all) depending on whether smaller or greater dietary inputs were used. During these years, environmental exposures to PCB may have been lower than exposures to DDE and DDT.

Although we did not include it in our model (Fig. 4), a third principle may further refine organochlorine compound estimates. (*c*) Weight gain over time leads to lower organochlorine compound levels and weight loss leads to higher levels regardless of initial BMI. The effect of weight change to dilute the body burden, as in principle (*a*). This effect has been seen longitudinally in pharmacokinetic models for tetrachlorodibenzodioxin (dioxin), where serial levels of tetrachlorodibenzodioxin and weight change were available (see figures and tables in ref. 59). However, such pharmacokinetic models require data on organochlorine compound levels and weight change over time, and they use more sophisticated variables, such as a time-dependent transfer function to predict changes in levels related to BMI-gain instead of a simple exponential function (59).

The timing of crossover (i.e., when levels in a cross-sectional study become positively correlated with BMI as shown in Fig. 4B) seems to depend mainly on how high the levels are at the moment exposure stops and elimination

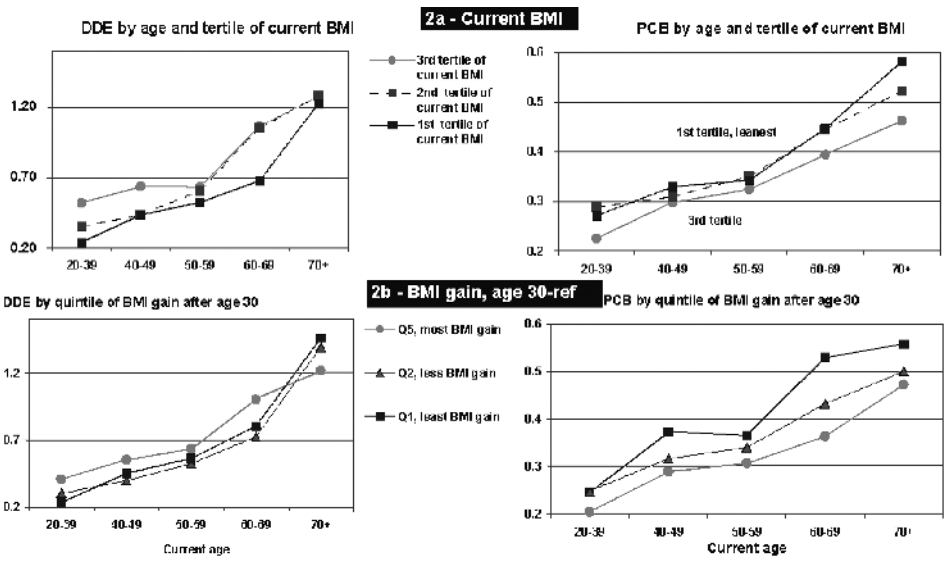

Figure 2. Levels of serum DDE and PCB (μg/g lipid based) by tertile of current BMI and by quintiles of BMI-gain (Q1-Q5) from age 30 years-reference. DDE values in Q3 of BMI gain were near Q5; in Q4, they were low (near Q2) at young ages and high above age 60 years. For PCB, Q2 and Q3 values were close to Q4. Both DDE and PCB levels by age were higher in the third tertile than the first tertile of BMI30 (data not shown).

Table 4. DDE and PCB model variables and predicted values, LIBCSP, 1996-1997

	ln DDE, n = 1,007, R^2 = 0.328				ln PCB,* n = 999, R^2 = 0.302			
	β	SE	P	Partial r^2 †	β	SE	P	Partial r^2 †
Intercept	−1.01	0.16			−0.61	0.094		
Age at reference date (y)	0.036	0.0022	<0.0001	0.213	0.021	0.0013	<0.0001	0.220
Triglycerides (g/L)	0.16	0.032	<0.0001	0.023	0.081	0.018	<0.0001	0.030
Cholesterol (g/L)	0.086	0.063	0.175	0.002	0.14	0.035	<0.0001	0.012
Race (White = referent)								
Black	0.74	0.094	<0.0001	0.045	0.25	0.053	<0.0001	0.012
Current BMI tertile (0, 1, 2)	0.27	0.046	<0.0001	0.028	0.053	0.026	0.0427	0.005
BMI30-gain quintile (0, 1, 2, 3, 4)	−0.13	0.027	<0.0001	0.0003	−0.066	0.017	<0.0001	0.015
Lactation history			<0.0001	0.018			0.330	0.003
Never lactated (referent)								
1-56 wk lactation	−0.15	0.060	0.015		0.087	0.058		
>56 wk lactation	−0.46	0.095	<0.0001		0.019	0.086		
BMI30-gain × lactation interaction	NA ‡						0.021	0.006
BMI30-gain × 1-56 wk lactation					−0.056	0.024		
BMI30-gain × >56 wk lactation					−0.075	0.040		

NOTE: The BMI30 variable instead of current BMI tertiles was not significant for DDE, but BMI30 predicted almost identical results for PCBs. Lactation variables were categorical, and the P is for the group. Models predicting lipid-corrected values had similar results: DDE: R^2 = 0.291 (P < 0.0001, except as noted), intercept = −1.94, βs = age 0.035, race 0.075, BMI30-gain −0.13, current BMI tertile 0.26, triglycerides 0.034 (P = 0.28), cholesterol −0.28, lactation <57 weeks −0.14, >56 weeks −0.46. PCB: R^2 = 0.268, intercept = −1.54, βs = age 0.021, race 0.27, BMI30-gain −0.066, BMI 0.048 (P = 0.066), triglycerides −0.043 (P = 0.016), cholesterol −0.226, lactation (P = 0.26 for group) <57 weeks 0.096, >56 weeks 0.032, BMI30-gain × lactation (P = 0.016 for group) <57 weeks −0.058, >56 weeks −0.078.

*Fish intake (quartiles) was also significant in the ln PCB model for women with this information, n = 796, R^2 = 0.297, intercept = −0.63, β = 0.045 (fish quartile values = 0, 1, 2, 3; partial r^2 = 0.009). The other βs in this model were almost identical to those for 796 women without fish intake, with similar Ps (R^2 = 0.288) and those in the model for 999 women.

†Partial r^2 based on type I SS from GLM.

‡NA, not applicable.

exceeds intake. At this time, an obese and a lean person may have the same organochlorine compound concentration because the obese person has absorbed a larger lifetime amount compared with the lean person (i.e., mg organochlorine compound / kg body lipids). In this situation, levels in obese persons will always be higher afterward than in lean persons despite their slower elimination rate. In contrast, if obese and lean persons have a similar absorbed dose, organochlorine compound levels are lower in obese individuals, proportional to the amount of body lipids, as in Fig. 4. Using the time-dependent transfer function examples in ref. (59), and dilution in obese adipose levels by 20% (i.e., lean body concentration multiplied by 0.8 for obese), the crossover occurs at 10 years after last exposure, an interval equivalent to that shown in our pharmacokinetic model. The bigger the difference between obese and lean model estimates at peak exposure (i.e., more dilution by higher adipose lipid yielding lower initial concentration in obese persons), the later the time point at which the crossover occurs (e.g., lean body concentration multiplied by 0.5 for obese results in a 23-year crossover).

Discussion

One or more organochlorine compounds were detected in all women in the LIBCSP, although median levels were as much as 10-fold lower than those reported earlier in the 20th century. Multivariate models reconciled the different directions of correlations of DDE and PCB with BMI that were found in simple or age-adjusted correlations (Tables 1 and 2; Fig. 2), in a manner consistent with the pharmacokinetic models. When both BMI and weight gain were included in multivariate models, the direction of the associations was identical for DDE and PCB. Therefore, the statistical models corrected the apparent positive association of DDE with BMI-gain (e.g., Fig. 3) to a negative coefficient in the model (e.g., Table 4), whereas at the same time, after multivariate adjustment, the inverse correlation of PCBs with BMI became positive.

From predicted organochlorine model shown in Fig. 3, highest DDE levels were in women who were heaviest, had the least adult weight gain, and did not lactate. Lowest levels were in the leanest women with the most gain who lactated longest. Consequently, women with long lactation and no weight gain had DDE levels similar to women who never lactated but had the most weight gain. For DDE, the effect of BMI and BMI-gain on current levels were equivalent (top versus bottom quantiles). Therefore, the statistical model is consistent with an effect of higher BMI to lengthen elimination rate, weight gain to reduce levels and the pharmacokinetic model. Notably, the models predict effects of BMI, BMI-gain, and lactation that are as great as the effect of age on organochlorine compound levels.

With PCBs, BMI30-gain lowered and BMI raised predicted PCB levels, but the magnitude of the two effects was not the same. Unlike DDE, the effect of BMI-gain on PCBs was much greater than that of BMI (Table 4; Fig. 3). A possible explanation is that BMI-gain was more influential than BMI because it occurred more recently in the PCB elimination pattern compared with DDE. Hence, BMI-gain exerts a bigger effect on tetrachlorodibenzodioxin levels ~7 years after elimination begins than at 0 or 20 years after exposure (59). Lactation, unlike DDE, where it had a strong effect, altered predicted PCB levels only among women with large weight gains during adulthood (i.e., the third to fifth quintiles of BMI30-gain). In the first and second quintiles of BMI30-gain, there was no lactation effect (first and fifth quintiles are shown in Fig. 3B). By way of explanation, if the timing of BMI-gain is important, as suggested above, then the point at which lactation occurred during the period of elimination might differentially affect later PCB levels more than BMI. In addition, ongoing additional absorption, which we suspect occurs to some extent for PCBs, might reduce the BMI effect (both by artificially prolonging elimination and by body fat dilution of new residues). When the BMI-gain × lactation interaction was not included

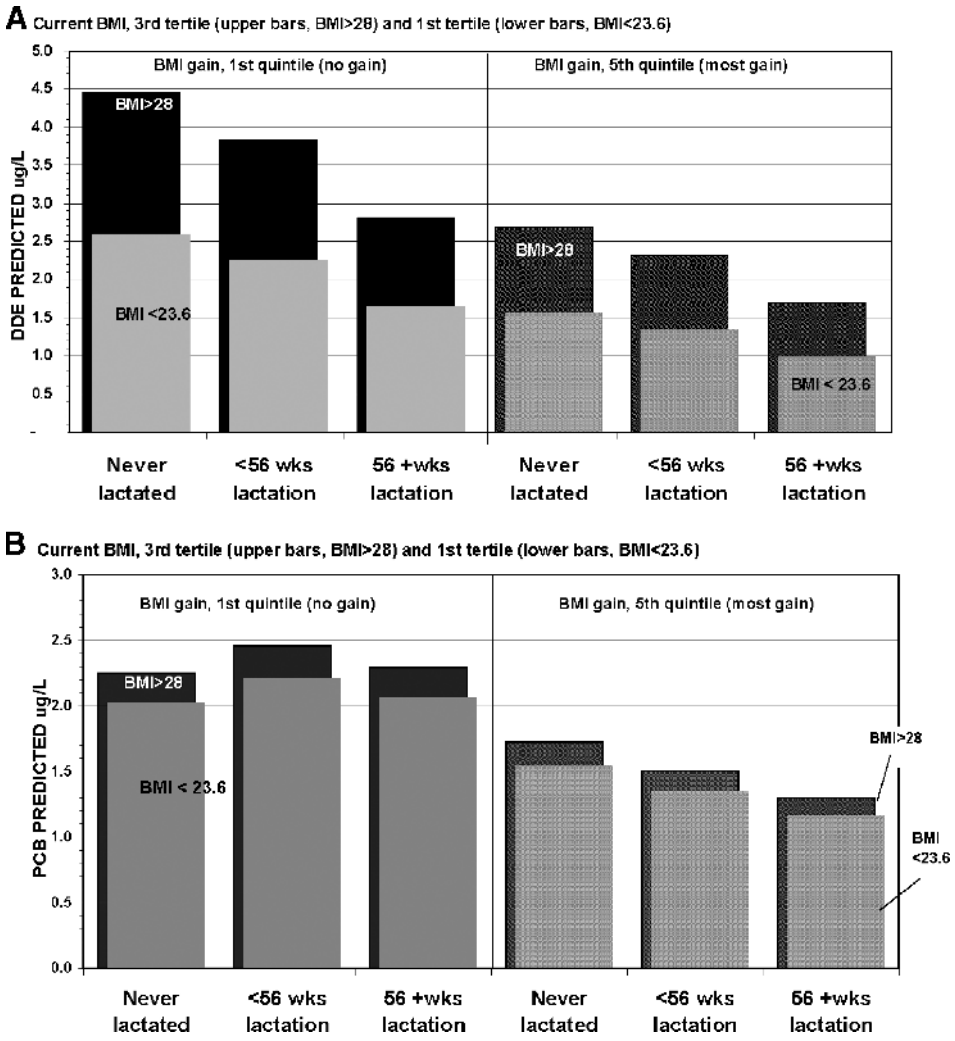

Figure 3. Predicted organochlorine compound serum levels (multivariate adjusted) for highest and lowest quantiles of current BMI and BMI-gain by lactation history. Values are from model variables in Table 4 using White race, age 45 years, and median values for triglycerides and cholesterol (1.19 and 1.97 g/L, respectively).

in the statistical model, the lactation effect on PCBs was limited to long lactation (>56 weeks; 10% reduction in levels).

Except for fish intake, all predictors were stronger for DDE than PCBs. The marked effect of lactation on DDE across all ages (multivariate adjusted) and the smaller effect on PCBs that we observed are similar to some but not all studies of older women (11, 36). In part, this may be because both the average and the range of levels of PCB are much lower than DDE and because PCB exposures continue. In addition, some data sets indicate that temporal trends of cross-sectional measurements differ for DDE and PCBs (e.g., ref. 13). Further, in the past, reported dietary intakes of PCBs have generally been lower than DDE. For example, compared with DDT/DDE dietary levels shown in Fig. 4, PCB dietary levels are 0.01 to 0.5 times lower (51, 52). However, geographic differences are wide (36); in particular, among LI women, the PCB exposure may have continued longer than shown in the nationwide Food and Drug Administration dietary intake (2, 3). The R^2s for models, including all of the variables in Table 4, were not much better than simpler models with one or two BMI variables and without the BMI-gain × lactation interaction. However, in terms of biological plausibility, our models are more informative. Our r^2s are similar in magnitude to those reported by Laden et al. (36), who obtained βs positive for BMI and negative for lactation as well as several statistically significant dietary predictors. We found no positive dietary predictors for DDE and only fish for PCBs. Among women in Buffalo, Moysich et al. (11) found r^2s of 0.13 for DDE and 0.20 for PCBs in their models. Similar to our data, they found BMI to decrease levels of higher PCBs. Both of these studies considered only control (not case) women in their analyses and only current BMI, and the study populations were smaller than ours [n = 212 (36) and n = 192 (11)].

Limitations in our data set are those present in most environmental studies of this kind, including a single measure of organochlorine compound, a likely biased recall of weight that may be worse at longer intervals, and blood samples that were nonfasting and that were taken as long as a few months after diagnosis for cases. Nonfasting blood samples are not likely to introduce significant error, as lipid adjustments were made, and we did not see large or statistically significant differences in organochlorine compound among case women tested before and several months after diagnosis (6).

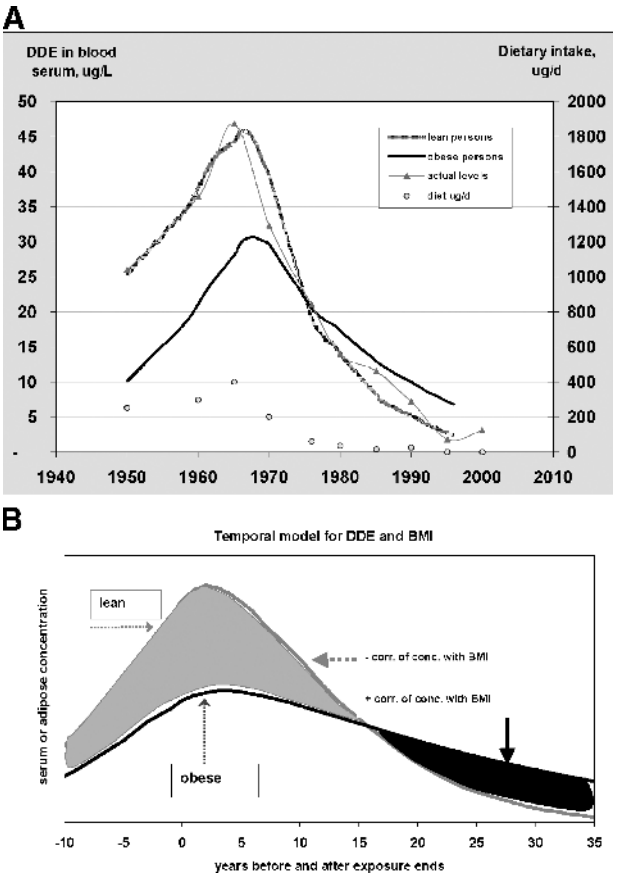

Figure 4. A. Pharmacokinetic models of DDE blood levels for lean and obese persons derived from dietary intake (shown) and elimination rates of DDT/DDE. Also shown are actual reported serum levels of DDE in 10 studies from 1950 to 2000. The model is: [adipose] = [added DDE] + [DDE before] $\times e^{-k} \times {}^{dt}$, where k is the first-order elimination rate constant and dt is years from [DDE before] to [added DDE]. Rate constants and dilution differ for obese and lean models. Further model details and references for DDT/DDE dietary intake and for actual serum concentrations are given in Materials and Methods. **B.** Pharmacokinetic model, with areas shaded to indicate temporal windows when the organochlorine compound-BMI correlation should be inverse (*gray area*) or positive (*black area*). For fat and lean DDE, refer to the model in Fig. 3A for obese and lean persons.

The phenomenon of weight gain in reducing levels of organochlorine compounds is a familiar one in the children's literature. Both height and weight gain in children are known to dilute organochlorine compound and lead levels as they grow (62, 63), and the pharmacokinetic models for tetrachlorodibenzodioxins (59) bear this out in adults over longer time spans.

Although the correlations of organochlorine compound with BMI in various studies differ considerably (Table 1), the apparent trend is that the correlations become more positive for DDE from 1965 to 1997, which is consistent with temporal changes implied by Fig. 4. In contrast, the correlations are more often negative for PCBs. Inverse associations are also found in reports concerning polybrominated biphenyls and polybrominated diphenyl ethers (15, 25, 63), where point source or recent exposures are likely to have existed. Opposing directions of such correlations, as in our data, may be removed using a model that adjusts for BMI-gain over time. To some extent, therefore, the converse associations of DDE and PCB with BMI reflect temporality of exposure, or windows, because the findings together suggest lower but continuing recent exposure to PCB and more distant cessation of exposure at high levels to DDE. Thus, an inverse association of PCB with BMI is consistent with the simple dilution, within a recent timeframe, of a specific amount of organochlorine compound (mg) across the study population's adipose lipids (kg). For DDE, such a period, where at a single time point an inverse correlation would be seen with BMI, should exist before 1975, which was a time point less than one half-life after 1972. The more complex relationships with BMI found in our models also likely reflect a balance between ongoing and past exposure levels. For example, DDE levels in 2000 were approximately one-tenth those in 1972, a much more precipitous decline than PCBs (approximately one-third to one-half). In addition to continuing longer, PCB levels have historically been lower than DDE and DDT. Variables representing specific windows of exposure for lactation and BMI did not improve our model, suggesting that other factors are involved in determining organochlorine compound levels. Better models might be possible if earlier BMI were available (e.g., in adolescence) or at least two measures of organochlorines were available at least one to two half-lives apart.

To improve exposure classification, factors affecting the pharmacokinetics of organochlorine compound over the lifetime should be considered when evaluating associations between biomarkers of persistent organochlorine compounds and cancer risk. In our models, for example, ignoring either lactation or BMI or BMI-gain could create as great a bias in DDE levels as a 10-year age difference, with the accompanying attenuation of the measure of effect due to such exposure misclassification. For environmental epidemiology, it would be useful if, based on knowledge of BMI over time, models for more distant or more recent exposure could be devised to improve precision of organochlorine compound biomarkers. Thus, for PCBs, where negative correlations were seen, the model was influenced more by BMI-gain than BMI at any age, whereas with DDE, where positive correlations with BMI were seen, current BMI was more important. We may be able to gain further understanding by comparing these models for the LIBCSP with results in other populations and with other organochlorine compounds. BMI-gain and organochlorine compound exposure may be competing risk factors for disease (64). Therefore, incorporating appropriate pharmacokinetic variables may also improve risk estimates. As an example, McElroy et al. found an adjusted odds ratio of 1.7 (95% confidence interval, 1.16-2.50) for premenopausal breast cancer associated with fish consumption (as a surrogate for organochlorine compounds); covariates included BMI at age 18 years and BMI-gain after that age (65).

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