Organochlorines and Risk of Prostate Cancer

Justine M. Ritchie, PhD
Scott L. Vial, MS
Laurence J. Fuortes, MD
Haijun Guo, MS
Victoria E. Reedy, BS
Elaine M. Smith, PhD

This pilot study examined the relationships of organochlorine pesticides (OCPs) and polychlorinated biphenyls (PCBs) with prostate cancer. Ninety-nine controls were frequency matched by age in 5-year increments to 58 prostate cancer patients. Thirty PCBs and 18 OCPs were measured in serum by gas chromatography. Multiple logistic regression was used to assess the magnitude of association. Seven organochlorines, dieldrin, p,p′-DDE, trans-nonachlor, oxychlordane, heptachlor epoxide, and PCBs 153 and 180 were detected in at least 20% of all study participants. Adjusting for age, body mass index, and a history of prostatitis, oxychlordane and PCB 180 were associated with an increased risk of prostate cancer. This study suggests that long-term, low-dose exposure to specific OCPs and PCBs in the general population may contribute to an increased risk of prostate cancer and supports further investigation in this area. (J Occup Environ Med. *2003;45: 692–702*)

Prostate cancer is a disease of older men, with about 70% of the cases diagnosed at 65 years of age or older.[1] The age-adjusted incidence rate of prostate cancer in the United States is 165 per 100,000.[2] It is the leading cause of cancer among men in Iowa, accounting for 29.2% of male cancers in the state.[3] With the exception of age, race, and familial genetic predisposition, other risks remain unclear.[4–6] Excess incidence has been shown to be associated with occupational exposure to pesticides.[7] Several but not all studies have found higher incidence and mortality from prostate cancer among farmers.[8–14] Current research is primarily focused on genetic polymorphisms and the role of the endocrine system in regulating prostate cell control and growth.

Organochlorines include pesticides, such as DDT, DDE, and lindane, and chemically related compounds, such as polychlorinated biphenyls (PCBs). Although many of these compounds have been removed from the US market for more than 20 years, they are persistent in the environment. The primary source of exposure in the general population is believed to be through diet from fish, meat, and dairy products.[15] Other possible sources of exposure include water, soil, and dust. Organochlorine pesticides (OCPs) and PCBs are known to have long half-lives and to persist for decades in adipose tissue and blood lipids.[16] In animal studies, OCPs and PCBs have been shown to be carcinogenic and tumor promoters.[7,17]

In recent years several case-control studies have examined the relationship between serum levels of OCPs and PCBs with the risk of

From the Department of Biostatistics, College of Public Health, University of Iowa, Iowa City (Dr Ritchie); Department of Epidemiology, College of Public Health, University of Iowa, Iowa City (Mr Vial, Dr Fuortes, Dr Smith); Department of Environmental and Occupational Health, College of Public Health, University of Iowa, Iowa City (Dr Fuortes); Department of Statistics and Actuarial Science, College of Liberal Arts and Sciences, University of Iowa, Iowa City (Mr Guo); University of Iowa Hygienic Laboratory, University of Iowa, Oakdale Campus, Iowa City (Ms Reedy); and Department of Obstetrics/Gynecology, College of Medicine, University of Iowa, Iowa City (Dr Smith), Iowa.

Address correspondence to: Justine M. Ritchie, PhD, Department of Biostatistics, College of Public Health, University of Iowa, Iowa City, IA 52242; E-mail: jritchie@mail.public-health.uiowa.edu.

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cancers of the breast[18–29] and pancreas,[30,31] and non-Hodgkin lymphoma (NHL).[32–34] Findings from the numerous breast cancer studies have not been consistent, but some have found significant associations with OCPs and PCBs.[18,22,25,27,28] Results from NHL and pancreatic cancer investigations also have tended to suggest that higher serum levels of certain OCPs and PCBs are associated with an increased risk of these cancers.

Many of the OCPs and PCBs are known endocrine disrupters and may modulate steroid sex hormones as agonists, antagonists, or as mixed agonist–antagonists, particularly with regard to estrogen or testosterone activity.[15,16,27,35–38] As a result, it is plausible that these chemicals contribute to the development of prostate cancer through hormone-mediated effects.[15,16,27,35–37,39] However, to date, the effects of these chemicals on the prostate, using possible biomarkers of exposure, have not been explored in humans as opposed to cell lines and animal models. This pilot study was undertaken to generate new hypotheses for future studies by comparing detection rates and serum levels of OCPs and PCBs between prostate cancer cases and controls and by examining the associations of specific OCPs and PCBs with the risk of prostate cancer in the general population.

Methods

Participants

After consultation with the NCI Iowa SEER Registry, two clinics were identified as diagnosing and treating incident prostate cancer cases (ICD-O 61.9) in the surrounding county areas. All cases were recruited from these two clinics, which included a university hospital urology clinic ($n = 54$) and a group practice of urologists ($n = 4$) associated with the other hospital in the area. Cases were pathologically confirmed, newly diagnosed prostate cancer patients enrolled between May 2000 and May 2001. All 58 of the cancers were adenocarcinomas. Based on the Gleason score, all tumors were moderately or poorly differentiated (31 moderate, 19 moderate/poor, and 8 poor).[40] All stages of disease were included (36 II, 7 III, 1 III/IV, 3 IV, and 11 currently unstaged).[40] Controls ($n = 99$) included men without a previous history of prostate cancer who were receiving physicals and annual check-ups in the internal medicine and family care clinics from the university hospital. Similar to the prostate cancer cases, controls come to these university clinics from a wide variety of areas and distances. All controls were asymptomatic for prostate cancer. Seventy-one percent of the controls had prostate specific antigen levels available; 87% were taken within 1 year before and/or after study enrollment, 9% were taken more than 1 year before study enrollment, and 4% were taken more than one year after study enrollment. There were seven controls with prostate-specific antigen levels greater than 4; all were diagnosed with benign prostatic hyperplasia not prostate cancer after biopsy. Controls were frequency matched by age in 5-year increments to cases and were enrolled in the study between January and June of 2001. All patients were administered an IRB approved consent form prior to enrollment, completed a questionnaire and had blood drawn for assessment of the OCPs and PCBs under study. Blood draws for organochlorine levels were obtained before treatment for 54 of the 58 cases; 4 cases had received one dose of some form of hormonal treatment within 3 months before drawing the blood. Five prospective controls and no cases declined participation.

Questionnaire

The questionnaire included demographic and risk characteristics such as age, race, family history of prostate cancer, tobacco and alcohol usage, number of sexual partners, history of sexually transmitted diseases (STDs), and sex hormone usage. Participants also completed a chemical checklist that inquired about exposure to solvents, cleaning fluids, dyes and adhesives, dusts, gases, sterilants, pesticides, fumigants, wood preservatives, metals, and radiation sources. The research nurse completed a medical history form for all study participants.

Laboratory Procedures

Serum extracts were prepared by processing 2-mL aliquots of protein-denatured sera using methods described by Brock et al.[41] One-milliliter aliquots were used for lipid analyses. The serum extracts were injected using splitless injection onto a programmable gas chromatograph (Agilent 6890; Wilmington, DE) equipped with dual, chemically dissimilar 30 m columns (CLPesticides, CLPesticides II, Restek Corporation; Bellefonte, PA) and micro-cell electron-capture detectors. Spikes, method blanks and instrument blanks were injected sequentially with samples to monitor recoveries and potential contamination from the extraction process or other sources. The limit of detection (LOD) for each analyte was determined as 3 standard deviations plus the mean background noise observed from multiple method blanks. Study analyte and surrogate recoveries obtained from the fortified bovine spikes averaged 54.9% to 93.8% and did not exceed established upper and lower control limits. Mean percent analyte recoveries were 70.9% for OCPs and 67.3% for PCBs, with coefficients of variation of 18.3% and 13.8%, respectively.

Analytical methods and quality control criteria were based on established EPA SW-846, Method 8000B for solid waste.[42] Analyte identification was confirmed by retention time comparison and retention time windows established for each compound on the two columns. Reagent standards were injected to establish calibration curves with a minimum of

five concentration levels ranging from 0.2 to 10 ppb. Quantification was derived from internal standard and analyte response factors generated from the curves. Initial calibration correlation coefficients greater than 0.995 and coefficients of variation less than or equal to 20% for a single compound (less than 10% mean) were criterion for curve linearity acceptability. Comprehensive quality control also included the monitoring of baseline peak to noise ratios, peak Gaussian factors, peak integration, compound resolution, degradation, and column relative percent difference, to minimize systematic and random errors.

A reporting limit of 0.2 ng/mL was established from the highest method detection limit except when the LOD, or sample background necessitated raising the reporting limit or when analyte detection was confirmed at a measurable, lower reporting limit.[43] Results were obtained for five DDT analogs (*o,p′*-DDT, *p,p′*-DDT, *o,p′*-DDE, *p,p′*-DDE, *p,p′*-DDD), lindane, β-hexachlorocyclohexane (β-BHC), hexachlorobenzene, chlordane (α- and γ-isomers), oxychlordane, *trans*-nonachlor, heptachlor, heptachlor epoxide, aldrin, dieldrin, endrin, mirex, and 30 PCB congeners (IUPAC numbers 18, 28, 52, 56, 65, 66, 74, 99, 101, 105, 110, 118, 138, 146, 153, 156, 170, 172, 177, 178, 180, 183, 187, 189, 193, 194, 195, 201, 203, 206). Total cholesterol and total triglycerides, quantified in mg/dL by enzymatic assay, were used to lipid adjust the gas chromatography results according to the alternative formula by Phillips et al.[44]

Statistical Analysis

Patient characteristics and organochlorine data of cases and controls were compared by the Wilcoxon rank sum test for quantitative variables and by the chi-square test or Fisher's exact test for categorical variables. Data for the organochlorine levels were analyzed using both the unadjusted and lipid-adjusted serum values, but conclusions were similar. Thus, only the results from the lipid-adjusted analyses are reported. Lipid-adjusted values (μg/g) for the OCPs and PCBs were calculated as the serum concentrations divided by the total serum lipids. For analyses involving individual OCPs and PCBs, nondetectable values were set to half the lowest detectable level.[45] The sum of the PCBs was based on the detectable values only. Summations for individuals without detectable levels for any of the PCBs were assigned to half the smallest sum. After the comparison of the detection rates between cases and controls, analyses involving the individual organochlorines were restricted to those with detection rates of at least 20% in cases and 20% in controls to avoid sparse data. Spearman correlation coefficients were used to assess the associations between individual OCPs and PCBs and with age and body mass index (BMI) among controls.

Odds ratios (ORs) were estimated from the unconditional logistic regression models. Ninety-five percent confidence intervals (CIs) for the ORs were based on normal approximations. Tertiles were determined from the control distributions and were used for the following organochlorines: *p,p′*-DDE, *trans*-nonachlor, PCB 153, and oxychlordane. For heptachlor epoxide, PCB 180, and dieldrin, the cutoffs were based on an attempt to include an equal number of controls in the categories with detectable values.

A backward stepwise selection procedure with significance set to $P < 0.10$ was used to develop a multivariate model for risk of prostate cancer. A forward stepwise procedure also was evaluated and led to the same final model as that reported. Variables included in the modeling process were age, BMI, total lipids, tobacco status (ever vs never), average drinks per week, a history of prostatitis, a history of STDs, the sum of the PCBs, and the individual organochlorines meeting the 20% detection criterion. Regardless of statistical significance, age and BMI were included in the adjustment since organochlorines are known to bioaccumulate. All analyses were performed using the SAS statistical package.[46]

Results

Patient Characteristics

Demographic and lifestyle characteristics of the cases and controls are displayed in Table 1. The study population was primarily white with a median age of 64.5 years for cases (range, 47 to 85 years) and 62.0 years for controls (range, 44–85 years). Education, tobacco status and alcohol usage were similar between the two groups. Cases were more likely than controls to be married or living as married ($P < 0.01$). Although there was not a significant difference in the median body mass index (BMI) values between cases and controls (29.7 vs 28.8 kg/m^2; $P = 0.46$), a higher percentage of cases had a BMI between 25 and 30 as opposed to less than 25 kg/m^2 ($P = 0.04$). Cases also had higher median total lipids, 745.5 mg/dL, than controls, 696.0 mg/dL ($P = 0.09$) and were more likely to have a history of prostatitis (OR = 2.8, 95% CI, 1.2–6.9). There were no significant differences between cases and controls in a history of having a first-degree relative with prostate cancer (20% vs 15%; $P = 0.33$), colon cancer (14% vs 17%; $P = 0.64$), breast cancer (23% vs 25%; $P = 0.81$), or ovarian cancer (9% vs 8%; $P = 0.77$). When stratified by age, there was a non-significant elevated risk of prostate cancer associated with a family history of prostate cancer among those 60 years of age and younger (OR = 2.4), but not among those over 60 (OR = 1.1).

Chemical Exposures

There were no significant differences between the two groups in self-reported exposure to the general chemical categories presented in Fig.

TABLE 1
Demographics, Risk Factors, and Medical Conditions of Prostate Cancer Cases and Controls

Characteristic	Case n = 58 (%)	Control n = 99 (%)	P value*
Age			
≤ 60	34.5	42.4	–
> 60	65.5	57.6	0.33
Marital status			
Married/like mar.	89.7	69.7	–
Other†	10.3	30.3	<0.01
Education			
≤ 12 yrs	46.5	46.5	0.99
> 12 yrs	53.5	53.5	–
Income			
<$40,000	32.8	44.4	0.61
$40,000–$59,999	32.8	16.2	0.07
≥ $60,000	31.0	34.3	–
Race			
White	98.3	99.0	–
Other	1.7	1.0	0.99
Partners			
≤ 2	44.8	45.5	–
> 2	43.1	52.5	0.60
Tobacco status			
Never	34.5	27.3	–
Past	55.2	57.6	0.45
Current	10.3	15.2	0.27
Average drinks/week			
Never	29.3	30.3	–
≤ 9	39.7	35.4	0.71
> 9	31.0	34.3	0.87
Body mass index (kg/m^2)			
<25	8.6	20.2	–
25–30	51.7	39.4	0.04
≥ 30	37.9	40.4	0.16
Total lipids (mg/dL)‡			
< 638	22.4	33.3	–
638–766	29.3	33.3	0.54
> 766	48.3	33.3	0.06
Triglycerides (mg/dL)			
< 120	20.7	33.3	–
120–216	36.2	34.3	0.22
> 216	43.1	32.3	0.07
Cholesterol (mg/dL)			
< 184	24.1	34.3	–
184–217	32.8	32.3	0.39
> 217	43.1	33.3	0.14
Sex Hormone			
Never	98.3	93.9	–
Ever	1.7	6.1	0.26
Prostatitis			
Yes	24.1	10.1	0.02
No	76.0	89.9	–
STD§			
Yes	12.1	6.1	0.23
No	87.9	93.9	–
Family history of prostate cancer‖			
Yes	20.7	15.2	0.33
No	69.0	76.8	–
Unknown	10.3	8.1	0.56

* P value based on comparison to referent group denoted with dashed lines.
† Includes never married, separated, divorced, and widowed.
‡ Total lipids = 2.27 (total cholesterol) + triglycerides + 62.3.
§ STD = sexual transmitted disease, includes gonorrhea, syphilis, genital herpes, chlamydia, and genital warts.
‖ Family history among first-degree relatives (father or brothers).

1, including pesticides. Exposure rates for individual pesticide classes also did not significantly differ between cases and controls (organochlorines 9% vs 9%; organophosphate and carbamate insecticides 19% vs 23%; herbicides 28% vs 33%; fungicides 10% vs 15%, data not shown in Fig. 1). The only difference noted for individual items within a general chemical category was that controls had greater exposure to paints than cases (46% vs 31%, $P = 0.06$).

OCPs and PCBs

Blood samples were assayed for 48 different individual organochlorines. Twenty were detected in at least one study participant (Table 2). Dieldrin, *p*,*p*′-DDE, *trans*-nonachlor, oxychlordane, heptachlor epoxide, and PCBs 153 and 180 were detected in at least 20% of cases and 20% of controls; subsequent analyses were restricted to these analytes. Cases were more likely than controls to have detectable levels of *trans*-nonachlor ($P = 0.03$) and PCB 180 ($P = 0.07$). These results remained after adjusting for total lipids (data not shown).

Table 3 presents the medians for the lipid-adjusted serum levels of the individual OCPs and PCBs as well as the sum of the PCBs. Although none is significantly different, it is interesting that for five of the six comparisons presented in Table 3, the median levels among cases were higher than among controls.

Examination of the relationships among the individual organochlorines suggested that the strongest correlation among individual organochlorines was between oxychlordane and *trans*-nonachlor ($R = 0.86$, $P < 0.0001$). Oxychlordane was also correlated with heptachlor epoxide and PCB 153 (R values ranged between 0.4 and 0.5). PCB 180 was strongly associated with PCB 153 ($R = 0.61$), but not oxychlordane ($R = 0.31$). To examine the bioaccumulation effects of the organochlorines within our data, the

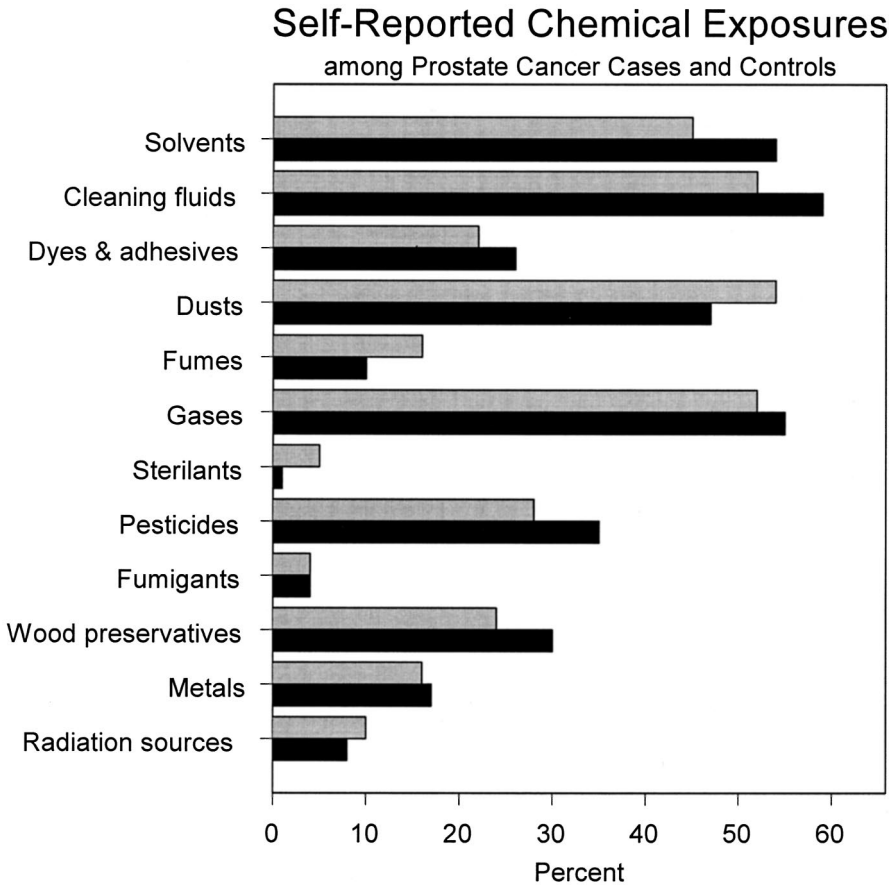

Fig. 1. Self-reported chemical exposures among prostate cancer cases and controls. The gray bars are for the prostate cancer cases ($n = 58$). The black bars are for the controls ($n = 99$).

relationships of the individual analytes with age and BMI among controls were examined. PCB 153 had the strongest correlation with age ($R = 0.41$). Age was not significantly correlated with heptachlor epoxide or dieldrin. The Spearman correlation coefficients between age and the other OCPs and PCBs ranged from 0.2 to 0.4. The strongest correlation with BMI was with heptachlor epoxide ($R = 0.48$). PCB 180 and the sum of total PCBs were negatively correlated with BMI ($R = -0.2$). None of the other organochlorines was significantly correlated with BMI.

The ORs of prostate cancer for the lipid-adjusted serum levels of the OCPs and PCBs after adjusting for a history of prostatitis, age, and BMI are given in Table 4. A significant elevated risk of prostate cancer was observed for the middle concentration groupings of oxychlordane (OR = 3.1, 95% CI = 1.3–7.6) and PCB 180 (OR = 3.1, 95% CI = 1.3–7.3). The odds ratios for the highest concentrations of both organochlorines also were elevated but not to the same extent as those for the middle groupings possibly suggesting a nonlinear dose response. There were no significant linear trends in the tests of association between prostate cancer status and concentration levels for any of the OCPs and PCBs presented in Table 4 (all $P > 0.11$). Those with the highest levels of dieldrin appeared to have a reduced risk of prostate cancer (OR = 0.3, 95% CI = 0.1–0.9) compared with those in whom dieldrin was not detected.

Results from the multivariate analyses are presented in Table 5. The odds of prostate cancer among those with a history of prostatitis was between three to four times that among those without such a history. Consistent with the unadjusted analyses presented in Table 1, factors, such as tobacco status, alcohol usage, and self-reported history of STDs, did not contribute to the model (all $P > 0.15$). Among the lipid-adjusted serum levels of the OCPs and PCBs, oxychlordane ($P = 0.02$) and PCB 180 ($P = 0.05$) were included in the multivariate model with the middle categories being significantly associated with prostate cancer status. Although not significant, the adjusted OR for the upper concentrations of PCB 180 was also elevated. Dieldrin did not remain in the model ($P = 0.13$).

Discussion

This is the first study to investigate the possible relationship between serum levels of OCPs and PCBs with prostate cancer. The results of this pilot study suggest that PCB 180 and oxychlordane are each associated with an increased risk of prostate cancer. This association remained after adjusting for age and BMI. Patients were not required to fast prior to the blood draws, so results were reported for lipid-adjusted levels. This adjustment removes variation introduced by fluctuating lipid levels in the blood and takes into account in our analyses that cases had higher total lipids than controls ($P < 0.10$). Interestingly, results based on the mass per blood volume levels were similar to those reported for lipid adjustment.

Elevated standard incidence and mortality rates for prostate cancer have been noted in several cohort studies[10,47–49] of pesticide applicators but not all.[39,50] In addition, other case-control studies among the general population have found pesticide usage to be associated with an increased risk of prostate cancer. One such study[51] conducted in Canada found the odds of prostate cancer to be over 2 times (95% CI = 1.3–4.2) for those exposed to pesticides or garden sprays during leisure. Van der

TABLE 2
Prostate Cancer Case-Control Comparison of Detection Rates for Organochlorines

Organochlorines	Case *n* = 58 (%)	Control *n* = 99 (%)	*P* value
β-BHC	13.8	15.2	0.82
p,p′-DDE	100.0	99.0	0.99
p,p′-DDT	0.0	2.0	0.53
Dieldrin	29.3	38.4	0.25
Heptachlor epoxide	24.1	34.3	0.18
Hexachlorobenzene	5.2	4.0	0.71
trans-nonachlor	98.3	87.9	0.03
Oxychlordane	91.4	81.8	0.10
PCB 18	1.7	0.0	0.37
PCB 28	1.7	1.0	0.99
PCB 99	12.1	11.1	0.86
PCB 118	6.9	6.1	0.99
PCB 138	0.0	1.0	0.99
PCB 146	0.0	1.0	0.99
PCB 153	87.9	83.8	0.48
PCB 170	3.5	5.1	0.99
PCB 180	53.5	38.4	0.07
PCB 187	10.3	7.1	0.55
PCB 194	5.2	7.1	0.75
PCB 201	0.0	1.0	0.99

TABLE 3
Lipid-Adjusted Serum Levels of Organochlorines among Prostate Cancer Cases and Controls*

Organochlorines	Median	Range	*P* Value
Sum PCBs†			
Case	0.055	0.008–0.501	0.18
Control	0.042	0.008–0.365	
p,p′-DDE			
Case	0.290	0.045–1.600	0.68
Control	0.270	0.015–2.000	
trans-nonachlor			
Case	0.033	0.006–0.120	0.38
Control	0.033	0.006–0.210	
Oxychlordane			
Case	0.027	0.007–0.063	0.58
Control	0.026	0.007–0.100	
PCB 153			
Case	0.040	0.008–0.120	0.41
Control	0.033	0.008–0.150	
PCB 180			
Case	0.022	0.009–0.100	0.10
Control	0.009	0.009–0.130	

* 58 prostate cancer cases vs. 99 controls; descriptive statistics reported only for those organochlorines with at least 50% detectables in cases or controls; units for organochlorines are μg/g.

† Includes: PCBs 18, 28, 99, 118, 138, 146, 153, 170, 180, 187, 194, 201.

PCBs, polychlorinated biphenyls.

Gulden et al.[52] found an elevated risk associated with frequent pesticide exposure. Another investigation,[53] which included cases and controls from seventeen different occupations and eleven different industries, found substantial exposure to pesticides to be associated with prostate cancer risk. A recently published case-control study[54] showed an increased risk of prostate cancer among farmers exposed to organochlorine insecticides and acaricides including DDT (OR = 2.5, 95% CI = 1.4–4.2). These studies were based on self-reported exposure assessment.

Although these studies suggest an association between pesticide exposure and prostate cancer, the conclusions are somewhat limited and as such support the need for further study. Self-reported data are known to be subject to recall, case response, and misclassification biases. In this study, to reflect total body burden, we used serum levels to evaluate exposure to individual OCPs and PCBs. Serum levels of organochlorines can be used as surrogate measures of long-term exposure as a result of these compounds being lipophilic, resistant to metabolism, and stored in adipose tissue.[44,55] Our study focused on persistent organochlorine compounds for which residues could be detected in the blood. We were only able to assess rapidly metabolized and excreted agrichemicals, such as atrazine, organophosphates, and carbamates, through self-reported data. Although no significant differences were found, a lower percentage of cases reported a history of exposure to each agrichemical, a result observed by others.[56] In contrast to the self-reported data on pesticide exposure, cases had higher median levels than controls for the total sum of the PCBs and for four of the five individual organochlorines with the highest detection rates (Table 3).

Several studies have looked at OCPs and PCBs in association with cancers of the breast, pancreas, and NHL. Since ours is the first study in prostate cancer, we compare our results to these other investigations. Comparisons with the breast cancer studies seem appropriate given that both types of cancers are believed to be hormonally mediated. Most of the earlier breast cancer studies focused their attention on DDE, total PCBs, and biological groupings of PCBs[37,57–59] rather than on individual PCB congeners. Almost all of the studies have failed to establish a

TABLE 4
Adjusted Odds Ratios of Prostate Cancer According to Lipid-Adjusted Serum Levels of Organochlorines*

Organochlorines†	Case *n* = 58 (%)	Control *n* = 99 (%)	Adj. OR*	95% Wald CI
Sum PCBs‡				
≤ 0.029	24.1	33.3	1.00	–
0.030–0.064	36.2	33.3	1.36	0.56–3.32
>0.064	39.7	33.3	1.67	0.66–4.22
p,p′-DDE				
≤ 0.180	34.5	33.3	1.00	–
0.181–0.340	25.9	33.3	0.72	0.31–1.71
>0.340	39.7	33.3	1.08	0.47–2.50
Dieldrin				
Nondetectable	70.7	61.6	1.00	–
0.006–0.024	20.7	19.2	0.97	0.40–2.36
>0.024	8.6	19.2	0.28	0.09–0.88
Heptachlor epoxide				
Nondetectable	75.9	65.7	1.00	–
0.006–0.021	12.1	16.2	0.58	0.21–1.64
>0.021	12.1	18.2	0.33	0.10–1.03
trans-nonachlor				
≤ 0.025	20.7	31.3	1.00	–
0.026–0.043	48.3	34.3	1.96	0.83–4.66
>0.043	31.0	34.3	1.18	0.45–3.08
Oxychlordane				
≤ 0.019	17.2	33.3	1.00	–
0.020–0.032	58.6	34.3	3.11	1.27–7.63
>0.032	24.1	32.3	1.23	0.42–3.55
PCB 153				
≤ 0.027	24.1	32.3	1.00	–
0.028–0.045	44.8	34.3	1.76	0.76–4.07
>0.045	31.0	33.3	0.98	0.37–2.59
PCB 180				
Nondetectable	46.6	61.6	1.00	–
0.009–0.041	31.0	18.2	3.13	1.33–7.34
>0.041	22.4	20.2	1.47	0.58–3.73

* Odds ratios adjusted for age, body mass index, and a history of prostatitis; presented for organochlorines with at least 20% detectables in cases and controls.
† Units in μg/g.
‡ Includes: PCBs 18, 28, 99, 118, 138, 146, 153, 170, 180, 187, 194, 201.
PCBs, polychlorinated biphenyls.

relationship between DDE and breast cancer. Lack of association with DDE also was observed in the NHL studies as well as in our prostate cancer study.

A majority of the breast cancer studies also do not support the hypothesis that total PCB exposure has a substantial impact on the risk of breast cancer. Similarly, no association was found in this study between total PCB concentrations and prostate cancer. Two NHL studies[33,34] found a synergistic effect between higher concentrations of total PCBs and the Epstein–Barr virus, and one pancreatic cancer study[30] found a significant dose-trend in total PCBs. The lack of association in our study and the breast cancer studies may be explained by the fact that the various PCB congeners have different biological activities, including estrogenic and anti-estrogenic effects. This would support the examination of individual PCBs as was done in this investigation.

We found PCB 180 to be associated with an increased risk of prostate cancer. Several breast cancer studies using serum levels that evaluated individual PCBs did not find an association with PCB 180.[18,19,24,26] Two breast cancer studies[60,61] using adipose tissue samples and one pancreatic cancer study[31] using serum levels found an adverse effect for PCB 180. Similar to our study, Aronson et al.[60] observed a non-linear trend for PCB 180 with the middle concentration category being significantly elevated (OR = 2.4) but not the highest concentration category (OR = 1.8). It has been suggested that PCB 180 is a congener with activity like phenobarbital inducing CYP1A and CYP2B cytochrome P450 enzymes.[37,57] Interestingly, one epidemiologic study[62] found that CYP1A1 polymorphism may increase the risk of prostate cancer and two other studies[63,64] found a gene environment interaction for CYP1A1 polymorphism and PCB exposure for risk of breast cancer.

We also observed an elevated risk of prostate cancer for the middle concentration category of oxychlordane compared to the lowest concentration grouping. Although no breast cancer studies[19,26,60] identified oxychlordane as a possible risk factor, Hardell et al.[33] found higher levels of oxychlordane and *trans*-nonachlor to be associated with an increased risk of NHL with their effects being enhanced even more among cases with higher antigen levels of the Epstein-Barr virus. In our study, oxychlordane and *trans*-nonachlor were highly correlated (R = 0.86). This makes sense given that oxychlordane is a metabolite of chlordane and trans-nonachlor is a component of technical grade chlordane. As a result of these two OCPs being highly related, only one could be in the multivariate model at a time. Oxychlordane appeared to be more significantly associated with prostate cancer than *trans*-nonachlor. Examination of the combined effects of these two analytes revealed that the risk estimates were not enhanced. At this point, the mechanisms of toxicity of agents such as oxychlordane and PCB 180 are unclear but most

TABLE 5
Multivariate Results of Risks for Prostate Cancer

Effect	OR	95% Wald CI	*P* Value
Prostatitis	3.44	1.30–9.13	0.01
Age*	1.01	0.96–1.06	0.70
BMI*	1.03	0.96–1.11	0.39
Oxychlordane†			0.02
0.020–0.032 vs ≤ 0.019	2.76	1.10–6.95	0.03
>0.032 vs ≤ 0.019	0.99	0.33–2.99	0.98
PCB 180†			0.05
0.009–0.041 vs ND	2.93	1.21–7.11	0.02
>0.041 vs ND	1.87	0.70–5.00	0.21

* OR estimates on a per-unit incremental effect.
† Lipid-adjusted data; units are μg/g.
BMI, body mass index; ND, nondetectable; PCB, polychlorinated biphenyl.

likely are not limited to hormonal effects and may even include immunomodulatory, genotoxic, or enzymatic/metabolic effects.

Our laboratory tested for 48 different organochlorines, including 30 PCBs, a relatively large number in comparison with most studies. Seven of the organochlorines were detected in at least 20% of controls which included *p,p′*-DDE, dieldrin, heptachlor epoxide, *trans*-nonachlor, oxychlordane, and PCBs 153 and 180. All but one control had detectable levels of *p,p′*-DDE in our study, a result consistent with all other such studies. The median values for *trans*-nonachlor and oxychlordane, two of the three OCPs with the highest percentage of detectables in this investigation, were similar to those reported elsewhere among controls.[26,30,33,55,60] However, our serum concentrations for most of the other OCPs and PCBs were lower than those reported in controls from other investigations. This might be explained by differences in the LODs, the laboratory methods, or the statistical handling of non-detectable values. The technique used by our laboratory was also cited in other articles[19,20,30] and our LOD was lower than that reported in some of the breast cancer studies.[21,22,27,29]

Other possible explanations for the differences in levels between our study and others include gender, geographical, and duration differences in exposures. Many of the case-control studies[20,22,25,27–30,34,55] involved participants from the eastern and western coastlines of the United States, including some from counties of Superfund sites[65] documented with past contamination with PCBs or pesticides. Interestingly, a breast cancer study,[19] conducted in Columbia, Missouri, found, similar to our investigation that many of the OCPs and PCBs were below the LOD.

The main purpose of this pilot study was to generate new hypotheses. The sample size was small resulting in the possibility of some true differences in the populations being missed. While a genotype-environment interaction such as with CYP1A1 polymorphism might be a possible explanation, the observed non-linear dose response for oxychlordane and PCB 180 might also be due to the small sample size. We included four men who had received one dose of hormonal treatment prior to their blood draw, which might have affected their serum OCP and PCB levels. However, conclusions from analyses that excluded these four cases were similar to those presented. In addition, although none of the controls was symptomatic, because all controls were not screened for prostate cancer at the time of study enrollment, there is a possibility of latent or asymptomatic carcinoma among controls. However, based on follow-up data of prostate cancer incidence among the controls, none of the controls have been diagnosed with prostate cancer through December 2002. Moreover, the results would be biased toward the null if controls had latent prostate cancer and yet in multivariate analyses, two organochlorines were associated with an increased risk of prostate cancer.

Given the strong link between inflammatory states and carcinogenesis in other types of cancers, chronic prostatitis has been suggested as a possible cause for prostate cancer.[4,66] In a recent meta-analysis[67] of eleven different case-control studies, a significant association between prostate cancer and prostatitis was determined. However, it remains unclear as to whether prostatitis is a cause or an effect of prostate cancer.[68] In our study, a history of prostatitis was found to be associated with both prostate cancer status and a few of the organochlorines including PCB 180, suggesting that this factor should be adjusted for in the analyses.

BMI, tobacco or alcohol use, or a history of STDs were not identified as significant risk factors for prostate cancer. Most epidemiologic studies have generally not supported an association of BMI, tobacco or alcohol use with prostate cancer.[4,5,69–71] It has been suggested that smoking is a stronger risk factor for prostate cancer mortality than for incidence and that heavy alcohol consumption may be required to produce an increased risk.[5,71] The median number of drinks per day among our cases that drank regularly for a year or more was 1.7 (range 0.1–7.1), a value much lower than the one suggested as a risk factor by Dennis et al.[71] Although several investigations have noted an elevated prostate cancer risk among individuals reporting ever having an STD, many have failed to reach statistical significance.[72] This was also observed from our data (unadjusted OR = 2.1, 95% CI = 0.7–6.7). None of these other possible risks was found to be a

confounder in the analyses involving OCPs and PCBs.

Several case-control studies involving at least 100 cases have found that a family history of prostate cancer in a first-degree relative is associated with an increased risk of prostate cancer.[73,74] However, it has been estimated that only 5 to 10% of prostate cancers are attributable to hereditary factors possibly suggesting the connection may be in shared environmental factors.[5,74] In this study, approximately 5% more of the cases reported a family history of prostate cancer compared to controls, with a larger difference noted in those 60 years of age or younger (OR = 2.4). The lack of statistical significance for the association with family history of prostate cancer is most likely due to the previously discussed sample size issue, which was further decreased by unknown responses among 9% of participants. This result may also suggest a selection bias among controls with a higher percentage of controls with a family history of prostate cancer participating in the study. However, similar to the argument concerning the effects of latent carcinomas, the estimates regarding the association between organochlorines and risk of prostate cancer would most likely be biased toward the null if some of our controls are at increased risk of prostate cancer. When a family history of prostate cancer among first-degree relatives was added to the multivariate model, the OR estimates for the other factors, including PCB 180 and oxychlordane, remained similar to those reported in Table 5.

In conclusion, our results support the undertaking of larger investigations using serum levels as biomarkers of exposure to examine whether specific OCPs and PCBs play a role in the etiology of prostate cancer. Much larger studies also would allow examination of this relationship within certain occupations and industries that have been suggested to be at increased risk for prostate cancer, such as farmers, metal workers, nursery workers, and meat workers.[8,12,14,39,52,53,75] Besides pesticide and occupational exposures, men with increased levels of sex steroid hormone levels such as testosterone have been shown to have a higher risk of prostate cancer.[76] Unfortunately, at this time, serum sex steroid hormone levels and CYP1A1 polymorphism data were not available, but in the future, we plan to relate these values to the serum OCP and PCB levels from this study.

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