Pancreatic Cancer and Serum Organochlorine Levels[1]

Jane A. Hoppin,[2] Paige E. Tolbert,[3] Elizabeth A. Holly, John W. Brock, Susan A. Korrick, Larisa M. Altshul, Rebecca H. Zhang, Paige M. Bracci, Virlyn W. Burse, and Larry L. Needham

Department of Environmental and Occupational Health [J. A. H., P. E. T.], Department of Epidemiology [P. E. T.], and Department of Biostatistics [R. H. Z.], Rollins School of Public Health, Emory University, Atlanta, Georgia 30322; Department of Epidemiology and Biostatistics, School of Medicine, University of California, San Francisco, California 94109 [E. A. H., P. M. B.]; National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia 30341 [J. W. B., V. L. B., L. L. N.]; Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, [S. A. K.]; and Environmental Health Department, Harvard School of Public Health [S. A. K., L. M. A.], Boston, Massachusetts 02115

Abstract

Occupational exposure to *p,p′*-dichlorodiphenyltrichloroethane (DDT) has been associated with increased pancreatic cancer risk. We measured organochlorine levels in serum obtained at the study enrollment from 108 pancreatic cancer cases and 82 control subjects aged 32–85 years in the San Francisco Bay Area between 1996 and 1998. Cases were identified using rapid case-ascertainment methods; controls were frequency-matched to cases on age and sex via random digit dial and random sampling of Health Care Financing Administration lists. Serum organochlorine levels were adjusted for lipid content to account for variation in the lipid concentration in serum between subjects. Median concentrations of *p,p′*-dichlorodiphenyldichloroethylene (DDE, 1290 *versus* 1030 ng/g lipid; $P = 0.05$), polychlorinated biphenyls (PCBs; 330 *versus* 220 ng/g lipid; $P < 0.001$), and *trans*-nonachlor (54 *versus* 28 ng/g lipid; $P = 0.03$) were significantly greater among cases than controls. A significant dose-response relationship was observed for total PCBs (P for trend < 0.001). Subjects in the highest tertile of PCBs (≥360 ng/g lipid) had an odds ratio (OR) of 4.2 [95% confidence interval (CI) = 1.8–9.4] compared to the lowest tertile. The OR of 2.1 for the highest level of *p,p′*-DDE (95% CI = 0.9–4.7) diminished (OR = 1.1; 95% CI = 0.4–2.8) when PCBs were included in the model. Because pancreatic cancer is characterized by cachexia, the impact of this on the serum organochlorine levels in cases is difficult to predict. One plausible effect of cachexia is bioconcentration of organochlorines in the diminished lipid pool, which would lead to a bias away from the null. To explore this, a sensitivity analysis was performed assuming a 10–40% bioconcentration of organochlorines in case samples. The OR associated with PCBs remained elevated under conditions of up to 25% bioconcentration.

Introduction

Pancreatic cancer is the fifth leading cause of cancer death in the United States and has few identified risk factors (1). Cigarette smoking is the most consistently identified risk factor, and it is associated with an estimated 2-fold increased risk of pancreatic cancer (2). Dietary factors, including high intake of animal protein and fat, coffee and alcohol consumption, and low fruit and vegetable intake have been reported as risk factors, although results have been inconsistent (2).

Occupational and environmental exposures may contribute to risk of pancreatic cancer, although no consistent pattern of occupational exposures has been identified. The most compelling evidence for a specific occupational exposure as a risk factor for pancreatic cancer comes from a study of workers in a DDT[4] manufacturing plant (3). In this nested case-control study, a 7-fold increased risk for pancreatic cancer was observed among workers whose average length of exposure to DDT was 47 months. An elevated risk for pancreatic cancer also was observed for occupational exposure to DDD and ethylan, DDT derivatives. In a population-based case-control study of pancreatic cancer in southeastern Michigan, pancreatic cancer patients were 10 times more likely to report having used ethylan than controls; however, there were no measured values of reported exposures (4). Additionally, pesticide exposure has been suggested as the most likely explanation for an increased risk of pancreatic cancer among farmers (5, 6), female Vietnam veterans (7), and flour millers (8).

Exposure to organochlorine chemicals occurs in the environment and in occupational settings due to the presence of these long-lived compounds and their metabolites in food and other environmental media (9, 10). Although DDT and PCBs, another class of organochlorine chemicals structurally similar to DDT, were removed from the United States market in the 1970s, exposure continues as a result of their environmental persistence. Organochlorine compounds, such as DDT's primary metabolite DDE, are lipophilic, resistant to metabolism,

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[2] Present address: Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709.
[3] To whom requests for reprints should be addressed, at Department of Environmental and Occupational Health, Rollins School of Public Health, Emory University, 1518 Clifton Road, NE, Room 210, Atlanta, GA 30322. Phone: (404) 727-3801; Fax: (404) 727-8744; E-mail: ptolber@sph.emory.edu.

[4] The abbreviations used are: DDT, *p,p′*-dichlorodiphenyltrichloroethane; DDD, dichlorodiphenyldichloroethane; PCB, polychlorinated biphenyl; DDE. *p,p′*-dichlorodiphenyldichloroethylene; RDD, random digit dial; HCFA, Health Care Financing Administration; HCB, hexachlorobenzene; OR, odds ratio; CI, confidence interval; TCDD, 2,3,7,8-tetrachlorodibenzodioxin.

and have long-term storage in adipose tissue. Serum lipid levels of these contaminants are in equilibrium with adipose tissue levels, resulting in an easily accessible measure of body stores presumed to be representative of cumulative exposures over many years (9–13). Because the amount serum lipids varies between individuals, organochlorine values are adjusted for serum lipid content to estimate the chemical concentration in the lipid fraction of the body. We obtained serum measurements of organochlorine chemicals from pancreatic cancer case and control participants in an ongoing population-based case-control study in the San Francisco Bay Area to explore the relationship of environmental exposure to these chemicals with pancreatic cancer.

Materials and Methods

Population. This study was conducted as part of an ongoing population-based case-control study of pancreatic cancer in the San Francisco Bay Area. Cases were obtained using rapid case ascertainment to identify all patients diagnosed as having cancer of the exocrine pancreas in the San Francisco Bay Area counties of San Francisco, Alameda, Marin, Contra Costa, San Mateo, and Santa Clara. Eligible subjects, both cases and controls, were aged 21–85 years, residents of one of the above six counties at the time of diagnosis, had no physician-indicated contraindication to contact, and were able to speak either English or Spanish at the time of contact. Controls were frequency-matched to cases by sex and age within 5 years to the extent possible in this substudy. Controls were selected via two mechanisms: (*a*) RDD and (*b*) from random samples of the HCFA lists for subjects aged ≥65. No proxy interviews were conducted. For this serum study, case subjects were recruited between October 2, 1996, and May 1, 1998, and control subjects were recruited between May 14, 1997, and May 1, 1998. Analyses were restricted to subjects who provided a blood sample for organochlorine analysis.

A total of 113 pancreatic cancer cases and 82 frequency-matched controls provided blood for organochlorine analysis. During the period of rapid case-recruitment, information was received on 611 potential study cases; 335 (55%) of these were deceased and thus, ineligible, and 32 (5%) did not meet other study criteria. Of the 244 pancreatic cancer patients known to be eligible for the study interview, 19% were too ill to be interviewed, 9% refused to participate, 3% could not be located, and 4% had medical contraindications to contact as reported by their physicians. The response rate for blood draw for organochlorine analyses among the 158 cases who were interviewed was 71%. There were 36 (23%) patients who were unable to provide a blood sample and 9 (6%) who refused. Serum samples from five of these cases could not be extracted for chemical analysis.

Control subjects were identified from the same counties as the pancreatic cancer patients using RDD and HCFA files. During the time period of control recruitment for this substudy, 253 control subjects, 84 of whom were obtained from HCFA files, were eligible and completed interviews for inclusion in the main study. A total of 82 of these controls were matched to the substudy participants. Among these participants 78% of the RDD controls and 65% percent of HCFA controls agreed to have their blood drawn. Thus, 108 cases and 82 controls were available for statistical analysis.

Interview and Blood Collection. Detailed in-person interviews were conducted in the subject's home or at a location convenient to the subject. Topics included questions on occupational and chemical exposures, tobacco use, diet, medical history, and demographics. An ancillary questionnaire regarding symptoms before diagnosis was administered between November 1996 and November 1997 to pancreatic cancer cases, 74 of whom are among the 108 cases included here. Upon completion of the interview, subjects were asked to provide blood samples for chemical and other analyses. A nonfasting blood sample was drawn by a trained phlebotomist from subjects who agreed to have their blood drawn. For this analysis, blood was collected in a 10-ml red-top vacutainer tube. Serum samples were spun, aliquoted, and then frozen at −80°C before analysis. Field blanks of bovine serum were processed in the serum processing laboratory to identify contamination introduced during sample processing.

Chemical Analysis. Study samples were arranged in batches of 10 consisting of sets of cases and controls and field quality assurance samples (field blanks of bovine serum and pooled samples). Additionally, laboratory quality assurance and quality control samples, including spiked bovine serum as matrix spikes and reagent blanks, were added to each batch of 10 submitted samples. Nine samples of pooled human serum were interspersed in the actual study samples to assess the between-batch coefficients of variation. All study samples were analyzed without knowledge of case or control status at the National Center for Environmental Health, Centers for Disease Control and Prevention. For interlaboratory validation, an additional three pooled serum samples were independently analyzed by an outside laboratory at Harvard University (Boston, MA) using liquid/liquid extraction and gas chromatography with electron capture detection.

The analysis method has been fully described previously (14) and is summarized here. Each sample was extracted using solid phase extraction and then analyzed on two separate gas chromatographs with electron capture. The two chromatographs used different columns (DB5 and DB1701) to reduce interferences and improve selectivity. Results in ng/ml serum were obtained for DDE, DDT, 11 PCB congeners, HCB, *trans*-nonachlor, and five other organochlorine compounds. All results from the quality control materials were compared to limits established in the National Center for Environmental Health laboratory using Clinical Laboratory Improvement Act criteria. Values were not reported, and samples were reanalyzed when the quality control results were outside the control limits. Values below the method detection limit were reported when quantifiable to provide the best estimate of the organochlorine level; levels that were nondetectable were assigned a value of zero. The interset coefficients of variation based on the pooled serum samples were 6.1% and 10.5% for DDE and total PCBs, respectively. Recovery of target analytes differed by the extraction method; for the pooled serum samples, the organochlorine values reported using solid phase extraction were 57 and 65% of the values for total PCBs and DDE, respectively, reported using liquid/liquid extraction. As a result, all organochlorine values were corrected for recovery using the values reported in Brock *et al.* (14).

Serum specimens were analyzed for cholesterol and triglycerides using enzymatic methods. Total lipids were calculated from total triglycerides and total cholesterol using the formula in Phillips *et al.* (15). To account for differences in lipophilic chemical levels between fasting and nonfasting samples, lipid-corrected organochlorine levels were created by dividing the recovery-adjusted estimates by the lipid content of the serum sample (15).

Total PCBs were estimated using the sum of all congener values measured (International Union for Pure Applied Chem-

istry numbers 28, 52, 74, 105, 118, 138, 153, 170, 180, 194, 203). These congeners represent ~70% of the total PCBs by weight in human serum (16, 17).

Statistical Analysis. Statistical analyses were limited to those chemicals that were detected above the method detection limit in >50% of all samples: DDE, total PCBs, HCB, and *trans*-nonachlor. After descriptive analysis, each organochlorine compound was evaluated individually in separate logistic regression models. Organochlorine exposure was examined in two ways: (*a*) as categorical variables using tertiles of the sample distribution for all contaminants (with the exception of *trans*-nonachlor, which had categories of 0, 0 to median, ≥median) and (*b*) as continuous variables. Unconditional logistic regression models were adjusted for race and the matching factors of age and sex. Models were examined for potential confounding by smoking, history of diabetes, ulcer surgery, and pancreatitis, as well as pregnancy and lactation, factors that may alter organochlorine levels in women (17). Interactions between age category and pesticide level were explored. Final models included only race**,** the matching factors, and the organochlorine measures. All analyses were conducted using SAS (SAS Institute Inc., Cary, NC).

Pancreatic cancer cachexia may affect the pharmacokinetics of organochlorine lipid levels. A bias away from the null would occur if cachexia leads to the bioconcentration of organochlorines in lipids. As a result, the potential effect of the bioconcentration of organochlorine compounds during fat mobilization was explored by adjusting the concentration of the cases to assume three hypothesized levels of bioconcentration related to pancreatic cancer cachexia: 10%, 25%, and 40% concentration in serum lipids. Values were selected based on the differences in median lipid levels between cases and controls (26% lower in cases) and the crude estimate of the percent adipose tissue lost in pancreatic cancer patients at the time of presentation (20%). The crude estimate of adipose tissue loss was based on the literature-reported weight loss by patients presenting with pancreatic cancer (18), anecdotal reports by physicians treating our study population (up to 10%), and the percent of adipose tissue in older adults in California (40–50%; Ref. 19). Assuming that adipose tissue was lost first during the wasting process (20, 21), we estimated that up to 20% of adipose tissue may have been lost by the time of presentation with pancreatic cancer. The levels of organochlorine compounds in cases, but not controls, were adjusted to account for possible bioconcentration with the levels reduced by 10%, 25%, and 40% and then compared with controls in logistic regression models.

Results

Demographic characteristics did not differ between cases and controls (Table 1). Subjects ranged in age from 32 to 85 years with an average age of 66 years. Medical history and distributions of weight-related factors were nearly identical for cases and controls before disease. Among cases who completed the ancillary questionnaire, 55% reported unintended weight loss before diagnosis. Total cholesterol and triglycerides levels were markedly lower among cases than controls ($P \leq 0.001$); median cholesterol levels were 26% lower among cases, and median triglyceride levels were 23% lower among cases than controls. Lipid levels did not differ among cases based on the time between diagnosis and blood draw.

Four organochlorine compounds, DDE, total PCBs, HCB, and *trans*-nonachlor were detected in >50% of the samples. Quantitation of organochlorines ranged from 100% for DDE and 96% for PCBs to 59% for *trans*-nonachlor and HCB. DDT was detected in <35% of all samples with both the mean and median values below the detection limit of 0.5 ng/ml serum. Table 2 presents chemical concentration in serum (ng/ml serum, *i.e.*, lipid-unadjusted values) and in lipid (ng/g lipid, *i.e.*, lipid-adjusted values). The lipid-adjusted values were used for all case-control comparisons. Cases had higher concentrations of all organochlorine compounds than controls, with median levels of DDE, PCBs, and *trans*-nonachlor significantly higher among cases (Table 2).

A significant dose-response trend was observed with increasing PCB concentration as measured by tertiles ($P < 0.001$) and as a continuous variable ($P < 0.001$; Table 3). Subjects in the highest tertile of PCBs (≥360 ng/g lipid) had an OR of 4.2 (95% CI = 1.9–9.4) compared to those in the lowest tertile (<185 ng/g lipid). When modeled as a continuous variable, the OR for pancreatic cancer was 1.003 (95% CI = 1.001–1.004) for each ng/g serum increase in total PCB level. In congener-specific analyses, significantly elevated ORs were observed for the highest tertiles of PCB-153 (OR = 3.0; 95% CI = 1.4–6.6) and PCB-180 (OR = 8.4; 95% CI = 3.4–21). ORs for the highest tertiles of the other chemicals were elevated compared

Table 1 Demographic and medical characteristics of pancreatic cancer cases and controls, San Francisco Bay Area, CA 1996–1998

	Cases (n = 108)		Controls (n = 82)		Wilcoxon P
Age (yr)					
Mean	65.5		65.7		
SD	11.5		11.6		
Median	67.5		68.5		
Range	32–84		40–85		
Usual adult weight (pounds)					
Mean	161		163		
SD	33		30		
Median	155		160		
Range	95–300		110–250		
Cholesterol[a] (mg/dL)					
Mean	165		214		
SD	40		38		
Median	159		215		<0.001
Range	63–302		139–323		
Triglycerides[a] (mg/dL)					
Mean	154		221		
SD	68		148		
Median	141		184		<0.001
Range	53–569		61–832		
Total lipids[b] (mg/dL)					
Mean	530		707		
SD	126		190		
Median	503		676		<0.001
Range	254–1019		377–1516		
	n	%	n	%	
Race					
White	88	81%	77	94%	
Black	7	6%	2	2%	
Asian	9	8%	2	2%	
other	4	4%	1	1%	
Sex					
Female	47	44%	38	46%	
Male	61	56%	44	54%	

[a] Nonfasting blood specimens were used.
[b] Total lipids were calculated per Phillips *et al.* (16): total lipids = [2.27 total cholesterol] + triglycerides + 0.623.

Table 2 Serum organochlorine concentrations for chemicals detected in >50% of all samples among pancreatic cancer cases and controls, San Francisco Bay Area, CA 1996–1998

Chemical	Cases (n = 108)				Controls (n = 82)				Wilcoxon P
	Mean	Median	SD	Range	Mean	Median	SD	Range	
Results unadjusted for lipid content of serum[a] (ng/ml serum)									
DDE	11.9	7.7	12.9	1.00–79.7	12.1	7.8	14.8	0.5–90.4	
HCB	0.17	0.13	0.20	ND[b]–1.1	0.18	0.13	0.23	ND–0.94	
Total PCBs	2.5	1.9	2.2	ND–12.5	1.9	1.9	1.3	ND–7.2	
t-Nonachlor	0.37	0.34	0.43	ND–2.5	0.32	0.18	0.38	ND–1.5	
Lipid-adjusted results[c] (ng/g lipid)									
DDE	2054	1287	2038	187–16679	1572	1029	1797	97–11148	0.05
HCB	28	22	31	ND–174	22	17	26	ND–111	0.22
Total PCBs	433	329	412	ND–2642	246	220	166	ND–892	<0.001
t-Nonachlor	63	54	78	ND–478	39	28	45	ND–187	0.03

[a] All values have been adjusted for recovery using the values in Brock *et al.* (14).
[b] ND, not detected. Detection limits in ng/ml serum are 0.4 (DDE), 0.05 (HCB), 0.2 (each PCB congener), and 0.9 (*t*-nonachlor).
[c] All comparisons were based on lipid-adjusted results due to the collection of nonfasting samples.

Table 3 ORs and 95% CIs for serum organochlorine levels (ng/g lipid) and pancreatic cancer, San Francisco Bay Area, CA, 1996–1998

Chemical (ng/g lipid)	Cases n = 108	Controls n = 82	OR[a]	95% CI	P for trend
DDE					
<850	30	32	1		0.08
850–1880	37	28	1.5	0.7–3.3	
≥1880	41	22	2.1	0.9–4.7	
Continuous[b]			1.0001	0.998–1.002	0.20
HCB					
0	41	34	1		0.22
0.1–32	25	24	0.9	0.4–1.9	
≥32	42	24	1.6	0.8–3.4	
Continuous[b]			1.01	0.998–1.022	0.10
Total PCBs					
<185	27	35	1		<0.001
185–360	34	31	1.3	0.6–2.8	
≥360	47	16	4.2	1.9–9.4	
Continuous[b]			1.003	1.001–1.004	<0.001
t-Nonachlor					
0	40	37	1		0.22
0.1–75	28	25	0.9	0.5–1.9	
≥75	40	20	1.7	0.8–3.5	
Continuous[b]			1.006	1.001–1.012	0.03

[a] All models adjusted for age interval (four categories), race and sex.
[b] OR for each ng/g increase in organochlorine concentration.

Table 4 Spearman correlations between organochlorine chemicals for 190 pancreatic cancer case and control subjects, San Francisco Bay Area, CA, 1996–1998[a]

	HCB	Total PCBs	*t*-Nonachlor
DDE	0.29	0.58	0.42
HCB		0.45	0.42
Total PCBs			0.60

[a] All correlation coefficients are significantly different from 0 at $P < 0.01$.

to the lowest tertile, although none achieved statistical significance. The OR for *trans*-nonachlor was significantly elevated only when *trans*-nonachlor was modeled as a continuous variable (OR = 1.006 per ng/g lipid; 95% CI = 1.001–1.012). Results were not confounded by cigarette smoking and reported medical conditions.

The organochlorine variables were highly correlated (Table 4), and the correlations did not differ between cases and controls. However, the variables were not so strongly correlated as to add instability to mutually adjusted regression models and thus, logistic models containing both DDE and PCBs, and *trans*-nonachlor and PCBs were constructed. When DDE and PCBs were considered simultaneously, the increased OR associated with the highest tertile of PCBs remained (OR = 4.0; 95% CI = 1.6–9.8), whereas the OR for highest tertile of DDE was diminished to 1.1 (95% CI = 0.4–2.8). When the *trans*-nonachlor level was included in the model with PCBs, the OR for the highest level of PCBs increased ~20% (OR = 5.2; 95% CI = 2.0–13.5), whereas the OR for *trans*-nonachlor was not significantly different from unity.

The elevated OR associated with the highest tertile of PCBs persisted under conditions of both 10% and 25% bioconcentration in the sensitivity analysis, although the OR for 25% bioconcentration did not achieve statistical significance (Table 5). Under conditions of 40% bioconcentration, there was no increased OR associated with the highest tertile of PCBs.

Discussion

Pancreatic cancer cases were found to have elevated serum levels of PCBs when compared to control subjects. Evaluation of exposure to organochlorines using serum lipid levels enabled us to quantify long-term exposure to these substances without recall bias. Due to cachexia among pancreatic cancer patients, the possible effect of wasting on organochlorine levels, and PCBs in particular, is difficult to predict and complicates the interpretation of our findings.

On the basis of a Medline search of the English language literature, we found no other published study that evaluated pancreatic cancer and organochlorine exposure in the general population using serum measures rather than questionnaire data. Our primary *a priori* hypothesis was that DDE would be elevated in cases relative to controls given the strong evidence from studies of DDT manufacturing workers (3). Secondary hypotheses were that other organochlorine chemicals, including PCBs, would be elevated given the suggestive but inconsistent findings of these compounds from earlier work (22–25). In the present study, PCBs emerged as most strongly associated with pancreatic cancer status. However, epidemiological evidence for PCBs and pancreatic cancer is limited. Increased pancreatic cancer mortality has been observed among Canadian transformer workers (24), but this finding has not been demonstrated consistently among occupational cohorts with presumed higher

Table 5 Sensitivity analysis to examine potential influence of cachexia on OR estimates; ORs and 95% CIs for total PCB concentration in serum for pancreatic cancer cases and controls, San Francisco Bay Area, CA, 1996–1998[a]

Total PCBs (ng/g lipid)	No bioconcentration in cases			10% bioconcentration in cases			25% bioconcentration in cases			40% bioconcentration in cases		
	OR[b]	95% CI	*P* trend	OR[b]	95% CI	*P* trend	OR[b]	95% CI	*P* trend	OR[b]	95% CI	*P* trend
			<0.001[c]			0.007[c]			0.16[c]			0.61[c]
<185	1.0			1.0			1.0			1.0		
185–360	1.3	0.6–2.8		1.2	0.6–2.4		0.7	0.4–1.5		0.7	0.4–1.4	
≥360	4.2	1.9–9.4		3.1	1.4–7.0		1.9	0.9–4.2		0.9	0.4–2.0	
Continuous[d]	1.003	1.001–1.004	<0.001	1.002	1.001–1.004	0.004	1.001	1.000–1.003	0.07	1.000	0.999–1.002	0.88

[a] Based on models assuming 0, 10, 25, and 40% bioconcentration in cases.
[b] All models adjusted for age interval (four categories), sex, and race.
[c] *P* value for categorical trend test.
[d] OR for each ng/g increase in PCB concentration.

PCB exposures and with sufficient follow-up time and power to detect an increase in pancreatic cancer (22, 23, 25).

The association of DDE serum levels with pancreatic cancer was weak in this study. Lipid-adjusted DDE levels were significantly higher among cases than controls, and the highest tertile of DDE was associated with an OR of 2.1 that decreased to 1.1 after controlling for PCB level. Among DDT manufacturing workers, a 7-fold increased risk of pancreatic cancer has been shown using work history records to estimate DDT exposure (3). Our results are not directly comparable due to differences in concentrations, exposure routes, and parent compound. The subjects in our study are more likely to have been exposed to DDT's metabolite DDE primarily via food than to the parent compound DDT as experienced by the workers in the earlier report (3). Higher levels of DDT exposure are expected for occupationally exposed subjects compared with those who are environmentally exposed, and their exposure is more likely to occur via inhalation and dermal contact rather than ingestion.

Serum measurements of organochlorine pesticides provide a sensitive estimate of total body burden in healthy subjects. In the blood stream, organochlorine compounds are adsorbed on the hydrophobic sites of plasma proteins (26, 27). As a consequence, the concentration of organochlorines in the serum is related to lipid content and therefore, serum organochlorine levels increase after the consumption of meals containing fat (15, 27, 28). To account for the collection of nonfasting samples, all analyses of these data were conducted using the lipid-adjusted organochlorine levels.

The impact of weight loss**,** especially adipose tissue loss, by cases on this analysis requires thorough consideration because 55% of the cases interviewed with the ancillary questionnaire reported some weight loss before diagnosis. Many cases are likely to have experienced some weight loss by the time of blood collection because the median time between diagnosis and blood draw was 2.9 months. The extent of weight loss cannot be directly evaluated in our data because weight at diagnosis and weight at blood draw were unavailable. Whereas serum lipid levels in cases are lower than controls, the lipid levels among cases do not differ based on time since diagnosis, potentially suggesting that lipid levels drop with pancreatic cancer diagnosis and then stabilize or that our sample represents the healthier cases who are not undergoing dramatic wasting. However, there are no longitudinal data to evaluate these possibilities.

Cases had significantly lower serum lipid concentrations than controls, such that lipid adjustment increased cases' organochlorine concentrations relative to controls. Because the behavior of fat-stored compounds in cancer patients with cachexia has not been studied directly, it is difficult to know how accurately serum levels of organochlorine compounds among cases reflect exposure before disease. Cachexia differs from starvation and entails increased resting energy expenditure, catabolism of both fat and lean body mass, and decreased protein synthesis (29). Animal data generally are limited to the starvation studies of rodents exposed to high initial doses of pesticides or PCBs, whereas human data address the metabolic changes associated with cachexia and weight loss regimens. This complementary, although incomplete, information is consistent with three plausible scenarios for the effect of cachexia on the concentration of organochlorines in serum lipids: (*a*) concentrations in fat do not change during fat mobilization due to concomitant increased metabolism and/or excretion of fat-soluble compounds proportional to the mobilization of fat, (*b*) bioconcentration of fat-soluble compounds occurs due to the removal of fat but not the contaminant, and (*c*) mobilization of organochlorine compounds from fat is differential.

Our case-control analysis was conducted under scenario a, assuming no bias between cases and controls based on the underlying disease process. Animal studies and human cadaver data have shown a decrease in serum levels of organochlorines during weight reduction, but these data were not adjusted for the subsequent reduction in lipid content (11, 30). Autopsy samples showed no difference in adipose tissue levels of organochlorines based on recent weight loss, although cancer patients had greater organochlorine levels in adipose tissue than did subjects who had died of other causes (31). If adipose tissue loss results in lower serum levels of PCBs and other organochlorine chemicals, then our analysis is conservative.

The bioconcentration of fat-stored contaminants is likely (scenario b). Animal data are suggestive of bioconcentration of lipophilic chemicals, including DDT, during starvation-induced weight loss (32–34). The human data are limited to one case report in the literature from a follow-up of workers exposed to TCDD during a reactor accident. Zober and Papke (35) measured blood levels of TCDD in a worker with pancreatic cancer. This patient had extremely elevated blood levels of TCDD 8 months before death. At death and after profound cachexia, blood levels of dioxins ranged from 2 to 25 times higher than 8 months earlier. To explore whether bioconcentration may have affected our results, we conducted a sensitivity analysis using bioconcentration levels consistent with the lower serum lipid levels of the cases and the estimated range of adipose tissue loss. Although the OR estimates were attenuated, results of these adjusted analyses did not alter the pattern of increased pancreatic cancer risk in association with increased PCB exposure at levels up to 25% bioconcentration.

Animal and human evidence suggests the possibility that individual organochlorine chemicals have differential mobili-

zation from adipose tissue during physiological changes such as starvation and pregnancy (scenario c), although no data are available under cachectic conditions. Animal studies have illustrated differential mobilization of organochlorines from fat reservoirs during starvation (36, 37) and pregnancy (38). In environmentally exposed women, serum levels of DDE and PCBs were differentially associated with pregnancy and lactation history (17), suggesting that mobilization from fat of individual chemicals may differ during these events.

Aside from the primary limitation of the timing of serum sample collection, this study has a number of strengths, including the use of a direct biological measure of organochlorine body burden. Organochlorine concentrations in serum lipids integrate overall exposure sources, reflect overall body burden, and are not subject to recall bias. Because the concentrations observed here, even among the cases, are consistent with those measured in other studies of environmentally exposed adults in the United States (17, 39, 40), it is unlikely that our subjects had unusual organochlorine exposures.

Pancreatic cancer has been hypothesized to result from high lifetime exposures to insulin (41), and PCBs have been shown to stimulate insulin release in hormone producing cells (42). If PCBs stimulate insulin release *in vivo* as well as *in vitro*, then this may provide a plausible mechanism for PCBs as pancreatic carcinogens.

Our analytical strategy considered both the possibility of no change in organochlorine levels with pancreatic cancer and the possibility of bioconcentration in fat due to adipose tissue loss. Bioconcentration in cases would need to be >25% for the observed association to be entirely an artifact. Bioconcentration is plausible given that: (*a*) little is known about the pharmacokinetics of organochlorines in cachectic cancer patients, (*b*) percent adipose tissue lost in patients presenting with pancreatic cancer is estimated to be 20% (18, 21, 43) and (*c*) total lipid levels in the present study were 26% lower in cases than controls. However, if bioconcentration is the basis of the observed association with PCBs, differential mobilization would need to occur because PCBs were much more elevated than the other organochlorines studied. A better understanding of the pharmacokinetics of organochlorines during cachexia and prospective assessments with exposure ascertained before development of pancreatic cancer will further elucidate the role of organochlorine chemicals and pancreatic cancer.

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