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Abbreviations: DDE, *p,p'*-dichlorodiphenyldichloroethylene ; PCB-153, polychlorinated biphenyl congener 153; EDCs, endocrine-disrupting chemicals ; POPs, persistent organic

pollutants ; LOD, limit of detection; HR, hazard ratio; CI, confidence interval ; PSA, prostate-specific antigen.

Research Article

Novelty and Impact: Environmental chemicals with hormonal properties, also called endocrine-disrupting chemicals are suspected to favor the occurrence of prostate cancer. These chemicals are obviously still present at the beginning of therapy, and beyond, and consequently they could influence the treatment outcome. Here we report for the first time that exposure to the estrogenic insecticide chlordecone, determined at the time of diagnosis, increases the risk of biochemical recurrence after radical prostatectomy of organ-confined disease.

Abstract

Previous studies have suggested that exposure to environmental chemicals with hormonal properties, also called endocrine disrupting chemicals, may be involved in the occurrence of prostate cancer. Such exposure may also influence the treatment outcome as it is still present at the time of diagnosis, the beginning of therapy, and beyond. We followed 326 men in Guadeloupe (French West Indies) who underwent radical prostatectomy as primary treatment of localized prostate cancer. We analyzed the relationship between exposure to the estrogenic chlordecone, the anti-androgenic dichlorodiphenyldichloroethylene (DDE, the main metabolite of the insecticide DDT), and the non-dioxin-like polychlorinated biphenyl congener 153 (PCB-153) with mixed estrogenic/anti-estrogenic properties and the risk of biochemical recurrence after surgery. After a median follow-up of 6.1 years after surgery, we found a significant increase in the risk of biochemical recurrence, with increasing plasma chlordecone concentration (adjusted hazard ratio = 2.51; 95% Confidence Interval: 1.39-4.56 for the highest versus lowest quartile of exposure; p trend = 0.002). We found no associations for DDE or PCB-135. These results shown that exposure to environmental estrogens may negatively influence the outcome of prostate cancer treatment.

Introduction

Prostate cancer is the most common hormone-sensitive malignancy in men.[1] Endogenous steroid sex hormones play a key role in the initiation and progression of this disease.[2]

In vitro and *in vivo* experimental research has increasingly suggested that environmental chemicals with hormonal properties, also called endocrine-disrupting chemicals (EDCs), particularly those that mimic steroid sex hormones, may modulate the risk of developing prostate cancer.[3-5]. Among these, persistent organic pollutants (POPs) have attracted attention because of their long-term presence in the environment and for some of them their ability to interfere with steroid sex hormone-regulated processes. [6-10]

Several epidemiological studies using exposure biomarkers have been conducted to investigate the relationship between human exposure to POPs with hormonal properties during adulthood and the risk of prostate cancer.[11-19] Conclusions have been divergent, sometimes even demonstrating associations in opposite directions, depending on the chemical considered or the aggressiveness of the disease at the time of diagnosis. Such disparities may be explained by the different hormonal properties of these compounds, agonistic or antagonistic, on different members of the steroid sex receptor superfamily, the clinical and molecular heterogeneity of the disease, or differences in exposure windows.

The influence of human exposure to EDCs on the development of prostate cancer is still an open question. Nonetheless, patients are still exposed at the time of diagnosis and subsequent treatment. This raises the question of the influence of EDCs on disease progression after treatment. Surgical resection of the entire gland, radical prostatectomy, is a common therapeutic option, for curative purposes, for men with organ confined prostate

cancer. However, approximately 20-40% of patients will present biochemical recurrence (rising prostate-specific antigen, PSA) of the disease. Many studies, have identified clinical and pathological features to be significant risk factors of biochemical recurrence [20-22] but nothing is known about the influence of environmental chemicals

We sought to analyze the association between blood concentrations of various POPs at the time of diagnosis and the risk of biochemical recurrence after radical prostatectomy, a common surgical procedure for the complete removal of the prostate for men with clinically organ-confined prostate cancer.

Among POPs, we have focused our attention on the most prevalent ones such as the estrogenic insecticide chlordecone, the anti-androgenic *p*, *p'*-dichlorodiphenyldichloroethylene (DDE, the main and most stable metabolite of the insecticide *p*, *p'*-dichlorodiphenyltrichloroethane, DDT), and the non-dioxin-like polychlorinated biphenyl congener 153 (PCB-153), which displays both estrogenic and anti-estrogenic properties.

Material and Methods

Study population

This study took place in Guadeloupe (French West Indies), a Caribbean archipelago, where most of the inhabitants are of African descent. It was prospectively conducted on incident prostate cancer patients who initially participated in a population-based case-control study between June 2004 and December 2007,[14] subsequently underwent radical prostatectomy in one single center (Urology Department of the University Hospital of Guadeloupe) (n = 392), and from whom we were able to obtain plasma samples and determine the POPs

concentrations one to three months before surgery (n = 340). All patients were followed by serial PSA determinations and clinical visits every six months for the first three years after surgery and annually thereafter. Biochemical recurrence was defined as two consecutive (usually four weeks apart) PSA measurements above 0.2 ng/ml, with the date of the first increase after nadir as the recurrence date.[23] Fourteen patients were excluded because they were treated with neoadjuvant hormonal therapy or radiotherapy or because the PSA value did not return below 0.2 ng/ml six weeks after surgery. The study was approved by the Guadeloupean ethics committee for studies involving human subjects. Each participant received, completed, and signed written informed consent.

Before surgery, we collected information on the demographic characteristics, Caribbean origin (French West Indies, Haiti or Dominica), education (primary, secondary, high school or higher), weight and height allowing the calculation of body mass index (kilograms per meter squared), smoking (never, former or current), alcohol consumption (never, former, or current), diabetes type 2 (no, yes), and family history of prostate cancer (first degree relatives: no, yes, not known), and preoperative PSA level. After surgery, we collected data on the pathological stage, prostatectomy ISUP Gleason grade,[24] surgical margins, tumour density, and follow-up PSA levels.

Laboratory Assays.

A high-resolution gas chromatograph (Thermo Quest Trace 2000, Milan, Italy) equipped with a Ni63 electron capture detection system was used to determine the blood concentration of chlordecone, *p,p´*-DDT, *p,p´*-DDD (dichlorodiphenyldichloroethane), *p,p´*-DDE, the α, β, and γ isomers of hexa-chlorocyclohexane (HCH), and 24 PCB congeners (International Union of

Pure and Applied Chemistry number): 6 dioxin-like (77, 105, 118, 126, 156, and 169) and 18 non-dioxin-like (18, 28, 52, 101, 110, 128, 138, 143, 149, 153, 170, 180, 183, 187, 194, 195, 206, and 209). The limit of detection (LOD) was 0.05 µg/L for all POPs except 0.06 µg/L for chlordécone (0.06 µg/L).[12]. Detailed information about sampling, analysis, and quality assurance and control has been provided elsewhere. [14, 25] Plasma total cholesterol and total triglyceride concentrations were determined enzymatically (DiaSys Diagnostic Systems GmbH; Holzheim, Germany) and total lipid concentration was calculated as previously described. [26]

Statistical Analysis.

We restricted our analysis to chemicals detected at a rate of more than 80% (DDE; PCB congeners 138, 153, and 180; and chlordecone). Correlations between concentrations of the frequently detected PCBs were explored by Spearman's rank correlation analysis (Supporting information, supplemental Table 1). The concentrations of the various PCBs were highly correlated (Spearman's rho ≥ 0.75; all *p*-values < 0.001), so we restricted further analysis to PCB-153.

Plasma POPs concentrations were categorized into quartiles, based on their distribution among patients. Time to event was defined as the duration between the date of surgery and the PSA value that defined the recurrence event. Patients who did not relapse, or were lost to follow-up, were censored at the last normal post-operative PSA measurement before October 30, 2017. Five-year BCR-free survival analysis were carried out using the Kaplan−Meier method and log-rank test for trend. The Cox proportional hazards method was used to compute adjusted survival curves and test for trend were assessed with quartiles of

exposure scored as ordinal variables in ascending order. We also used multivariable Cox proportional hazards regression models and 95% confidence intervals (CI) to estimate the hazard ratio (HR) of biochemical recurrence associated with POPs exposure. Potential confounders were included in all statistical models if they predicted ($p < 0.05$) biochemical recurrence status: body mass index, family history of prostate cancer, pathological Gleason grade, pathological stage, surgical margins, tumor density (Table 1) and then selected by applying a backward selection procedure at $p < 0.1$. Missing data for covariates varied from none to two (0.6 %) for education, two (0.6 %) for alcohol, two (0.6 %) for family history of prostate cancer, three (0.9 %) for smoking, and eight (2.5 %) for diabetes. Missing data were handled using missing value indicator categories. The proportional hazards assumption was verified by the log-negative-log survival distribution function of all variables. Tests for linear trend across exposure categories were performed, with the natural log transformed POPs concentration treated as a continuous variable. Exposure levels equal to or below the LOD were estimated by a maximum likelihood estimation method.[27] Sensitivity analyses were conducted by excluding patients with positive surgical margins or prostatectomy ISUP Gleason grade 3 or higher, or advanced pathological stage (pT3 or pT4 or N+). Statistical analyses were carried out using SAS software version 9.3 (SAS Institute, Cary, NC, USA). All tests were two-sided, and $p < 0.05$ were considered statistically significant.

Results

The results presented here were obtained from a study population of 326 patients. During 1,923 person-years of follow-up after surgery, 93 men (28.5%) experienced biochemical recurrence. The median follow-up time was 6.1 years and among men without progression 7.3

years. The baseline characteristics of the study population and HR for risk of biochemical recurrence are presented in Table 1. Detection levels and plasma concentrations of POPs are presented in Table 2.

The crude five-year BCR-free survival rates were 83.8%, 79.8%, 86.6%, and 65% for men in the 1st, 2rd, 3rd, and 4th quartile of chlordecone exposure, respectively (Log-rank test for trend, p = 0.01). For DDE and PCB-153 exposure, the five-year biochemical recurrence-free survival rates were 78.7, 83.8, 70.7, and 81.1 and 81.5, 79.0, 79.7, and 75.0 for men in the 1st to 4th quartile, respectively (DDE: Log-rank test for trend, p = 0.85; PCB-153: Log-rank test for trend, p = 0.83). Crude and adjusted survival curves are presented in supporting information (supplemental figures 1 to 3).

Adjusted Cox analysis showed that men in the highest quartile of chlordecone plasma concentration had a significantly higher risk of biochemical recurrence than those in the lowest quartile (HR= 2.51, 95% CI: 1.39-4.56) (Table 3). The linear relationship between exposure and response was significant (p-trend = 0.002). We obtained comparable results if DDE and PCB-153 concentrations were additionally included in the multivariable model (HR= 2.62, 95% CI: 1.40-4.90 for the highest quartile relative to the lowest quartile; p-trend = 0.002). DDE and PCB-153 exposure were not associated with a risk of BCR, irrespective of the model (Table 3).

Sensitivity analysis revealed that chlordecone exposure was still significantly associated with a risk of BCR after excluding patients with positive surgical margins or prostatectomy ISUP Gleason grade 3 or higher, or advanced pathological stage (Table 4). Men who were in the highest quartile of chlordecone plasma concentration had a higher risk

of BCR than those in the lowest quartile (Adjusted HR = 2.98, 95% CI: 1.06-8.38) and the linear relationship between exposure and response was significant *(p*-trend = 0.003). Here again, DDE and PCB-153 exposure were not associated with a risk of BCR (Table 4).

Discussion

This is the first study to investigate the association of POPs plasma concentrations, measured at the time of diagnosis, with biochemical recurrence following primary curative surgical treatment of prostate cancer.

In our study population, the highest quartile of exposure to chlordecone was consistently associated with a more than two-fold increased risk of biochemical recurrence, with a significant exposure-response relationship. This was still true after taking into account well-known prognostic clinic-pathological features of biochemical recurrence as confounding factors and in sensitivity analysis restricted to patients who did not present these adverse clinic-pathological features. In contrast, exposure to DDE or PCB-153 was not associated with BCR.

Chlordecone was extensively used from 1973 to 1993 in the French West Indies, to control the banana root borer. This pesticide undergoes no significant biotic or abiotic degradation in the environment, so permanently polluted soils and waters have remained the primary source of foodstuffs contamination, and human beings continue to be exposed to this chemical [28]. In our study population, chlordecone plasma concentration was in the range of values observed for residents in the neighborhoods near the chlordecone factory in Hopewell (VA, U.S.). [29] Such exposure resulted from the air pollution and illegal dumping of waste

laden into Hopewell's sewer system which in turn contaminated the James River and fish resources. There is currently no data on exposure to chlordecone in other populations. Concerning other POPs, DDE and PCB congeners 138, 153, and 180 were the most prevalent found in the blood in our population, as expected and found in most populations worldwide. Moreover, blood concentrations of these pollutants are in the range of background environmental levels currently found in the US population of similar age range [30]. This is not surprising, because the use of DDT in agricultural supplies or for disease vector control in the French West Indies was sporadic and industrial activities involving the significant use or emission of PCBs has only been very limited. Consequently, exposure to these chemicals is likely to be associated with background contamination of the food chain.

Biomonitoring of human tissues is considered to be a gold standard approach for assessing aggregated environmental chemical exposure, because it integrates all sources of exposure from different absorption pathways.[31] The exposure to POPs observed in this study was assessed based on plasma concentrations at the time of diagnosis, prior to surgery, and before the outcome occurrence. These chemicals have a long half-life in the body, varying from six months for chlordecone to several years for DDE and PCB-153. Although the use of POPs is mostly banned worldwide, they are still present in the environment and populations are continuously exposed through food consumption. Thus, a single measurement of POPs concentration in the blood reflects the body burden under steady-state conditions and provides a sufficiently confident estimation of exposure over an extended period. However, the levels of each POPs varies depending on the type of foodstuffs (*i.e.* chlordecone is preferentially found in root vegetables, fish, and meat of local origin, DDE in food crops, fish and meat, and

PCB in meat and milk). Thus, any significant changes in dietary habits may result in changes in the body burden over several years. However, no specific dietary recommendations have been made and we are not aware of any changes in the dietary habits of our patients after surgery.

Although radical prostatectomy is considered as a definitive therapy for organ-confined prostate cancer, an increase in PSA levels after a variable period of undetectable or low detectable-stable PSA indicates the presence of residual prostatic cells in the body, which may be benign or malignant and in the surgical bed or disseminated. We do not know whether the positive association between chlordecone exposure and biochemical recurrence reflects a direct effect on the PSA production of residual cells or the proliferation of these cells, which in turn secrete PSA. PSA secretion is generally under androgen regulation, but chlordecone shows low affinity binding to the androgen receptor (AR) and acts as an AR antagonist rather than agonist.[8] Moreover, there is currently no data supporting the involvement of chlordecone in AR-dependent or AR-independent mechanisms driving PSA mRNA expression or protein secretion.

We previously reported that chlordecone exposure was associated with an increased risk of prostate cancer occurrence and suggested that the estrogenic properties of the molecule may explain this association.[14] Chlordecone interferes with estradiol signaling through binding to the nuclear estrogen receptors α (ERα) and β (ERβ), eliciting agonistic and antagonistic effects, respectively. [7,32,33] The ERα mediates the adverse effects of estrogen, such as aberrant proliferation, inflammation, and malignancy, whereas the ERβ exerts opposite and beneficial effects, such as anti-proliferative, pro-apoptotic, anti-inflammatory,

and, potentially, anticarcinogenic effects.[34] Thus, the combined interaction between the agonistic effects of chlordecone on the ERα and the antagonistic effects on the ERβ could lead to an imbalance, promoting cell proliferation. It is possible that such interplay could also play a role in the proliferation of residual prostatic tumor cells, if present, after radical prostatectomy.

Although biochemical recurrence is never followed by disease progression for some patients, it is almost certainly an indicator of persistent disease and an unquestionable risk factor for the development of subsequent distant metastases. Indeed, chlordecone has been found to promote angiogenesis through ERα activation,[35] and both chlordecone and estradiol increase expression of the homeostatic chemokine receptor type 4 and enhance vascular cell adhesion protein 1 levels.[36] Moreover, chlordecone disrupts cell-adherence junctions by modulating E-cadherin and β-catenin expression.[37] Collectively, these effects participate in the tumor cell-microenvironment signaling involved in tumor and metastasis progression for several types of cancers, including prostate cancer.[38-42] Whether biochemical recurrence associated with chlordecone exposure is predictive of an increased risk of metastasis remains to explored through the long-term follow up of patients.

Several epidemiological studies in different locations, including in French West Indies, have suggested that exposure to DDE is associated with a higher risk of prostate cancer occurrence.[12,15,19] However, we did not find a significant association between DDE exposure and the risk of biochemical recurrence. DDE is known to inhibit AR-mediated effects through direct binding to the AR.[8] A recent study has also shown that DDE lowers PSA mRNA and protein levels in human prostate cancer cell lines in a dose-dependent

manner.[43] DDE exposure of healthy men is negatively associated with serum concentration of 5α-dihydrotestosterone,[44] the most potent ligand and activator of the AR. Given these properties, DDE would have been expected to be associated with a decreased risk of biochemical recurrence due to a possible direct effect on PSA production or prostate cell growth, itself an AR-mediated effect. DDE may also have an agonistic effect on ERα. [45] It is therefore difficult to predict the net effect of DDE on the prostate, given the potential effects on both the AR and ERα.[46, 47]

The literature concerning PCBs is less clear, as there are contradictory and even opposite observations regarding their association with the risk of PCa occurrence.[11-13,16-18] Here, we did not observe a significant association between PCB-153 exposure and the risk of biochemical recurrence, in either direction. Unlike dioxin-like PCBs, non-dioxin-like PCBs (including PCB-153), which are the most highly prevalent PCBs in the environment,[48] do not interact substantially with the aryl hydrocarbon receptor and may act through other pathways, such as steroid hormone signaling.[6] Non-dioxin-like PCBs may interact with genomic and non-genomic ER pathways and exhibit both estrogenic and anti-estrogenic properties, depending on the *in vivo* or *in vitro* experimental models.[6,9,10] The multiple potential steroidal mechanisms of non-dioxin-like PCBs are yet to be totally deciphered and it is thus difficult to have a clear picture of their actions.

In conclusions, our results shown that exposure to chlordecone, an environmental EDCs with estrogenic properties, at the time of prostate cancer diagnosis is significantly associated with a risk of biochemical recurrence after prostatectomy. Increasing evidence suggests that estrogens are critical players in human prostate cancer.[49,50] Our findings add

support to the hypothesis that human exposure to environmental estrogens may influence prostate cancer progression

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Table 1

Baseline characteristics of patients and HR (95% CIs) of biochemical recurrence of prostate cancer

Characteristic	n (%)	HR (95%CI)
Age (years), [mean (interquartile range)]	63.7 (58.5-67.9)	1.01 (0.98-1.04)
Caribbean origin		
French West Indies	313 (96.0)	1.0 (reference)
Haiti or Dominica	13 (4.0)	1.43 (0.58-3.43)
Education		
Primary	165 (60.0)	1.0 (reference)
Secondary	97 (29.9)	0.64 (0.39-1.04)
High school and higher	62 (19.1)	0.98 (0.38-1.20)
Missing data	2	
Body mass index (kg/m²)		
< 25	141 (43.3)	1.0 (reference)
25 to 30	154 (47.2)	1.19 (0.76-1.85)
≥ 30	31 (9.5)	2.18 (1.15-4.14)
Smoking		
Never	202 (62.5)	1.0 (reference)
Former or current	121 (37.5)	0.91 (0.59-1.40)
Missing data	3	
Alcohol consumption		
Never	49 (15.1)	1.0 (reference)
Ever	275 (84.9)	1.02 (0.58-1.80)
Missing data	2	
Type 2 diabetes		
No	266 (83.7)	1.0 (reference)
Yes	52 (16.3)	1.03 (0.59-1.79)
Missing data	8	
Family history of prostate cancer		
No	180 (55.6)	1.0 (reference)
Yes	89 (27.5)	1.60 (1.01-2.54)
Do not know	55 (16.9)	1.47 (0.85-2.55)
Missing data	2	
Pre-operative PSA (ng/mL) [median (interquartile range)]	7.3 (5.5-10.5)	1.32 (0.90-1.94)
Total lipids (g/L) [median (interquartile range]	5.2 (4.6-5.6)	0.96 (0.78-1.18)
Pathological Gleason grade		
ISUP Gleason grade 2 or lower	280 (85.9)	1.0 (reference)
ISUP Gleason grade 3 or higher	46 (14.1)	3.68 (2.36-5.74)
Pathological stage		
pT2 and N0	269 (82.5)	1.0 (reference)
pT3a or pT3b, or N⁺	57 (17.5)	2.90 (1.88-4.49)
Surgical margins		
Negative	233 (71.5)	1.0 (reference)
Positive	93 (28.5)	2.72 (1.80-4.10)
Tumor density (%) [median (interquartile range)]	9.0 (5.0-17.0)	2.62 (1.60-4.29)
Biochemical recurrence status		
No	233 (71.5)	
Yes	93 (28.5)	
Follow-up time (years) [median (interquartile range)]	6.1 (2.8-8.9)	

Table 2

Detection and concentrations of persistent organic pollutants in plasma samples from the study population (µg/L)

POPs [a]	Detection frequency (%)	Percentile				
		10th	**25th**	**50th**	**75th**	**Maximum**
Chlordecone	80.1	<LOD	0.16	0.38	0.69	19.1
DDE	94.7	0.38	0.93	2.33	4.68	40.1
DDD	22.1	<LOD	<LOD	<LOD	<LOD	0.95
DDT	28.0	<LOD	<LOD	<LOD	0.06	2.3
PCB-28	47.7	<LOD	<LOD	<LOD	0.24	2.94
PCB-52	50.0	<LD	<LD	0.05	0.39	6.72
PCB-101	45.7	<LOD	<LOD	<LOD	0.12	0.83
PCB-118	57.3	<LOD	<LOD	0.07	0.16	2.38
PCB-138	98.3	0.16	0.29	0.53	0.82	3.60
PCB-153	97.0	0.20	0.38	0.76	1.17	5.96
PCB-180	96.3	0.23	0.35	0.59	0.86	3.16
α-HCH	28.0	<LOD	<LOD	<LOD	<LOD	1.1
β-HCH	35.3	<LOD	<LOD	<LOD	0.05	2.2
γ-HCH	19.5	<LOD	<LOD	<LOD	<LOD	0.60

[a] Chlordecone was measured in 326 plasma samples, and other POPs in 300 plasma samples.

PCB congeners 18, 77, 101, 105, 110, 126, 128, 143, 149, 156, 169, 170, 183, 187, 194, 195, 206, and 209 were below the LOD in all plasma samples.

Table 3

HR (95% CIs) of biochemical recurrence of prostate cancer according to quartile of chlordecone, DDE and PCB-153 exposure

Exposure	Without biochemical recurrence (n)	With biochemical recurrence (n)	Crude HR (95% CI)	Adjusted HR (95% CI) [a]	Adjusted HR (95% CI) [b]
Chlordecone (µg/L)					
< 0.16	62	18	1.0 (reference)	1.0 (reference)	1.0 (reference)
0.16 - 0.37	57	27	1.50 (0.83-2.73)	1.63 (0.89-2.98)	1.55 (0.81-2.93)
0.38 - 0.68	64	18	0.97 (0.50-1.86)	1.03 (0.53-2.00)	0.94 (0.46-1.90)
≥ 0.69	50	30	1.96 (1.09-3.52)	2.51 (1.39-4.56)	2.62 (1.40-4.90)
P trend			0.01	0.002	0.002
DDE (µg/L)					
< 0.93	54	21	1.0 (reference)	1.0 (reference)	1.0 (reference)
0.93 - 2.31	53	21	0.84 (0.46-1.54)	0.54 (0.29-1.01)	0.54 (0.27-1.04)
2.32 - 4.66	48	27	1.18 (0.67-2.09)	0.91 (0,50-1.66)	0.87 (0.45-1.71)
≥ 4.67	59	17	0.71 (0.37-1.35)	0.55 (0.29-1.06)	0.50 (0.24-1.05)
P trend			0.89	0.51	0.35
PCB-153 (µg/L)					
< 0.38	54	20	1.0 (reference)	1.0 (reference)	1.0 (reference)
0.38 - <0.74	51	25	1.28 (0.71-2.30)	1.09 (0.59-1.99)	1.19 (0.62-2.28)
0.75 - 1.16	55	20	0.94 (0.50-1.74)	0.88 (0.47-1.64)	1.05 (0.53-2.06)
≥ 1.17	60	21	1.04 (0.56-1.92)	0.93 (0.49-1.76)	1.12 (0.55-2.28)
P trend			0.81	0.41	0.82

[a] For chlordecone: adjusted for pathological Gleason grade, pathological stage, surgical margins, body mass index, and family history of prostate cancer; For DDE or PCB-153: adjusted for pathological Gleason grade, pathological stage, surgical margins, and body mass index.

[b] For chlordecone: adjusted for pathological Gleason grade, pathological stage, surgical margins, family history of prostate, body mass index, DDE, and PCB-153; For DDE: adjusted for pathological Gleason grade, pathological stage, surgical margins, body mass index, chlordecone, and PCB-153; For PCB-153: adjusted for pathological Gleason grade, pathological stage, surgical margins, body mass index, chlordecone, and DDE.

Table 4

Sensitivity analysis among patients with negative surgical margins, low-grade pathological Gleason score, and organ-confined disease.

HRs (95% CIs) of biochemical recurrence of prostate cancer according to quartile of chlordecone, DDE and PCB-153 exposure

Exposure	Without biochemical recurrence (n)	With biochemical recurrence (n)	Crude HR (95% CI)	Adjusted HR (95% CI) [a]
Chlordecone (µg/L)				
< 0.16	35	6	1.0 (reference)	1.0 (reference)
0.16 - 0.37	43	6	0.87 (0.28-2.70)	0.61 (0.18-2.09)
0.38 - 0.68	42	3	0.44 (0.11-1.75)	0.42 (0.10-1.79)
≥ 0.69	34	15	2.48 (0.96-6.39)	2.98 (1.06-8.38)
P trend			0.008	0.003
DDE (µg/L)				
< 0.93	38	6	1.0 (reference)	1.0 (reference)
0.93 - 2.31	31	7	1.24 (0.42-3.70)	0.99 (0.30-3.32)
2.32 - 4.66	34	8	1.24 (0.43-3.58)	1.32 (0.39-4.48)
≥ 4.67	39	8	1.25 (0.43-3.62)	1.21 (0.36-4.05)
P trend			0.66	0.96
PCB-153 (µg/L)				
< 0.38	42	7	1.0 (reference)	1.0 (reference)
0.38 - <0.74	31	8	1.49 (0.54-4.10)	1.36 (0.48-3.85)
0.75 - 1.16	30	8	1.33 (0.48-3.68)	0.92 (0.29-2.92)
≥ 1.17	33	6	0.98 (0.33-2.93)	0.82 (0.25-2.72)
P trend			0.94	0.89

a For chlordecone: adjusted for family history of prostate cancer, body mass index, DDE and PCB-153; For DDE: adjusted for body mass index,

chlordecone, and PCB-153; For PCB-153: adjusted for body mass index, chlordecone, and DDE.

Some environmental chemicals can mimic human hormones, and may spur cancer progression. Here, the authors studied the effect of three prevalent organic chemicals on prostate cancer recurrence: the estrogenic insecticide chlordecone; DDE, a stable metabolite of DDT which has anti-androgenic properties; and PCB-153, which has estrogenic and anti-estrogenic properties. No effect was associated with DDE or PCB-153. However, those in the highest exposure quartile for chlordecone had 2-fold increased risk of biochemical recurrence, defined as two consecutive elevated PSA measurements, after prostatectomy. These findings add to the evidence that environmental estrogens could promote cancer progression.