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ORIGINAL REPORT

Chlordecone Exposure and Risk of Prostate Cancer

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ABSTRACT

Purpose
Determining whether environmental estrogens are associated with the risk of prostate cancer may have important implications for our general understanding of this disease. The estrogenic insecticide chlordecone was used extensively in the French West Indies, contaminating the population for more than 30 years. We analyzed the relationship between exposure to chlordecone and the risk of prostate cancer.

Patients and Methods
We investigated 623 men with prostate cancer and 671 controls. Exposure was analyzed according to case-control status, using either current plasma concentration or a cumulative exposure index based on years of exposure. We genotyped two single-nucleotide polymorphisms (rs3829125 and rs17134592) in the gene encoding chlordecone reductase.

Results
We found a significant increase in the risk of prostate cancer with increasing plasma chlordecone concentration (odds ratio [OR], 1.77; 95% CI, 1.21 to 2.58 for the highest tertile of values above the limit of detection [LD]; *P* trend = .002) and for cumulative exposure index (OR, 1.73; 95% CI, 1.04 to 2.88 for the highest quartile; *P* trend = .004). Stronger associations were observed among those with a positive family history of prostate cancer and among those who had lived in a Western country. The rs3829125 and rs17134592 allele variants were in complete linkage disequilibrium and were found at low frequency (0.04). Among subjects with plasma chlordecone concentrations above the LD, carriers of the allele variants had a higher risk of prostate cancer (OR, 5.23; 95% CI, 0.82 to 33.32).

Conclusion
These findings support the hypothesis that exposure to environmental estrogens increases the risk of prostate cancer.

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INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer among men in developed countries. However, little is known about the risk factors associated with this cancer. Advancing age, ethnic origins, and a family history of prostate cancer are the only established risk factors.[1,2] Many lifestyle-related risk factors have been implicated, but their roles in prostate cancer etiology remain unclear.[1,2] The effect of exposure to synthetic chemicals in the environment on prostate cancer development remains a matter of debate with implications for public health. Chemicals with hormonal properties, also called endocrine disruptors, are thought to be involved.[3,4] However, no epidemiologic evidence of a positive link between environmental exposure to endocrine chemicals and prostate cancer has yet been established.

Chlordecone (also known as Kepone) is an organochlorine insecticide with well defined estrogenic properties.[5,6] It was extensively used from 1973 to 1993 in the French West Indies, to control the banana root borer. A few years after the introduction of chlordecone, the widespread pollution of soils, river water, wild animals, and vegetables growing in polluted soils was reported.[7,8] 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.[9-13]

Chlordecone is a potential carcinogen and has been shown to cause hepatic tumors in laboratory rats and mice.[14] The carcinogenic and hormonal properties of chlordecone and its long biologic half-life raise the possibility of long-term effects, such as cancer. We tested the hypothesis that chlordecone

exposure in adulthood, over a 30-year period, favors the development of prostate cancer in the French West Indies, where the incidence of this disease is particularly high.[15] Chlordecone reductase catalyzes the reduction of chlordecone to chlordecone alcohol, increasing the biliary excretion of chlordecone and decreasing its toxicity.[16] We therefore hypothesized that the prostate cancer-causing effects of chlordecone would be stronger in individuals with functional variants of the chlordecone reductase gene, rs3829125 and rs17134592, resulting in the production of a protein with low levels of enzymatic activity.

We report the results of a case-control study in which chlordecone exposure was evaluated by measuring its concentration in the blood.

PATIENTS AND METHODS

Study Population

This study was conducted in Guadeloupe, a French archipelago in the Caribbean, most of the 405,000 inhabitants of which are of African descent. This study was carried out on 709 consecutive incident cases of histologically confirmed prostate cancer (June 2004 to December 2007) and 723 controls without prostate cancer (January 2005 to December 2006). For details of the selection of cases and controls, see the Appendix (online only).

Trained nurses obtained information for both patients and controls, concerning demographic characteristics, anthropometrics, periods and places of residence since birth, lifestyle, occupational data, family history of prostate cancer, medical background, use of medication, and prostate cancer screening history. Weight, height, and the circumferences of the waist and hips were measured at the end of the face-to-face interview. Participants were also asked to provide a blood sample. The study was approved by the Guadeloupean ethics committee for studies involving human subjects. Each participant provided written informed consent.

Laboratory Procedures and Data Management and Statistical Analyses

Chlordecone analysis, total lipid determination, genotyping methods and linkage analysis are described in the Appendix (online only).

A reference date was assigned to each participant, corresponding to the date of histopathologic diagnosis of prostate cancer for patients and the last date of prostate-specific antigen (PSA) determination for controls. Plasma chlordecone concentrations were classified according to their distribution among control samples. Values equal to or below the limit of detection (LD) were used as the reference group and values above the LD were grouped into tertiles. Based on the realistic assumption that the Guadeloupean population has been continuously exposed from 1973 to the present day, we obtained a cumulative exposure index score for each subject. This score was calculated as the product of current plasma chlordecone concentration and the number of years of residence in the French West Indies between 1973 and the year of the reference date. We calculated such scores for subjects with plasma chlordecone concentrations above LD. The cumulative exposure scores were grouped into quartiles, based on their distribution among controls, the lowest quartile being the reference group.

Baseline covariates were compared between patients and controls (Table 1). Odds ratios (OR) and 95% CIs for the risk of prostate cancer were estimated by unconditional logistic regression. We investigated whether covariates were confounding factors or effect modifiers, by looking at the association between chlordecone exposure and prostate cancer separately for each of the following covariates: age, Caribbean origin, education, body mass index, waist to hip ratio, alcohol use, smoking, past urogenital infections, diabetes (type 2), viral infections, prostate cancer screening history (during the last 5 years), family history of prostate cancer (first degree), banana farming, past residence in Western countries, year of reference date, total plasma lipid concentration, and the series and batch number of chlordecone analysis. Missing data for covariates varied from none to lower than 5%, except for waist to hip ratio and genotype, for which 17% and 8.6%, respectively, of the data were missing. Categorical covariates, including missing data as an additional response, were modeled as dummy variables representing the different levels. Confounding covariates were included into the logistic model if they modified the OR estimates by more than 10%. Tests for linear trend across exposure categories were performed, with the natural log-transformed chlordecone concentration treated as a continuous variable. For values equal to or below the LD, we assigned a value of the LD divided by 2. We tested for a modifier effect, by creating an interaction term based on the cross product of these variables and exposure categories (treated as a continuous variable). Interactions were examined by entering the interaction terms into the logistic regression model. We quantified the significance of the interaction term using the Wald test. We used polytomous logistic regression to estimate risk simultaneously among controls and non ordered subgroups of cases, as a function of age at onset (< 60 *v* > 60) and prostate cancer stage (local *v* regional/distant stage). We also used a composite index of prostate cancer aggressiveness at diagnosis: high aggressive potential (PSA $>$ 30 ng/mL or regional/distant stage or Gleason score of 4 + 3 and higher) and low aggressive potential (PSA $<$ 30 ng/mL, local stage, and Gleason score of 3 + 4 and lower).[17] *P* values lower than .05 were considered significant. All statistical tests were two tailed and were carried out with SAS version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

The results presented here were obtained from a study population comprising 623 of the 709 eligible prostate cancer cases and 671 of the eligible 722 controls, from whom we were able to obtain blood samples and determinations of plasma chlordecone concentration. The baseline characteristics of the study participants are summarized in Table 1. Chlordecone was detected in the plasma of 68.7% of the cases and 66.8% of the controls.

Age-adjusted (5-year intervals) and multivariable-adjusted ORs and 95% CI for the association between prostate cancer and plasma chlordecone concentrations are presented in Table 2. Using plasma chlordecone concentration as a means of measuring exposure, we found that the highest exposure categories were associated with a significantly higher risk. Moreover, the relationship between exposure and response was significant ($P = .002$). When we used the cumulative exposure index as a means of measuring exposure, we found that the highest quartile was associated with a significantly higher risk of prostate cancer and that the exposure-response relationship was significant ($P = .004$).

When we looked for potential interactions, no modifier effects were observed for any covariates, other than a history of prostate cancer in first-degree relatives and previous residence in a Western country. Results for analyses stratified for these two covariates are presented in Table 3. Associations between chlordecone exposure and prostate cancer were stronger in men with a family history of prostate cancer and in men who had previously lived in Western countries, with significant linear relationships ($P = .03$ and $P = .005$, respectively). The interaction terms were found to be significant for family history of prostate cancer and past residence in a Western country (Table 3). Using chlordecone concentrations below the LD as the reference category and concentrations above LD as the exposure category, we carried out a double stratification, according to family history of prostate cancer and past residence in Western countries. Subjects with both a family history of prostate cancer and previous residence in a Western country had a higher risk of prostate cancer (OR, 4.94; 95% CI, 1.15 to 21.23). The risk did not differ from one for those with neither or only one of these factors (data not shown).

Table 1. Baseline Characteristics of Patients and Controls

Characteristic	Patients (n = 623)		Controls (n = 671)		P*
	No./Total No.	%	No./Total No.	%	
Median age, years	66.2		60.6		< .01
Interquartile range	60.5-71.5		54.0-67.1		
Caribbean origin					< .01
French West Indies (Guadeloupe or Martinique)		96.5		91.4	
Haiti or Dominica		3.5		8.6	
Education					.03
High school and higher		13.3		10.7	
Secondary		25.4		31.9	
Primary		61.4		57.4	
Body mass index†					.49
Normal (< 25)		44.0		47.0	
Overweight (25-29.9)		44.3		41.0	
Obese (≥ 30)		11.7		12.0	
Waist-to-hip ratio > 0.95		45.4		30.1	< .01
Current or past alcohol use		86.8		82.9	.05
Current or past smoking		38.3		37.1	.69
Past urogenital infection		16.1		17.2	.65
Type 2 diabetes		18.1		12.3	< .01
Viral infection		23.5		24.1	.66
Prostate cancer screening history‡		50.7		13.4	< .01
Family history of prostate cancer					
No		55.9		78.0	< .01
Yes		24.4		10.2	
Do not know		19.7		11.8	
Banana farming		11.9		10.0	.27
Past residence in Western countries, > 1 year§		29.9		23.9	.02
Median duration of residence in Western countries§	15.1		13.2		.04
Interquartile range	7.0-26.3		6.5-24.8		
Median years of residence in French West Indies from 1973 to reference date	32.8		32.7		.43
Interquartile range	31.5-33.8		30.0-33.3		
Median plasma chlordecone, μg/L	0.44		0.40		.39
Interquartile range	< 0.25-1.00		< 0.25-0.86		
Chlordecone reductase SNP (No./total No. with data)					
rs3829192					
Wild-type C	1,137/1,182	96.2	1,161/1,208	96.1	.91
Variant allele G	45/1,182	3.8	47/1,208	3.9	
rs17134592					
Wild-type C	1,137/1,182	96.2	1,161/1,208	96.1	.91
Variant allele G	45/1,182	3.8	47/1,208	3.9	
Median PSA levels, ng/mL	8.75				
Interquartile range	6.00-14.30				
Gleason score					
≤ 7 (3 + 4)		82.0		—	
4 + 3 and > 7		18.0		—	
TNM					
T1c or T2 and N0 and M0		13.8		—	
T3 or T4, or N+ or M+		86.2		—	

Abbreviations: SNP, single nucleotide polymorphism; PSA, prostate-specific antigen.

*P values for continuous variables are those for non parametric Mann-Whitney rank tests; for plasma chlordecone concentration values equal to or below the limit of detection, we assigned rank values corresponding to the value of the limit of detection divided by 2; for categorical variables, P values were obtained in tests for heterogeneity across levels and for SNPs, in tests for Hardy–Weinberg equilibrium among controls.

†The body mass index is the weight of the subject in kilograms divided by the square of the height in meters.

‡Within the 5-year period before the PSA test preceding the histological diagnosis of cases or allowing the selection of controls.

§All but four of the migrants had lived in mainland France. The remaining four migrants had lived in Germany.

We determined whether the chlordecone-prostate cancer association depended on clinical characteristics. We found a significantly higher risk for patients age 60 years or older (for the highest tertiles of detectable values, OR, 1.91; 95% CI, 1.24 to 2.94; *P* for trend < .001) whereas, for patients younger than 60 years, the OR was 1.22 (95% CI, 0.58 to 2.57; *P* for trend = .94). We found that the risk was significantly higher for both local (OR, 1.58; 95% CI, 1.07 to 2.35; *P* for trend = .021) and regional/distant stage (OR, 2.25; 95% CI,

Table 2. Plasma Chlordecone Concentration and Risk of Prostate Cancer

Chlordecone	No. of Patients	No. of Controls	Age Adjusted OR	Age Adjusted 95% CI	Multivariable* OR	Multivariable* 95% CI
Plasma concentration, μg/L						
≤ 0.25 (LD)	195	223		1.00		1.00
> 0.25-0.47	128	150	0.95	0.69 to 1.31	1.11	0.75 to 1.65
> 0.47-0.96	139	149	1.16	0.84 to 1.59	1.22	0.82 to 1.83
> 0.96	161	149	1.27	0.93 to 1.72	1.77	1.21 to 2.58
Cumulative exposure index by quartile, μg/L × No. of years†						
1 (lowest)	88	112		1.00		1.00
2	101	112	1.05	0.69 to 1.58	1.06	0.62 to 1.82
3	101	112	1.15	0.76 to 1.74	1.23	0.72 to 2.11
4	134	112	1.33	0.89 to 1.99	1.73	1.04 to 2.88

Abbreviations: OR, odds ratio; LD, limit of detection.
*The multivariable logistic model includes age (5-year intervals), total plasma lipid concentration (continuous), waist-to-hip ratio (≤ 0.95, > 0.95) and history of prostate cancer screening (no, yes).
†For subjects with values above LD.

1.16 to 4.34; *P* for trend = .018). However, using the composite index of aggressiveness, a significantly higher risk was found only for high aggressive forms (OR, 2.16; 95% CI, 1.33 to 3.51; *P* for trend = .004), with the OR for low aggressive forms being only 1.45 (95% CI, 0.96 to 2.19; *P* for trend = .04).

Both SNPs, rs3829125 and rs17134592, were in Hardy-Weinberg equilibrium in the controls ($P > .05$). These variants were in complete linkage disequilibrium with D' and r^2 of 1, and were present at identical frequencies in cases and controls. The frequencies of the allele variants were low (0.04). We therefore stratified the analysis according to genotype, using chlordecone concentrations at or below the LD as the reference category and concentrations above the LD as the exposure category. For carriers of variant alleles, a non significant increase in prostate cancer risk was observed (OR, 5.23; 95% CI, 0.82 to 33.32), whereas the OR for wild-type allele homozygotes was 1.30 (95% CI, 0.91 to 1.85).

DISCUSSION

This study reveals that chlordecone exposure, evaluated by determining plasma chlordecone concentration, is consistently associated with an increase in the risk of prostate cancer, and with a significant exposure-response relationship. This is the largest study to have investigated the effects of organochlorine compounds on prostate cancer risk through the evaluation of exposure by biologic measurement. Previous studies have been exploratory and based on less than 80 incident or prevalent prostate cancer cases.[18-21]

A significant increase in risk was observed after adjustment for covariates. This unusual finding is explained by the contribution of waist-to-hip ratio (abdominal obesity) and prostate cancer screening, which act as negative confounding factors. In our population study, both abdominal obesity and prostate cancer screening were associated with a significant increase in the risk of prostate cancer (data not shown), as reported for abdominal obesity in other populations,[22,23] and for prostate cancer screening. We also found that these two covariates were associated with lower plasma chlordecone concentrations in our study. In the case of abdominal obesity, peripheral fat may sequester organochlorine lipophilic compounds, leading to an inverse association between peripheral fat levels and circulating concentrations of organochlorine compounds.[24] Many factors may account for the observed inverse relationship between prostate cancer screening and plasma chlordecone concentration. For example, we found that individuals with a history of prostate cancer screening were more likely to have lived in Western countries, and were less likely to have worked on banana plantations, these factors in turn being associated with lower plasma chlordecone concentration. In addition, screening procedures may introduce distortions in the associations between exposures of interest and cancer outcomes if the study would have included fewer cases in the absence of screening.[25] This is particularly true for Guadeloupe, where the recorded incidence of prostate cancer

Table 3. Plasma Chlordecone Concentration and Interaction With Family History of Prostate Cancer, and Past Residence in Western Countries

Chlordecone Plasma Concentration (μg/L)	Without Family History of Prostate Cancer* No. of Patients	No. of Controls	OR	95% CI	With Family History of Prostate Cancer* No. of Patients	No. of Controls	OR	95% CI	Interaction *P*	Without Past Residence in Western Countries* No. of Patients	No. of Controls	OR	95% CI	With Past Residence in Western Countries* No. of Patients	No. of Controls	OR	95% CI	Interaction *P**
≤ 0.25 (LD)	116	161		1.00	45	26		1.00		137	165		1.00	58	56		1.00	
> 0.25 to 0.47	78	111	1.35	0.80 to 20.26	26	19	0.97	0.33 to 2.83		87	116	1.09	0.68 to 1.74	41	34	1.15	0.53 to 2.48	
> 0.47 to 0.96	81	115	1.13	0.66 to 1.95	34	8	3.22	1.03 to 10.05		103	110	1.12	0.69 to 1.82	36	39	1.33	0.62 to 2.86	
> 0.96	68	123	1.27	0.76 to 2.13	45	14	3.00	1.12 to 8.07	< .001	110	118	1.53	0.98 to 2.39	51	31	2.71	1.26 to 5.83	< .001

Abbreviations: OR, odds ratio; LD, limit of detection.
*The multivariable logistic model includes age (five-year intervals), total plasma lipid concentration (continuous), waist-to-hip ratio (≤ 0.95, > 0.95) and history of prostate cancer screening (no, yes).

increased dramatically during the study period,[15] mostly due to the development of PSA testing in the population. Consistent with this, it should be borne in mind that one of the potential negative consequences of prostate cancer screening is an increase in the diagnosis of indolent or latent tumors that will never be a problem to the patient and would not have been detected without screening. Such tumors, like those found in autopsy series,[26] may reflect the natural aging process rather than the consequences of exposure to chemicals, such as chlordecone, in the environment.

Cancer is generally thought to occur a long time after the first exposure and after long periods of continuous exposure. Our study population fits this requirement, with the median exposure period being almost 33 years. Moreover, given that chlordecone exposure in our study population began in adulthood, at a median age of 30.2 years (the youngest subject being 13 years old at the start of exposure), our study did not include cases of exposure during critical periods for carcinogenesis, such as the fetal or neonatal periods.

The prostate cancer risk associated with chlordecone exposure was higher in subjects with a family history of prostate cancer. Similar findings were reported for pesticide exposure in the Agricultural Health Study.[27-30] Study subjects and their first-degree relatives may have similar patterns of exposure, and this might lead to a statistical interaction between chlordecone exposure and family history of prostate cancer; alternatively, the observed interaction may be indicative of an inherited genetic trait, such as a polymorphism in a metabolic enzyme that alters the balance between bioactivation and detoxification in the body.

The prostate cancer risk associated with chlordecone exposure was particularly marked in subjects who had spent some time living in a Western country. Most such subjects in our study migrated to a Western country at the beginning of adulthood, remaining there for a mean duration of 14 years. Most of these subjects returned to the French West Indies at the time at which chlordecone use began. Many intervening factors may explain the interaction observed and any potential causal relationship should be interpreted with caution. Migration constitutes a period of exposure to specific environmental risk factors, including hazardous chemicals or nutritional agents. Residing in Western countries may induce significant changes in an individual, due, for example, to the adoption of a Western lifestyle, including, in particular, eating habits that may be risk factors for prostate cancer.[31] Such changes in lifestyle may then be maintained by these individuals after their return to the French West Indies.

Previous studies have shown differences in the interindividual activity of chlordecone reductase in the liver between white and Japanese individuals.[16,32] Such variability has been associated with a protein variant that arises from two nucleotide (C to G) substitutions at positions 434 and 931 of the cDNA.[32] We show here that these two mutations are in complete linkage disequilibrium and that the frequency of the variant allele (0.04) is lower than that previously reported in whites (0.10).[33] Although limited by the small number of subjects, the observed high risk associated with carrying at least one variant allele, for individuals with chlordecone concentrations above the LD, is consistent with the mutated enzyme being less efficient. This may lead to lower levels of biliary excretion and of chlordecone clearance from the circulation.

Chlordecone may act as a tumor promoter, through hormone-mediated effects. Chlordecone binds the estrogen receptors α (ERα) and β (ERβ), acting as an agonist of ERα and an antagonist of ERβ.[6,34,35] ERα mediates the adverse effects of estrogen on the prostate, such as aberrant proliferation, inflammation, and malignancy. ERβ exerts opposite and beneficial effects, such as antiproliferative, anti-inflammatory, and, potentially, anticarcinogenic effects.[36] The human prostate expresses both ERα and ERβ, with ERα expressed primarily on stromal cells and ERβ found in the differentiated epithelium.[37,38] The interplay between the agonistic effects on ERα and the antagonistic effects on ERβ of chlordecone may increase proliferation of estrogen-sensitive tissues, increasing the risk of cancer. In addition to its interaction with nuclear ER, chlordecone may activate alternative estrogen signaling pathways or other enzymes and receptors involved in steroidal homeostasis.[39-43] It remains unclear whether such mechanisms actually take place in human prostate and whether they trigger prostate cancer.

We are aware of the inherent limitations of patient-control studies. Several factors potentially generating bias must be considered, particularly those relating to differential errors in the measurement of disease or exposure. Patient identification was based on unequivocal histologic criteria and controls were selected on the basis of strict criteria, such as normal findings on digital rectal examination and PSA in the normal range for age, taking into account the ethnic origin of the population. We recruited incident rather than prevalent patients, and controls were selected from a representative sample of the male Guadeloupean population during the study period. Exposure was evaluated on the basis of objective determinations of plasma chlordecone concentration, rather than on questionnaires, which might generate recall bias. Single determinations of plasma chlordecone concentration have been shown to provide an accurate reflection of the load of this compound in the body.[44,45] Classical organochlorine compounds (determined in blood or fat tissues) have been found at lower concentrations in French West Indies populations than in most other populations and are not correlated with chlordecone levels.[13] The quantitative evaluation of chlordecone exposure-response is therefore unlikely to have been confounded by the presence of other organochlorine compounds in our study. However, we cannot exclude the possibility that some unknown confounding factors remain that may account for the associations observed.

In conclusion, our results suggest that there is a causal relationship between chlordecone exposure and prostate cancer risk. Our study also suggests that this association may be affected by genetic background, together with environmental agents related to diet or lifestyle. These findings require further investigation.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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