

Persistent organochlorine pesticides in periprostatic adipose tissue from men with prostate cancer: Ethno-geographic variations, association with disease aggressiveness

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PERSISTENT ORGANOCHLORINE PESTICIDES IN PERIPROSTATIC ADIPOSE TISSUE FROM MEN WITH PROSTATE CANCER: ETHNO-GEOGRAPHIC VARIATIONS, ASSOCIATION WITH DISEASE AGGRESSIVENESS.

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ABSTRACT

Although several studies have examined the relationship between organochlorine pesticides (OCPs) and prostate cancer (PCa) risk, no data are available concerning the association between OCPs concentrations in periprostatic adipose tissue (PPAT), which reflects cumulative exposure, and PCa aggressiveness. Moreover, no previous study has compared OCPs exposure in two distinct ethno-geographical populations. The objectives were to analyze OCPs in PPAT of PCa patients from either Mainland France or French West Indies in correlation with features of tumor aggressiveness, after adjusting for potential confounders such age, BMI, and polyunsaturated fatty acid (PUFA) content of PPAT .

PPAT was analyzed in 160 patients (110 Caucasians and 50 African-Caribbeans), 80 with an indolent tumor (ISUP group 1 + pT2), and 80 with an aggressive tumor (ISUP group more than 3 + pT3). The concentrations of 29 OCPs were measured in PPAT concomitantly with the characterization of PUFA content.

Exposure patterns of OCPs differed according to the ethno-geographical origin. Most OCPs were found at higher concentration in Caucasian patients, whereas pp'-DDE content was twice as high in African-Caribbeans. Chlordecone was only detected in PPAT from African-Caribbean patients. Most OCP concentrations were positively correlated with age, and some with BMI. After adjusting for age, BMI, and PUFA composition of PPAT, no significant association was found between OCPs content and risk of aggressive disease, except of mirex which appeared inversely associated with aggressive features of PCa in Caucasian patients.

These results highlight a significant ethno-geographic variation in internal exposure to OCPs, which likely reflects differences in consumption patterns. The inverse relationship observed between mirex concentration and markers of PCa aggressiveness need to be further investigated.

Keywords: prostate cancer; persistent organic pollutants; organochlorine pesticides; exposure; adipose tissue; fatty acids

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1. INTRODUCTION

Prostate cancer (PCa) is the most frequently diagnosed cancer in men in Western countries. Significant ethnic disparities in PCa risk have been reported, with a higher incidence among African-American men compared with European-Americans (1). Similarly, in the French West Indies, where at least 90% of the population is of African origin, the incidence of PCa is twice as high as in the rest of France (2). In addition to genetic parameters, it has been suggested that environmental factors including dietary intake, play a role in the risk and progression of PCa (3). We have previously shown that the polyunsaturated fatty acid (PUFA) composition of peri-prostatic adipose tissue (PPAT), which reflects PUFA intake, was associated with PCa aggressiveness, and differed according to the ethno-geographical origin. Linoleic acid (LA), an essential n-6 PUFA, was 2-fold higher in African-Caribbean PPAT than in Caucasian patients, and was inversely associated with features of PCa aggressiveness. In Caucasians, a negative association was observed between eicosapentaenoic acid (EPA) levels (an n-3 PUFA) and disease aggressiveness (4).

Organochlorine pesticides (OCPs) are a group of Persistent Organic Pollutants (POPs) with endocrine disrupting and bioaccumulative properties (5). OCPs have been widely used in agriculture and pest control, and most of them have now been banned for decades in Western countries, due to public health concerns. However, due to their persistent nature, they are still present in the environment, food, and consequently in human matrices (6). Food and drinking water are the main sources of contamination (7). In the human body, due to their highly lipophilic properties, they tend to accumulate in tissues with high fat content, mainly adipose tissue (8).

Several epidemiologic studies have investigated the relationship between OCP exposure levels and PCa risk, both in occupational exposure and in the general population, with mainly tenuous, inconsistent or opposite findings (9, 10, 11, 12). Furthermore, some studies have focused on the association between exposure to selected OCPs and aggressive disease in the general population, reporting significant associations of high risk or metastatic PCa, with p-p'DDE, oxychlordane, and chlordecone, respectively (13-16). In most of these studies, exposure to OCPs was evaluated either by questionnaires or by blood measurements. Because OCPs accumulates in fat, their measurement in adipose tissue represent cumulative internal exposure, accounting for all exposure routes and sources (17). Therefore, adipose tissue, when available, is a good indicator of long-term exposure for lipophilic chemicals.

In the present study, we aimed to determine the concentration levels of 29 OCPs and related metabolites from the Stockholm convention list, in PPAT from patients with PCa. The measurements

93 were performed in two populations of different ethno-geographical origin, and in association with
94 features of disease aggressiveness, after adjusting or not for PUFA composition.
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2. MATERIAL AND METHODS

2. 1. Studied population and collected biological tissues

PPAT has been sampled during the surgical procedure in patients treated by radical prostatectomy for clinically localized PCa in 6 University Hospitals. Five of these centers mainly recruited Caucasian patients, while the one located in the French West Indies recruited African-Caribbean patients. All patients have signed an informed consent, after agreement of the Ethical Committee/IRB, clinicaltrials registration number NCT03214315. Clinical and biological annotations included age, ethno-geographic origin, preoperative prostatic specific antigen (PSA), pathological stage, ISUP group, body mass index (BMI). From 1000 cases included in the database, patients with aggressive PCa have been selected on the criteria of high risk disease, i.e. ISUP group more than 3 and pT3 stage. Each of these patients have then been matched (within each center) for the age with one patient with indolent disease. Criteria for indolent PCa include ISUP group 1 and pT2 stage and preoperative PSA less than 10 ng/ml. At the end, PPAT from 160 patients (110 Caucasians, 50 African-Caribbeans) have been analyzed, including 80 with indolent disease and 80 with aggressive disease. The characteristics of this studied population are summarized in table 1.

2. 2. Organochlorine pollutants (OCP) extraction and quantification by gas chromatography-high resolution mass spectrometry (GC-HRMS) and liquid chromatography-tandem mass spectrometry (LC-MS/MS)

Sample preparation for adipose tissues consisted in 1 g freeze-dried sample extracted with a toluene/acetone mixture (70:30, v/v) using a Speed Extractor E-914 from Buchi (Rungis, France). Pressure and temperature were set at 100 bars and 120 ◦C respectively.

Tissue extracts were then purified on a Gel Permeation Chromatography (GPC) system. GPC extracts were split into two fractions. The first fraction was used for OCP analysis by GC–HRMS, the second for chlordecone analysis by LC–MS/MS. Extracts were carefully evaporated to dryness under a gentle stream of nitrogen before reconstituting the chlordecone fraction in 50 microL acetonitrile and the OCP fraction in 50 microL of ^{13}C-PCB-111 at 20 pg.L−1 (in nonane for GC–MS analysis).

The methodologies applied to isolate, detect, and quantify the targeted organochlorine pesticides except chlordecone, using GC-HRMS, have been described earlier (12). Briefly, ^{13}C-labeled congeners were added to each sample for quantification according to the isotopic dilution method. OC measurements were performed by gas chromatography (Agilent 7890A) coupled to high-resolution mass spectrometry (GC-HRMS) on electromagnetic sector instruments (JEOL MS 700D or 800D), operating at 10,000 resolution and in the single ion monitoring (SIM) acquisition mode. QA/QC

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procedures included systematic analysis of negative (procedural blank, n = 3) and positive (standard reference compounds, n = 1) quality control samples in each batch of analysis. All these methods were fully validated .

The methodology applied to isolate, detect, and quantify chlordecone using LC–MS/MS has been described earlier (18). An Acquity Ultra Performance Liquid Chromatography (UPLC) System (Waters, Milford, MA, USA) equipped with a C30 Thermo Accucore column (100 mm × 2.1 mm i.d., 2.6 µm granulometry) was used for liquid chromatography (LC) separation. The column temperature was set at 40 ◦C. A Xevo TQ-S triple quadrupole mass spectrometer (Waters, Milford, MA, USA) equipped with an electrospray ionization source was used in negative mode (ESI-). TargetLynx V 4.1 (Waters, Milford, MA, USA) software was used for the integration and assignment of all chromatographic peaks acquired in the selected reaction monitoring (SRM) mode.

The following OCPs were analyzed: hexachlorobenzene (HCB), pentachlorobenzene (PeCB), α-hexachlorocyclohexane (α-HCH), β-hexachlorocyclohexane (β-HCH), γ-hexachlorocyclohexane (γ-HCH), δ-hexachlorocyclohexane (δ-HCH), α-chlordane, γ-chlordane, cis-nonachlor, trans-nonachlor, heptachlor, cis-heptachlor-epoxyde, trans-heptachlor-epoxyde, oxychlordane, α-endosulfan, β-endosulfan, endosulfan-sulfate, aldrin, endrin, dieldrin, o,p'-DDT, p,p'-DDT, o,p'-DDD, p,p'-DDD, o,p'-DDE, p,p'-DDE, methoxychlor, mirex, chlordecone. Results are expressed as ng per g of extracted lipids.

2. 3. Fatty acid analysis of PPAT

Total lipids were extracted, according to the Folch method , with chloroform/methanol 2:1 and saline solution. Organic phase was collected and triglycerides were purified by preparative Thin Layer Chromatography. FA were transmethylated with 14% boron trifluoride in methanol, and FA methyl esters were dissolved in hexane and analyzed by capillary gas chromatography. FA were identified by comparison of their retention times with those of a standard mixture (Supelco™ 37 component FA methyl ester MIX, Supelco). Results for each FA expressed as mole % of total chromatogram fatty acids area.

2. 4. Statistical analysis

Statistical analyses were carried out with Addinsoft™ XLSTAT (New York, NY, USA). Comparison between groups was performed using the nonparametric Mann-Whitney U test. The relationship between 2 continuous variables was evaluated using the nonparametric Spearman rank correlation test. Logistic regressions were performed to evaluate the association between each OCP and features of aggressive versus indolent disease. OCPs were entered in the logistic models as 2 categories,

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above and below the median value. Each model was adjusted on age and BMI as continuous variables, because OCPs are known to bio-accumulate. The second model also adjusted for EPA and AL content of PPAT, PUFA that have been associated with features of PCa aggressiveness, in the Caucasian and African-Carribean population, respectively, and that are therefore confounders (4). The p values have not been corrected for multiplicity, because the study has been performed for descriptive purposes, focused on a few planned comparisons. Therefore the following results should clearly be labelled as exploratory.

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3. RESULTS

3. 1. OCP concentration levels in PPAT

The following OCPs were found below the limit of detection (LOD) in more than 70% of individuals in both group of patients: α–HCH, γ-HCH, δ-HCH, α-chlordane, γ-chlordane, heptachlor, trans-heptachlor-epoxyde, α-endosulfan, β-endosulfan, endosulfan-sulfate, aldrin, endrin, o,p'-DDT, o,p'-DDD, o,p'-DDE, methoxychlor.

The following OCPs were detectable in all patients in both groups: HCB, PeCB, β-HCH, trans-nonachlor, cis-heptachlor-epoxyde, oxychlordane, dieldrin, p,p'-DDE, mirex.

Cis-nonachlor, p,p'-DDT and p,p'-DDD were detectable in more than 70% of patients in both groups.

Chlordecone was detectable in around 70% of patients in PPAT from African-Caribbean patients, and below the LOD in PPAT from Caucasian patients. For the few cases below the LOD, non-detected values have been replaced by limits of detection (upper bound approach).

The main contributors to the OCP contamination profile observed in PPAT are p, p'-DDE, □-HCH, trans-nonachlor, HCB, and oxychlordane (figure 1).

3. 2. The OCP exposure patterns in PPAT differed according to the ethno-geographical origin

Most OCPs were found at higher concentration level in PPAT from Caucasian patients when compared to PPAT from African-Caribbean patients, including β-HCH, trans-nonachlor, HCB, PeCB, oxychlordane, dieldrine, cis-heptachlor-epoxyde, and cis-nonachlor (table 2). In contrast, OCP concentrations in PPAT were higher in African-Caribbean patients for p,p'-DDE (more than twice), p,p'-DDT, and mirex. Chlordecone was detected only in PPAT from African-Caribbean patients.

3. 3. Correlations between OCPs

Spearman's rank correlations between OCPs are represented in figure 2 as heatmaps built for each population. Strong correlations were observed between HCB, β-HCH, cis-nonachlor, trans-nonachlor, cis-heptachlor-epoxyde, oxychlordane, dieldrin, and p,p'-DDE, regardless of the ethno-geographic group. PeCB was slightly (but significantly) correlated with cis-nonachlor, trans-nonachlor, cis-heptachlor-epoxyde, oxychlordane, dieldrin, and mirex, but only in Caucasian patients.

In the Caucasian population, mirex appeared significantly correlated with HCB, PeCB, β-HCH, cis-nonachlor, trans-nonachlor, cis-heptachlor-epoxyde, oxychlordane, and dieldrin. In African-Caribbean patients, mirex was found significantly correlated with β-HCH, p,p'-DDE, and chlordecone.

3. 4. Correlation between OCP accumulation in PPAT, age and BMI

In Caucasian patients, most OCP concentrations were positively correlated with patient's age, including p, p'-DDE (Rho: 0.264, p=0.006, Spearman test), β-HCH (Rho: 0.367, p=0.0001), trans-nonachlor (Rho: 0.409, p<0.0001), HCB (Rho: 0.303, p=0.0015), oxychlordane (Rho: 0.411, p<0.0001), mirex (Rho: 0.362, p=0.0002), dieldrin (Rho: 0.373, p<0.0001), cis-heptachlor-epoxyde (Rho: 0.400, p<0.0001), and PeCB (Rho: 0.221, p=0.02). In African-Caribbean patients, only p, p'-DDE and oxychlordane increased statistically with patient's age (Rho: 0.358 and 0.308, p=0.01 and 0.03, respectively).

In Caucasian patients, the following OCPs were positively correlated with the BMI: β-HCH (Rho: 0.251, p=0.009), dieldrin (Rho: 0.219, p=0.02), and cis-heptachlor-epoxyde (Rho: 0.225, p=0.02). Mirex concentration in PPAT from Caucasian patients was associated with lower BMI (Rho: -0.251, p=0.009). In African-Caribbean patients, both dieldrin and chlordecone concentrations in PPAT were positively correlated withBMI (Rho: 0.343 and 0.381, p=0.07 and 0.008, respectively).

3. 5. OCP exposure and tumor aggressiveness

The association between OCP internal exposure levels and features of aggressive disease compared to indolent disease has been analyzed using logistic regression models adjusted for age and BMI (tables 3 and 4). Moreover, since EPA and AL were associated with aggressive disease in Caucasians and African-Carribeans, respectively (4), they have been included in a second model (tables 3 and 4). Results concerning omega 6 and omega 3 fatty acids content in PPAT are available in the supplemental table. In the Caucasian population, mirex was the only OCP significantly associated with features of aggressive disease, with an inverse association after adjustment for age and BMI (p=0.027), and after adjustment for age, BMI, and EPA content (p=0.029). In the African-Caribbean population, the inverse association between mirex and features of PCa aggressiveness was close to significancy (p=0.06 and 0.10 in models 1 and 2, respectively). In this population, we also found almost significant associations between aggressive disease and oxychlordane, dieldrine and cis heptachlorepoxyde, but only in the first model.

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4. DISCUSSION

Most of the considered OCPs have been withdrawn from the market for a long time, but their low ability to degrade leads to their persistence in the environment as well as their bioaccumulation. As a result, populations are still exposed, mainly through dietary intake. Measurement of OCPs and their metabolites in biological matrices is considered a reference method to assess exposure at steady state. Although most previous reports have analyzed OCPs content in blood, few studies have reported OCPs composition in adipose tissue, and none in PPAT. The concentration we found for p-p'DDT and its metabolite p-p'DDE is close or slightly higher to that described in populations of patients from Mainland France with either endometriosis (19) or gastric cancer (20), but is quite lower than those reported in Spanish or Danish women with breast cancer (21, 22), in non-cancer patients from Tunisia (23), and in PCa patients from Sweden (24). The differences observed could be due to the diversity of the populations studied, in terms of age, gender, geographical origin (and therefore exposure), and also in terms of location of the adipose tissue (subcutaneous versus deep fat). However, in all studies, the high ratio p-p'DDE/p-p'DDT reflects a preferential exposure to the metabolite and not to the parent molecule. Concerning the other OCPs, the concentration we found in the PPAT of Caucasian patients is of the same order as that reported in the most recent study performed in Mainland France (20).

We observed that most of OCPs concentrations increased with age, mainly in the Caucasian group, that reflects cumulative exposure, as previously reported (25). Some of them, including β-HCH, dieldrin, cis-heptachlor-epoxyde, and chlordecone in the African-Caribbean population, had concentrations increasing with the BMI. Although in some studies no significant relationship was found (24), high BMI has often been associated with higher POPs levels in adipose tissue (26). This association may be related to food intake, since individuals with a higher BMI are likely to have consumed more food and therefore more POPs. Alternatively, POPs are considered to have obesogenic effects through endocrine disruption (27). We observed herein that mirex is the only OCP which concentration in PPAT was inversely associated with BMI. Such an inverse relationship between BMI and mirex concentration has previously been reported (28). A potential explanation may be the dilution capabilities in adipose tissue of mirex, one of the most lipophilic compounds.

In the present study, we found a differential OCPs concentration in PPAT according to the ethno-geographical origin of the patients. β-HCH, trans-nonachlor, HCB, PeCB, oxychlordane, dieldrine, cis-heptachlor-epoxyde, and cis-nonachlor levels were higher in PPAT from Caucasian patients, whereas the concentrations of p,p'-DDE, p,p'-DDT, and mirex were higher in African-Caribbean patients. No previous study has compared the impregnation levels by OCPs in 2 distinct ethno-geographic

populations. However, the report of the serum concentration of OCPs in the Guadeloupean population by the Kannari Study (29) evidenced lower β-HCH and higher p,p'-DDE when compared to the levels identified in Mainland France by the French National Nutrition and Health Study (ENNS) (30). Since food is the main vector of exposure to OCPs, differences between Guadeloupe and Mainland France probably reflect differences in eating behaviors, but also differences in the geographical origins of food resources. In the West Indies, although some of the foodstuffs come from Mainland France, many others come directly from the USA, Central America, and other islands of the Caribbean. We found a pp'-DDE concentration twice as high in PPAT of African-Carribean patients compared to Caucasian patients. Such differences in pp'-DDE blood levels have already been reported between different parts of the globe (31). The difference in p,p-DDE between African-Caribbean and Caucasian men could be partly explained by more recent exposure in West indies, due to the sporadic use of DDT for disease vector control. Pesticides HCB, β-HCH, cis-nonachlor, trans-nonachlor, cis-heptachlor-epoxyde, oxychlordane, and dieldrin, that we found well correlated to each other and that are in higher concentrations in PPAT from Caucasian patients, could come mainly from foodstuffs of Mainland France origin. Mirex was discreetly used in Guadeloupe to control the fire ant, and has also been worldwide used as a flame retardant. The greatest concentration in African-Caribbean PPAT could be explained by the geographical origins of food resources and perhaps to a lesser extent by the use of the molecule in the West Indies until early 1980s. Chlordecone is an organochlorine insecticide used in the French West Indies between 1972 and 1993 to control banana weevil. This highly stable, persistent organic substance detected in soils is capable of contaminating plant or animal foodstuffs as well as aquatic environments (32). As expected, we detected chlordecone only in PPAT from African-Caribbean patients. Furthermore, chlordecone is poorly correlated with other contaminants, that clearly reflects its local food origin. We note that the only molecules for which a certain correlation is observed, are β-HCH, dieldrin and mirex, pesticides previously used in the French West Indies.

Several previous non occupational case-control studies have analyzed in the general population the relationship between PCa incidence and exposure to OCPs, determined by blood measurements. Although a meta-analysis failed to evidence an association between specific OCPs and increased incidence of PCa (10), individual studies led to conflicting results. Some reports found no significant associations (33-35), while others observed a positive association between PCa incidence and several OCPs, including β-HCH (36, 37), oxychlordane (38), and p-p'DDE (13). In another study, oxychlordane has also been found to be correlated with the risk of metastatic PCa (14). One case-control study has to date analyzed the link between chlordecone plasma concentrations and PCa in a Guadeloupean population, and the authors described a significant association with a dose-response positive

relationship (15). The follow-up of PCa patients included in this case-control study also evidenced a link between risk of biochemical recurrence after surgical treatment and plasma chlordecone concentration (16). Except for these above mentioned studies, most of the previous reports have focused on the association between OCPs and total PCa risk. In the present study, we used indolent cases as the reference group, that allowed to identify factors associated with aggressiveness, defined by both ISUP group more than 3 and pT3 stage. In the African-Caribbean group only, we found associations close to significancy between features of aggressive disease and oxychlordane, dieldrine and cis heptachlorepoxyde. However, this almost significance was lost when AL content of PPAT was entered into the model, PUFA that we previously found to be inversely associated with PCa aggressiveness, and which is therefore a confounder (4). We also observed an inverse association between mirex content in PPAT and aggressive PCa. This association was significant in the Caucasian group only, and remained significant after adjusting for age, BMI, and for EPA content in PPAT. (4). In the African-Caribbean population, the inverse association between mirex and features of aggressiveness was close to significancy, after adjusting or not for PUFA content. This inverse association has already been observed with other types of pesticides, such as polychlorinated biphenyls (PCBs) (13, 14). Moreover, the case-control study performed in a Canadian population also evidenced an almost significant inverse association between plasma mirex levels and PCa risk (34). Although it is unexpected that mirex could be protective for PCa, it is possible that this inverse association could reflect hormonal modifications linked to mirex exposure, and this finding warrants further studies. An inverse association between testosterone levels and mirex serum concentrations has previously been described in boys and men, after adjusting for potential confounders such age and BMI (39, 40). Also, we cannot excude that this inverse association could result from bias due to either unmeasured confounders, or socio-demographic variables that could impact both dietary intake or PSA screening.

The limit of the present study is first the low number of cases, particularly in the African-Caribbean population, that limits its power. Moreover, except for the ethnic origin, genetic determinants of PCa aggressiveness, including family history of PCa, were not available and therefore were not taken into account.

The study has nevertheless several strengths: first, OCPs concentrations were measured directly in adipose tissue, the preferential reservoir of lipophilic pesticides accumulation in the human body, and the most appropriate tissue for assessing long term exposure. In addition, the use of indolent PCa cases as a reference group exempts the study from the bias linked to the identification of control cases. Indeed, some OCPs, and particularly p-p'DDE, the main contributor of OCPs profile in PPAT, are known inhibitors of the androgen receptor, and have been shown to repress PSA levels in human

PCa cell lines at high concentration (41). Strong exposure to these OCPs may therefore produce a false-negative PSA test when screening for prostate cancer.

In conclusion, the present study showed a differential OCPs internal exposure levels and patterns in adipose tissue according to the ethno-geographical origin. The inverse relationship in adjusted models between mirex concentration and features of PCa aggressiveness deserves further mechanistic and epidemiological studies.

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FIGURE LEGENDS

Figure 1: Main contributors to the exposure profiles in PPAT in France mainland and in Guadeloupe.

Figure 2: Heatmaps displaying the Spearmen's rank correlation coefficients between OCPs in the African-Caribbean (A) and Caucasian (B) populations. The color relates to the direction of the association (blue: positive, red: negative), and the intensity to the correlation coefficient magnitude.

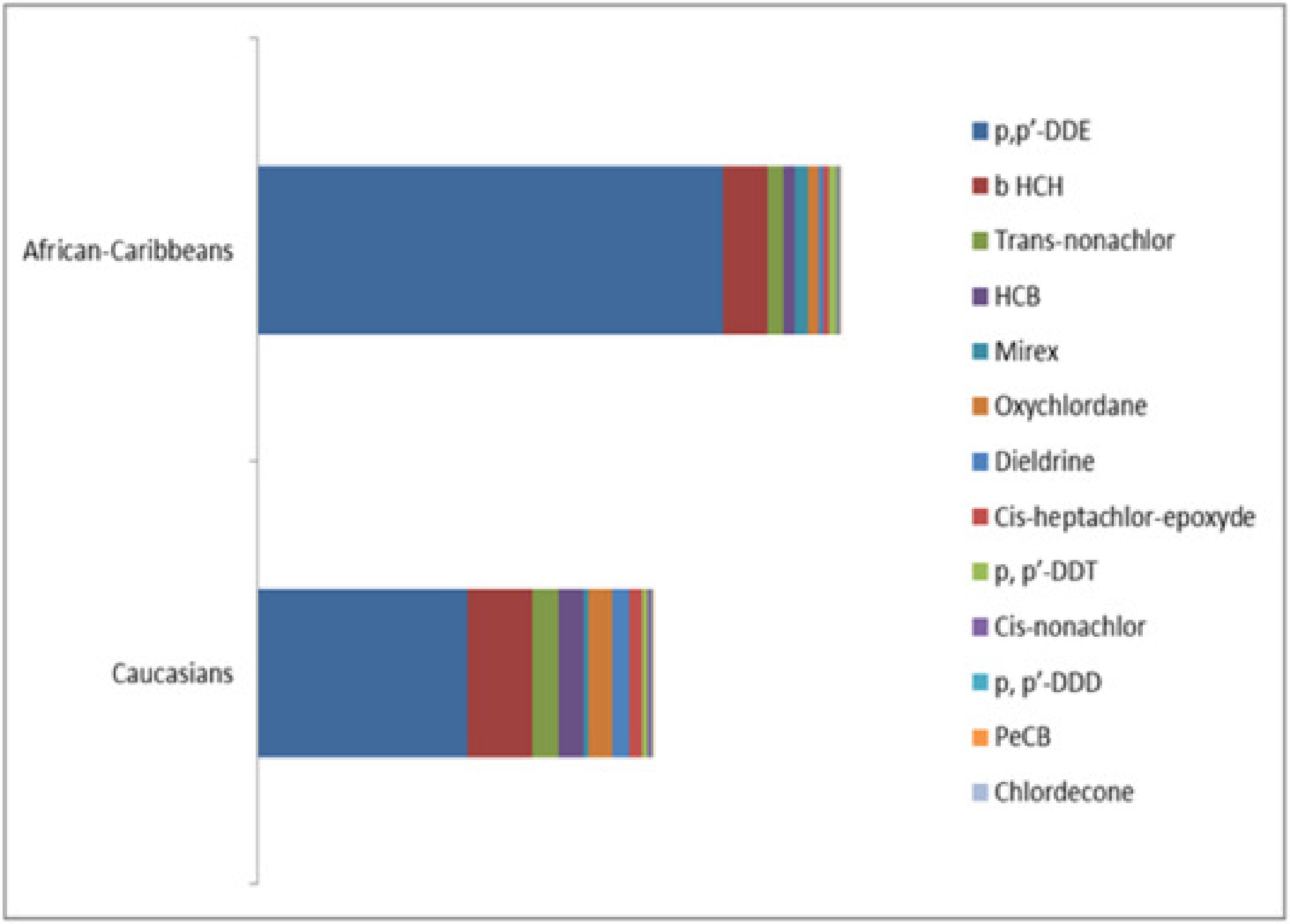
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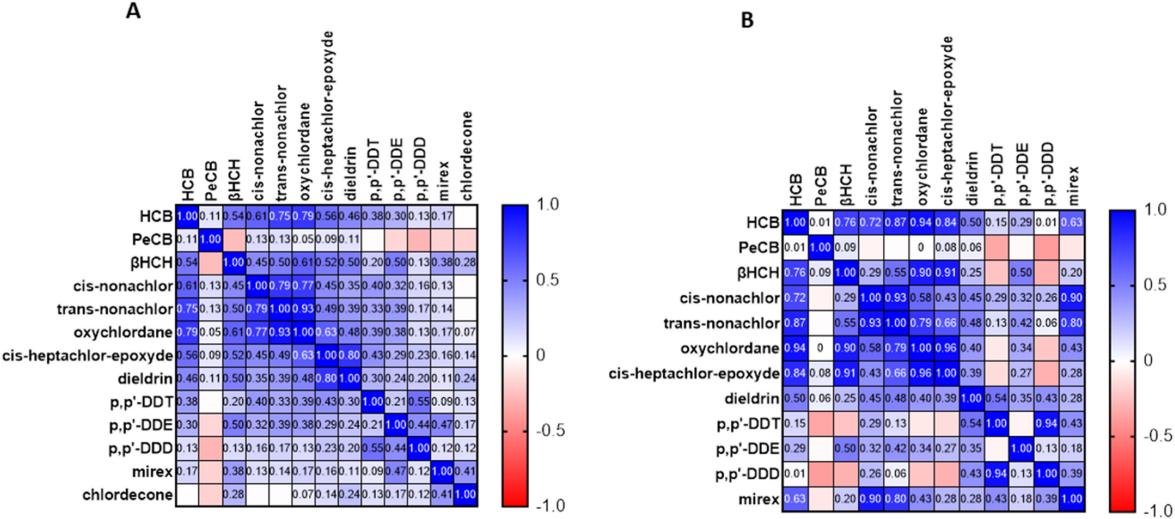
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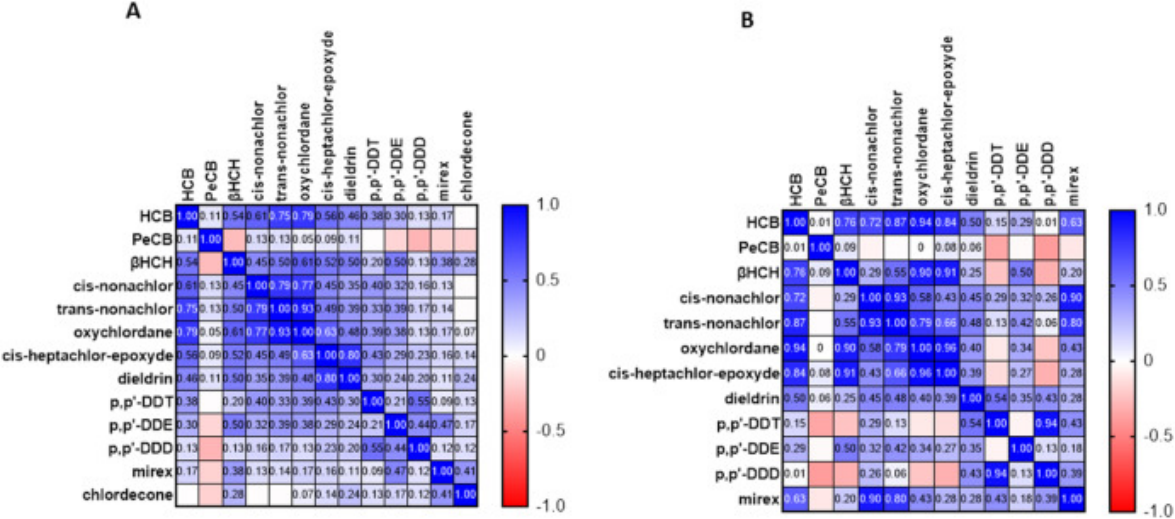
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African-Caribbeans
Caucasians
p,p'-DDE
b HCH
Trans-nonachlor
HCB
Mirex
Oxychlordane
Dieldrine
Cis-heptachlor-epoxyde
p, p'-DDT
Cis-nonachlor
p, p'-DDD
PeCB
Chlordecone


A
HCB
PeCB
βHCH
cis-nonachlor
trans-nonachlor
oxychlordane
cis-heptachlor-epoxyde
dieldrin
p,p'-DDT
p,p'-DDE
p,p'-DDD
mirex
chlordecone
1.00 0.11 0.54 0.61 0.75 0.79 0.56 0.46 0.38 0.30 0.13 0.17
0.11 1.00 0.13 0.13 0.05 0.09 0.11
0.54 1.00 0.45 0.50 0.61 0.52 0.50 0.20 0.50 0.13 0.38 0.28
0.61 0.13 0.45 1.00 0.79 0.77 0.45 0.35 0.40 0.32 0.16 0.13
0.75 0.13 0.50 0.79 1.00 0.93 0.49 0.39 0.33 0.39 0.17 0.14
0.79 0.05 0.61 0.77 0.93 1.00 0.63 0.48 0.39 0.38 0.13 0.17 0.07
0.56 0.09 0.52 0.45 0.49 0.63 1.00 0.80 0.43 0.29 0.23 0.16 0.14
0.46 0.11 0.50 0.35 0.39 0.48 0.80 1.00 0.30 0.24 0.20 0.11 0.24
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0.30 0.50 0.32 0.39 0.38 0.29 0.24 0.21 1.00 0.44 0.47 0.17
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B
HCB
PeCB
βHCH
cis-nonachlor
trans-nonachlor
oxychlordane
cis-heptachlor-epoxyde
dieldrin
p,p'-DDT
p,p'-DDE
p,p'-DDD
mirex
1.00 0.01 0.76 0.72 0.87 0.94 0.84 0.50 0.15 0.29 0.01 0.63
0.01 1.00 0.09 0 0.08 0.06
0.76 0.09 1.00 0.29 0.55 0.90 0.91 0.25 0.50 0.20
0.72 0.29 1.00 0.93 0.58 0.43 0.45 0.29 0.32 0.26 0.90
0.87 0.55 0.93 1.00 0.79 0.66 0.48 0.13 0.42 0.06 0.80
0.94 0 0.90 0.58 0.79 1.00 0.96 0.40 0.34 0.43
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A
HCB
PeCB
βHCH
cis-nonachlor
trans-nonachlor
oxychlordane
cis-heptachlor-epoxyde
dieldrin
p,p'-DDT
p,p'-DDE
p,p'-DDD
mirex
chlordecone
1.0
0.5
0
-0.5
-1.0
B
HCB
PeCB
βHCH
cis-nonachlor
trans-nonachlor
oxychlordane
cis-heptachlor-epoxyde
dieldrin
p,p'-DDT
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p,p'-DDD
mirex
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Tables

Table 1. Characteristics of the studied population.

	Indolent PCa		*p*	Aggressive PCa		*p*
	Caucasians (n = 55)	**AC (n = 25)**		**Caucasians (n = 55)**	**AC (n = 25)**	
Pre-operative PSA, median (range)	6.4 ng/ml (1.1–9.9)	5.7 ng/ml (0.3–9)	*0.07*	9.4 ng/ml (3.5–30)	9.2 ng/ml (3.7–30)	*0.87*
Age, median (range)	64 y (50–77)	64 y (44–75)	*0.62*	66 y (46–75)	65 y (48–76)	*0.71*
BMI, median (range)	26 (18.5–39.1)	26.8 (21.9–38.4)	*0.34*	26.1 (20.3–34)	25.6 (20.6–32.9)	*0.63*

AC: African-Caribbeans; BMI: Body mass Index.

Table 2. OCP internal concentration levels (ng/g lipid weight) measured in PPAT from Caucasian and African-Caribbean, in both indolent and aggressive groups.

OCP	LOD (ng/g l.w)	Ethno-geographic group	n (%) <LOD	Concentration (ng/g l.w) Median (range)	p
p,p'-DDE	0.32	Caucasian	0/110 (0%)	124.6 (16.6–1228.8)	**<0.0001**
		African-Caribbean	0/50 (0%)	277 (45.7–3828.4)	
β HCH	0.42	Caucasian	0/110 (0%)	38.5 (4.3–229.8)	**0.04**
		African-Caribbean	0/50 (0%)	26.1 (2.6–375.0)	
Trans-nonachlor	0.28	Caucasian	0/110 (0%)	15.7 (3.9–77.5)	**<0.0001**
		African-Caribbean	0/50 (0%)	9.7 (1.5–35.4)	
HCB	0.05	Caucasian	0/110 (0%)	14.7 (4.6–41.3)	**<0.0001**
		African-Caribbean	0/50 (0%)	7.2 (2.0–21.5)	
Mirex	0.06	Caucasian	0/110 (0%)	3.2 (0.86–14.5)	**<0.0001**
		African-Caribbean	0/50 (0%)	7.4 (2.8–150.9)	
Oxychlordane	0.22	Caucasian	0/110 (0%)	14.0 (3.7–38.8)	**<0.0001**
		African-Caribbean	0/50 (0%)	6.0 (1.0–28.6)	
Dieldrine	0.17	Caucasian	0/110 (0%)	10.5 (2.8–45.7)	**<0.0001**
		African-Caribbean	0/50 (0%)	3.7 (0.57–45.4)	
Cis-heptachlor-epoxyde	0.08	Caucasian	0/110 (0%)	7.9 (2.7–43.4)	**<0.0001**
		African-Caribbean	0/50 (0%)	3.0 (0.58–36.3)	
p, p'-DDT	0.54	Caucasian	23/110 (20.9%)	2.7 (0.54–17.3)	**0.004**
		African-Caribbean	14/50 (28%)	4.2 (0.70–105.0)	
Cis-nonachlor	0.28	Caucasian	0/110 (0%)	2.8 (0.45–14.8)	**<0.0001**
		African-Caribbean	9/50 (18%)	1.5 (0.28–4.2)	
p, p'-DDD	0.14	Caucasian	17/110 (15.4%)	0.66 (0.14–4.4)	0.09
		African-Caribbean	3/50 (6%)	0.73 (0.23–17.1)	
PeCB	0.05	Caucasian	0/110 (0%)	0.29 (0.05–2.2)	**<0.0001**
		African-Caribbean	0/50 (0%)	0.17 (0.07–1.2)	
Chlordecone	0.08	Caucasian	110/110 (100%)	ND	**<0.0001**
		African-Caribbean	5/50 (10%)	0.23 (0.08–9.49)	

Table 3. Association between OCP internal concentration levels in PPAT from Caucasians patients, and risk of aggressive versus indolent disease. Logistic regression after adjustment for age and BMI (model 1) and after adjustment for age, BMI, and EPA (model 2).

OCP	OR Model 1 (95%CI)	P	OR Model 2 (95% CI)	P
p,p'-DDE	1.00 (ref)	0.94	1.00 (ref)	0.99
Below median	1.032 (0.472–2.254)		0.997 (0.435–2.285)	
Above median				
β HCH	1.00 (ref)	0.72	1.00 (ref)	0.33
Below median	0.868 (0.394–1.915)		0.648 (0.272–1.544)	
Above median				
Trans-nonachlor	1.00 (ref)	0.41	1.00 (ref)	0.38
Below median	0.713 (0.317–1.604)		0.670 (0.277–1.624)	
Above median				
HCB	1.00 (ref)	0.21	1.00 (ref)	0.09
Below median	1.645 (0.760–3.562)		2.129 (0.894–5.070)	
Above median				
Mirex	1.00 (ref)	0.027	1.00 (ref)	0.029
Below median	0.381 (0.161–0.898)		0.358 (0.142–0.900)	
Above median				
Oxychlordane	1.00 (ref)	0.69	1.00 (ref)	0.84
Below median	1.175 (0.535–2.580)		1.090 (0.468–2.539)	
Above median				
Dieldrine	1.00 (ref)	0.76	1.00 (ref)	0.84
Below median	0.881 (0.388–2.001)		0.915 (0.379–2.208)	
Above median				
Cis heptachlorepoxyde	1.00 (ref)	0.37	1.00 (ref)	0.71
Below median	1.454 (0.644–3.286)		1.185 (0.492–2.855)	
Above median				
p, p'-DDT	1.00 (ref)	0.58	1.00 (ref)	0.66
Below median	0.809 (0.380–1.720)		0.833 (0.370–1.876)	
Above median				
Cis-nonachlor	1.00 (ref)	0.12	1.00 (ref)	0.29
Below median	0.538 (0.243–1.188)	0.09	0.629 (0.266–1.492)	0.12
Above median	1.00 (ref)		1.00 (ref)	
PeCB	0.517 (0.242–1.102)		0.530 (0.236–1.192)	
Below median				
Above median				
p, p'-DDD	1.00 (ref)	0.81	1.00 (ref)	0.88
Below median	0.913 (0.431–1.936)		0.942 (0.419–2.120)	
Above median				

Table 4. Association between OCP internal concentration levels in PPAT from African-Caribbean patients, and risk of aggressive versus indolent disease. Logistic regression after adjustment for age and BMI (model 1) and after adjustment for age, BMI, and AL (model 2).

OCP	OR Model 1 (95%CI)	P	OR Model 2 (95% CI)	P
p,p'-DDE	1.00 (ref)	0.94	1.00 (ref)	0.92
Below median	1.048 (0.279–3.933)		1.089 (0.185–6.424)	
Above median				
β HCH	1.00 (ref)	0.11	1.00 (ref)	0.29
Below median	2.891 (0.789–10.593)		2.481 (0.466–13.217)	
Above median				
Trans-nonachlor	1.00 (ref)	0.14	1.00 (ref)	0.30
Below median	2.561 (0.745–8.806)		2.232 (0.486–10.255)	
Above median				
HCB	1.00 (ref)	0.48	1.00 (ref)	0.73
Below median	1.514 (0.469–4.891)		1.296 (0.302–5.563)	
Above median				
Mirex	1.00 (ref)	0.06	1.00 (ref)	0.10
Below median	0.298 (0.085–1.050)		0.264 (0.052–1.347)	
Above median				
Oxychlordane	1.00 (ref)	0.06	1.00 (ref)	1.18
Below median	3.525 (0.982–12.657)		2.954 (0.610–14.300)	
Above median				
Dieldrine	1.00 (ref)	0.05	1.00 (ref)	0.64
Below median	3.794 (1.008–14.284)		1.462 (0.290–7.369)	
Above median				
Cis heptachlorepoxyde	1.00 (ref)	0.05	1.00 (ref)	0.30
Below median	3.375 (1.075–13.255)		2.216 (0.485–10.119)	
Above median				
p, p'-DDT	1.00 (ref)	0.86	1.00 (ref)	0.39
Below median	1.112 (0.343–3.610)		1.995 (0.415–9.595)	
Above median				
Cis-nonachlor	1.00 (ref)	0.81	1.00 (ref)	0.89
Below median	1.154 (0.361–3.687)	0.27	1.108 (0.255–4.803)	0.52
Above median	1.00 (ref)		1.00 (ref)	
PeCB	1.933 (0.598–6.249)		01.611 (0.376–6.902)	
Below median				
Above median				
p, p'-DDD	1.00 (ref)	0.23	1.00 (ref)	0.45
Below median	0.481 (0.146–1.591)		0.552 (0.119–2.560)	
Above median				
Chlordecone	1.00 (ref)	0.18	1.00 (ref)	0.86
Below median	0.446 (0.134–1.484)		0.875 (0.180–4.244)	
Above median				

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HIGHLIGHTS

- Organochlorine pesticides (OCPs) concentration in periprostatic adipose tissue from men with prostate cancer differed according to the ethno-geographical origin, which likely reflects differences in consumption patterns.
- Most OCPs were found at higher concentration in PPAT from Caucasian patients. Chlordecone was only found in PPAT of African-Caribbean patients, with moreover a DDE concentration twice as high as in Caucasian patients.
- After adjusting for age, BMI, and PUFA content, mirex concentration in PPAT from Caucasian patients was inversely associated with features of aggressive disease.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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