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

Jean-Philippe Antignac, Sandy Figiel, Michèle Pinault, Pascal Blanchet, Franck Bruyère, Romain Mathieu, Souhil Lebdai, Georges Fournier, Jérôme Rigaud, Karine Mahéo, et al.

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

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Jean-Philippe Antignac, Philippe Marchand, Ingrid Guiffard, Emmanuelle Bichon, Bruno le Bizec : OCP measurement

Sandy Figiel, Michèle Pinault, Karine Mahéo : Fatty acid analysis

Pascal Blanchet, Franck Bruyère, Romain Mathieu, Souhil Lebdaï, Georges Fournier, Jerome Rigaud, Luc Multigner : provide bioresources

Gaëlle Fromont, Luc Multigner : statistical analysis

Gaëlle Fromont, Jean-Philippe Antignac, Luc Multigner : manuscript writing

Gaëlle Fromont : study design

26 **ABSTRACT**

27

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

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

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

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

50

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

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## 1. INTRODUCTION

60  
61  
62 Prostate cancer (PCa) is the most frequently diagnosed cancer in men in Western countries.  
63 Significant ethnic disparities in PCa risk have been reported, with a higher incidence among African-  
64 American men compared with European-Americans (1). Similarly, in the French West Indies, where at  
65 least 90% of the population is of African origin, the incidence of PCa is twice as high as in the rest of  
66 France (2). In addition to genetic parameters, it has been suggested that environmental factors  
67 including dietary intake, play a role in the risk and progression of PCa (3). We have previously shown  
68 that the polyunsaturated fatty acid (PUFA) composition of peri-prostatic adipose tissue (PPAT), which  
69 reflects PUFA intake, was associated with PCa aggressiveness, and differed according to the ethno-  
70 geographical origin. Linoleic acid (LA), an essential n-6 PUFA, was 2-fold higher in African-Caribbean  
71 PPAT than in Caucasian patients, and was inversely associated with features of PCa aggressiveness. In  
72 Caucasians, a negative association was observed between eicosapentaenoic acid (EPA) levels (an n-3  
73 PUFA) and disease aggressiveness (4).

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

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

91 In the present study, we aimed to determine the concentration levels of 29 OCPs and related  
92 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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## 96 2. MATERIAL AND METHODS

97

### 98 2. 1. Studied population and collected biological tissues

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

112

### 113 2. 2. Organochlorine pollutants (OCP) extraction and quantification by gas chromatography-high 114 resolution mass spectrometry (GC-HRMS) and liquid chromatography-tandem mass spectrometry 115 (LC-MS/MS)

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

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

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

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

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

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

148

### 149 **2. 3. Fatty acid analysis of PPAT**

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

157

### 158 **2. 4. Statistical analysis**

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



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

171

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### 172 3. RESULTS

173

#### 174 3. 1. OCP concentration levels in PPAT

175 The following OCPs were found below the limit of detection (LOD) in more than 70% of individuals in  
176 both group of patients:  $\alpha$ -HCH,  $\gamma$ -HCH,  $\delta$ -HCH,  $\alpha$ -chlordane,  $\gamma$ -chlordane, heptachlor, trans-  
177 heptachlor-epoxyde,  $\alpha$ -endosulfan,  $\beta$ -endosulfan, endosulfan-sulfate, aldrin, endrin, o,p'-DDT, o,p'-  
178 DDD, o,p'-DDE, methoxychlor.

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

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

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

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

187

#### 188 3. 2. The OCP exposure patterns in PPAT differed according to the ethno-geographical origin

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

194

#### 195 3. 3. Correlations between OCPs

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

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

204

205

**206 3. 4. Correlation between OCP accumulation in PPAT, age and BMI**

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

214 In Caucasian patients, the following OCPs were positively correlated with the BMI:  $\beta$ -HCH (Rho:  
215 0.251, p=0.009), dieldrin (Rho: 0.219, p=0.02), and cis-heptachlor-epoxyde (Rho: 0.225, p=0.02).  
216 Mirex concentration in PPAT from Caucasian patients was associated with lower BMI (Rho: -0.251,  
217 p=0.009). In African-Caribbean patients, both dieldrin and chlordecone concentrations in PPAT were  
218 positively correlated with BMI (Rho: 0.343 and 0.381, p=0.07 and 0.008, respectively).

219

**220 3. 5. OCP exposure and tumor aggressiveness**

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

233

234 **4. DISCUSSION**

235

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

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

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

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

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

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

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

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

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

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

342

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- 480

481 **FIGURE LEGENDS**

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

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

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African-Caribbeans



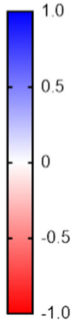
- p,p'-DDE
- b HCH
- Trans-nonachlor
- HCB
- Mirex
- Oxychlorane
- Dieldrine
- Cis-heptachlor-epoxyde
- p, p'-DDT
- Cis-nonachlor
- p, p'-DDD
- PeCB
- Chlordecone

Caucasians



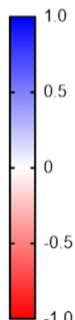
A

	HCB	PeCB	$\beta$ HCH	cis-nonachlor	trans-nonachlor	oxychlorthane	cis-heptachlor-epoxyde	dieldrin	p,p'-DDT	p,p'-DDE	p,p'-DDD	mirex	chlordecone
HCB	1.00	0.11	0.54	0.61	0.75	0.79	0.56	0.46	0.38	0.30	0.13	0.17	
PeCB	0.11	1.00		0.13	0.13	0.05	0.09	0.11					
$\beta$ HCH	0.54		1.00	0.45	0.50	0.61	0.52	0.50	0.20	0.50	0.13	0.38	0.28
cis-nonachlor	0.61	0.13	0.45	1.00	0.79	0.77	0.45	0.35	0.40	0.32	0.16	0.13	
trans-nonachlor	0.75	0.13	0.50	0.79	1.00	0.93	0.49	0.39	0.33	0.39	0.17	0.14	
oxychlorthane	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
cis-heptachlor-epoxyde	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
dieldrin	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
p,p'-DDT	0.38		0.20	0.40	0.33	0.39	0.43	0.30	1.00	0.21	0.55	0.09	0.13
p,p'-DDE	0.30		0.50	0.32	0.39	0.38	0.29	0.24	0.21	1.00	0.44	0.47	0.17
p,p'-DDD	0.13		0.13	0.16	0.17	0.13	0.23	0.20	0.55	0.44	1.00	0.12	0.12
mirex	0.17		0.38	0.13	0.14	0.17	0.16	0.11	0.09	0.47	0.12	1.00	0.41
chlordecone			0.28			0.07	0.14	0.24	0.13	0.17	0.12	0.41	1.00



B

	HCB	PeCB	$\beta$ HCH	cis-nonachlor	trans-nonachlor	oxychlorthane	cis-heptachlor-epoxyde	dieldrin	p,p'-DDT	p,p'-DDE	p,p'-DDD	mirex
HCB	1.00	0.01	0.76	0.72	0.87	0.94	0.84	0.50	0.15	0.29	0.01	0.63
PeCB	0.01	1.00	0.09			0	0.08	0.06				
$\beta$ HCH	0.76	0.09	1.00	0.29	0.55	0.90	0.91	0.25		0.50		0.20
cis-nonachlor	0.72		0.29	1.00	0.93	0.58	0.43	0.45	0.29	0.32	0.26	0.90
trans-nonachlor	0.87		0.55	0.93	1.00	0.79	0.66	0.48	0.13	0.42	0.06	0.80
oxychlorthane	0.94	0	0.90	0.58	0.79	1.00	0.96	0.40		0.34		0.43
cis-heptachlor-epoxyde	0.84	0.08	0.91	0.43	0.66	0.96	1.00	0.39		0.27		0.28
dieldrin	0.50	0.06	0.25	0.45	0.48	0.40	0.39	1.00	0.54	0.35	0.43	0.28
p,p'-DDT	0.15			0.29	0.13			0.54	1.00		0.94	0.43
p,p'-DDE	0.29		0.50	0.32	0.42	0.34	0.27	0.35		1.00	0.13	0.18
p,p'-DDD	0.01			0.26	0.06			0.43	0.94	0.13	1.00	0.39
mirex	0.63		0.20	0.90	0.80	0.43	0.28	0.28	0.43	0.18	0.39	1.00





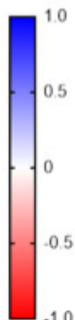
A

	HCB	PeCB	$\beta$ HCH	cis-nonachlor	trans-nonachlor	oxychlorane	cis-heptachlor-epoxyde	dieldrin	p,p'-DDT	p,p'-DDE	p,p'-DDD	mirex	chlordecone
HCB	1.00	0.11	0.54	0.61	0.75	0.79	0.56	0.46	0.38	0.30	0.13	0.17	
PeCB	0.11	1.00		0.13	0.13	0.05	0.09	0.11					
$\beta$ HCH	0.54		1.00	0.45	0.50	0.61	0.52	0.50	0.20	0.50	0.13	0.36	0.28
cis-nonachlor	0.61	0.13	0.45	1.00	0.79	0.77	0.45	0.35	0.40	0.32	0.16	0.13	
trans-nonachlor	0.75	0.13	0.50	0.79	1.00	0.93	0.49	0.39	0.33	0.39	0.17	0.14	
oxychlorane	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
cis-heptachlor-epoxyde	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
dieldrin	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
p,p'-DDT	0.38		0.20	0.40	0.33	0.39	0.43	0.30	1.00	0.21	0.55	0.09	0.13
p,p'-DDE	0.30		0.50	0.32	0.39	0.38	0.29	0.24	0.21	1.00	0.44	0.47	0.17
p,p'-DDD	0.13		0.13	0.16	0.17	0.13	0.23	0.20	0.55	0.44	1.00	0.12	0.12
mirex	0.17		0.38	0.13	0.14	0.17	0.16	0.11	0.09	0.47	0.12	1.00	0.41
chlordecone			0.28			0.07	0.14	0.24	0.13	0.17	0.12	0.41	1.00



B

	HCB	PeCB	$\beta$ HCH	cis-nonachlor	trans-nonachlor	oxychlorane	cis-heptachlor-epoxyde	dieldrin	p,p'-DDT	p,p'-DDE	p,p'-DDD	mirex
HCB	1.00	0.01	0.76	0.72	0.87	0.94	0.84	0.50	0.15	0.29	0.01	0.63
PeCB	0.01	1.00	0.09			0	0.08	0.06				
$\beta$ HCH	0.76	0.09	1.00	0.29	0.55	0.90	0.91	0.25		0.50		0.20
cis-nonachlor	0.72		0.29	1.00	0.93	0.58	0.43	0.45	0.29	0.32	0.26	0.90
trans-nonachlor	0.87		0.55	0.93	1.00	0.79	0.66	0.48	0.13	0.42	0.06	0.80
oxychlorane	0.94	0	0.90	0.58	0.79	1.00	0.96	0.40		0.34		0.43
cis-heptachlor-epoxyde	0.84	0.08	0.91	0.43	0.66	0.96	1.00	0.39		0.27		0.28
dieldrin	0.50	0.06	0.25	0.45	0.48	0.40	0.39	1.00	0.54	0.35	0.43	0.28
p,p'-DDT	0.15			0.29	0.13			0.54	1.00		0.94	0.43
p,p'-DDE	0.29		0.50	0.32	0.42	0.34	0.27	0.35		1.00	0.13	0.18
p,p'-DDD	0.01			0.26	0.06			0.43	0.94	0.13	1.00	0.39
mirex	0.63		0.20	0.90	0.80	0.43	0.28	0.28	0.43	0.18	0.39	1.00



## Tables

Table 1. Characteristics of the studied population.

	Indolent PCa		<i>p</i>	Aggressive PCa		<i>p</i>
	Caucasians (n = 55)	AC (n = 25)		Caucasians (n = 55)	AC (n = 25)	
<b>Pre-operative PSA, median (range)</b>	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
<b>Age, median (range)</b>	64 y (50–77)	64 y (44–75)	0.62	66 y (46–75)	65 y (48–76)	0.71
<b>BMI, median (range)</b>	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 Lw)	Ethno-geographic group	n (%) <LOD	Concentration (ng/g Lw) 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)	
Oxychlorane	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
<i>p,p'</i> -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				
$\beta$ 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				
Oxychlorane	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				
<i>p, p'</i> -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)	
PeCE	0.517 (0.242–1.102)		0.530 (0.236–1.192)	
Below median				
Above median				
<i>p, p'</i> -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
<b>p,p'-DDE</b>	1.00 (ref)	0.94	1.00 (ref)	0.92
<i>Below median</i>	1.048 (0.279–3.933)		1.089 (0.185–6.424)	
<i>Above median</i>				
<b>β HCH</b>	1.00 (ref)	0.11	1.00 (ref)	0.29
<i>Below median</i>	2.891 (0.789–10.593)		2.481 (0.466–13.217)	
<i>Above median</i>				
<b>Trans-nonachlor</b>	1.00 (ref)	0.14	1.00 (ref)	0.30
<i>Below median</i>	2.561 (0.745–8.806)		2.232 (0.486–10.255)	
<i>Above median</i>				
<b>HCB</b>	1.00 (ref)	0.48	1.00 (ref)	0.73
<i>Below median</i>	1.514 (0.469–4.891)		1.296 (0.302–5.563)	
<i>Above median</i>				
<b>Mirex</b>	1.00 (ref)	0.08	1.00 (ref)	0.10
<i>Below median</i>	0.298 (0.085–1.050)		0.264 (0.052–1.347)	
<i>Above median</i>				
<b>Oxychlordanes</b>	1.00 (ref)	0.08	1.00 (ref)	1.18
<i>Below median</i>	3.525 (0.982–12.657)		2.954 (0.610–14.300)	
<i>Above median</i>				
<b>Dieldrine</b>	1.00 (ref)	0.05	1.00 (ref)	0.64
<i>Below median</i>	3.794 (1.008–14.284)		1.462 (0.290–7.369)	
<i>Above median</i>				
<b>Cis heptachlorepoxide</b>	1.00 (ref)	0.05	1.00 (ref)	0.30
<i>Below median</i>	3.375 (1.075–13.255)		2.216 (0.485–10.119)	
<i>Above median</i>				
<b>p, p'-DDT</b>	1.00 (ref)	0.88	1.00 (ref)	0.39
<i>Below median</i>	1.112 (0.343–3.610)		1.995 (0.415–9.595)	
<i>Above median</i>				
<b>Cis-nonachlor</b>	1.00 (ref)	0.81	1.00 (ref)	0.89
<i>Below median</i>	1.154 (0.361–3.687)	0.27	1.108 (0.255–4.803)	0.52
<i>Above median</i>	1.00 (ref)		1.00 (ref)	
<b>PeCB</b>	1.933 (0.598–6.249)		01.611 (0.376–6.902)	
<i>Below median</i>				
<i>Above median</i>				
<b>p, p'-DDD</b>	1.00 (ref)	0.23	1.00 (ref)	0.45
<i>Below median</i>	0.481 (0.146–1.591)		0.552 (0.119–2.560)	
<i>Above median</i>				
<b>Chlordecone</b>	1.00 (ref)	0.18	1.00 (ref)	0.86
<i>Below median</i>	0.446 (0.134–1.484)		0.875 (0.180–4.244)	
<i>Above median</i>				

## 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.

**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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