Review

Why pesticides could be a common cause of prostate and breast cancers in the French Caribbean Island, Martinique. An overview on key mechanisms of pesticide-induced cancer

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Abstract

Prostate and breast cancers have become very frequent in Martinique. We previously conducted a multifactorial analysis in the French Caribbean Island, Martinique, in order to elucidate the aetiology of prostate cancer. Using a linear regression analysis, we found that the growth curves of incidence rates for Martinique and metropolitan France have been significantly diverging since 1983. Although a Caribbean genetic susceptibility factor may be involved in prostate carcinogenesis: this factor, because it could not have changed during the observation period, cannot per se account for the growing incidence of this cancer in the island. We therefore suggested that among possible environmental factors, the intensive and prolonged exposure to Carcinogenic, Mutagenic and/or Reprotoxic (CMR) or presumed CMR pesticides may account for the observed growing incidence of prostate cancer and thus may be involved in prostate carcinogenesis.

In this study, we further attempt to show that due to their carcinogenic properties, pesticides and especially organochlorine pesticides may in fact be causally implicated in the growing incidence of prostate cancer in Martinique. Also, we suggest that CMR or presumed CMR pesticides may be causally involved in the growing incidence of breast cancer through a common endocrine disruption mechanism.

We therefore propose that protective medical recommendations should be immediately set up and carried out by general practitioners, paediatricians, obstetricians, gynaecologists and urologists; and that public health measures of primary precaution and prevention should be urgently taken in close collaboration with health professionals in order to protect population, more especially pregnant women and children, with the final objective perhaps that these medical recommendations and public health measures will stop Martinique’s cancer epidemic.

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Keywords: Endocrine disruptors; Prostate cancer; Breast cancer; Cancer; Carcinogenesis; Pesticides; Foetus-susceptibility; Obesity; Low dose

Abbreviations: AMREC, association martiniquaise de recherche et d’épidémiologie sur le cancer; ARs, androgenic receptors; BPA, bisphenol A; CMR, carcinogenic mutagenic and/or reprotoxic; CYP450, cytochrome P450; DDE, 1,1-dichloro-2,2’-bis-p-chlorophenyl-ethylene; DDT, dichloro-diphenyl-trichloro-ethane; DHT, dihydrotestosterone; ERs, estrogen receptors; GJIC, gap junctional intercellular communication; HCB, hexachlorobenzene; HCH, hexachlorohexane; IARC, international agency for research on cancer; InVS, institut national de veille sanitaire; PCBs, polychlorobiphenyls; PIN, precancerous prostate intraneoplastic.

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1. Introduction

Using a linear regression analysis, we have found that the growth curves of prostate cancer incidence rates for Martinique and metropolitan France have been significantly diverging since 1983 [1]. Because these curves are not parallel, this suggests that although a Caribbean genetic susceptibility factor may be involved in prostate carcinogenesis, this factor, because it could not have changed during the observation period — the duration of this period is too short for effective genetic change associated with gene segregation -, cannot per se account for the observed growing incidence of prostate cancer in the island.

Estimation of the total amount of pesticides brought to the island and mapping analysis of soil pollution showed that water contamination originates from banana plantations and that people were permanently contaminated since 1955 by huge quantities of pesticides. Indeed, our analysis in 1972 revealed that all subjects investigated for the presence of pesticides in their adipose tissue have been contaminated by extremely high levels of organochlorine pesticides such as dichloro-diphenyl-trichloroethylene (DDE), 1,1-dichloro-2,2-ethylene (DDE), 1,1-dichloro-2,2-bis-p-chlorophenyl-ethyene (DDE), \( \gamma \) and \( \beta \) and several of them by \( \gamma \) Hexachlorohexane (HCH), and aldrin and dieldrin.

We therefore have suggested that environmental factors such as the intensive and prolonged exposure to Carcinogenic, Mutagenic and/or Reprotoxic (CMR) or presumed CMR pesticides may account for the observed growing incidence of prostate cancer and thus may be involved in prostate carcinogenesis.

In the present paper, we further attempt to show that due to their carcinogenic properties, pesticides and especially organochlorine pesticides may in fact be causally implicated in the growing incidence of prostate cancer in Martinique. Also, we suggest that these pesticides may be implicated in the growing incidence of breast cancer, since rise of incidence of breast and prostate cancers occurred approximately at a similar time and pesticides used in the island have been experimentally shown to cause both cancer types through common endocrine disrupting mechanisms. We therefore propose that public health measures of primary precaution and prevention should be immediately taken in order to protect population from pesticide exposure.

2. Demographic figures and epidemiological data

Martinique is one of the two main tropical islands in the French West Indies. Its relative geographical isolation, its limited land surface (1080 km\(^2\)), the low number of inhabitants (393,000), a presumably similar health care system and medical practice as in metropolitan France, the availability of a cancer registry using internationally-recognized standardized procedures and the possibility of estimating environment- and/or lifestyle-related factors and their time-related modifications; all these factors help to explain why Martinique constitutes a particularly relevant model for the investigation of environmental cancer-causing agents in humans.

As in our previous multidisciplinary life course study aiming to determine factors involved in prostate carcinogenesis [1], we used data from official institutional documents, scientific publications and specific investigations. For drawing epidemiological curves, we used data from the Institut National de Veille Sanitaire (InVS), the French institute of sanitary control. For histograms of age-related cancer incidence rates in Martinique, we used data from the Martinican cancer registry of the association Martiniquaise de recherche et d’épidémiologie sur le cancer (AMREC). Statistical analyses were done as previously described [1].

As indicated in Table 1, in 2002, the standardized incidence rate of prostate cancer reaches a value twice metropolitan France. Albeit it is less frequent than in metropolitan France (see Table 1), breast cancer is also clearly associated with increasing rates of incidence. Figs. 1 and 2 show that since 1985 (1983–1987) and 1990 (1988–1992), incidence rates are growing for prostate and breast cancer respectively, while during the subsequent period, despite the fact that therapeutic progresses have been made, mortality did not tend to decrease. This may be due to a younger age at diagnosis and increasing disease aggressivity as it is suggested for metropolitan France from studies showing a continuous higher relative risk increase of prostate and breast cancers in more recent birth cohorts [2]. For prostate cancer, median age of patients ranges a similar value in Martinique and metropolitan France, because of a large excess of prostate cancer cases after the age of 85 in Martinique (see Fig. 3), while for all younger age categories, prostate cancer rates are higher in Martinique than in metropolitan France. This is in contrast to breast cancer, since in Martinique, at the exception of categories before the age of 39, incidence rates are much lower than in metropolitan France (see Fig. 4). This relative discrepancy for cancer rates in younger age categories between prostate and breast cancers in Martinique may be due for prostate cancer, to a higher genetic susceptibility of martinicans to their environment, and for breast cancer to a lower genetic susceptibility to this environment, as compared to the genetic susceptibility of

Table 1

<table>
<thead>
<tr>
<th>Region</th>
<th>Prostate cancer incidence( \text{a} )</th>
<th>Breast cancer incidence( \text{a} )</th>
<th>Life expectancy at birth (males)( \text{b} )</th>
<th>Life expectancy at birth (females)( \text{b} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metropolitan France</td>
<td>75.3 91.9</td>
<td>77 82.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metropolitan departments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bas-Rhin</td>
<td>69.34 70.73 75 81.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calvados</td>
<td>72.12 71.48 74.5 82.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doubs</td>
<td>47.53 67.36 75.6 82.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isère</td>
<td>70.70 80.57 76.3 83.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somme</td>
<td>52.26 74.82 73.3 81.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tarn</td>
<td>80.77 66.05 76.4 83</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( \text{a} \) World standardized rates per 100,000; data source was obtained from Globocan 2002 [140].

\( \text{b} \) Data source was obtained from Score santé [141] (year 1999).
metropolitan populations to their environment. That genetic susceptibility to the environment is lower in Martinique than in metropolitan France for breast cancer is a further argument suggesting that genetic susceptibility cannot explain why incidence rates are increasing for both cancers in Martinique. Also, the demographic figures and especially the persisting high mortality rates associated with both cancers strongly suggest that albeit improvement in diagnosis methods and screening tests may lead to treat more efficiently earlier detected cancer cases, this improvement cannot account for the growing incidence of both of these cancer types since the detected cases included in the AMREC registry are documented as true invasive cases. Moreover, since diagnosis methods and screening tests were carried out approximately at the same time period in Martinique and in metropolitan France, the higher growing incidence of prostate cancer (see Fig. 5) and of breast cancer (data not shown) in Martinique as compared to metropolitan France cannot be explained by the use of these methods and tests. Furthermore, given that the growing incidence of prostate and breast cancers started approximately at a similar time (see Figs. 1 and 2), i.e. between 1985 and 1990, this suggests that genesis and development of both cancer types may be causally related to common aetiological factors. These observations therefore bring about a further argument suggesting that the recent drastic rise in incidence of prostate and breast cancers in Martinique may correspond to a genuine public health plague.

As indicated in Fig. 5, using a linear regression analysis, we have shown that the growth curve of prostate cancer incidence rates during the period 1983–2002 significantly differs from the one observed in metropolitan France, as determined from the 11 official metropolitan departmental registries used as reference, and that the latter curve fits in perfectly with the extrapolated curve for overall metropolitan France. Since the growth curve of prostate cancer incidence rates in Martinique has been significantly diverging from the one in metropolitan France, on the basis that gene segregation in one generation cannot account for change in genetic susceptibility to cancer, we therefore proposed that non genetic, i.e. environmental factors may be involved to account for the higher growing
incidence of prostate cancer in Martinique compared to metropolitan France [1]. In addition, given that rise in incidence for breast cancer occurred at approximately a similar time as for prostate cancer, we hypothesized that common environmental factors might be involved in breast and prostate carcinogenesis. Consequently, this prompted us to search for exogenous cancer-causing agents which may account for the growing incidence both of prostate and breast cancers in Martinique, and thus for a common biological pathway that may contribute to generate both cancer types.

3. Martinique’s pesticide exposure

During the last five decades, the soil and fresh water in Martinique as well as local agricultural food were highly and continuously contaminated by large amounts of numerous persisting organic pesticides, such as organochlorines [3,4]. Indeed, using a first desorption kinetics-based leaching model, it has been recently estimated that andosol pollution by chlordecone, a CMR organochlorine pesticide, may last half a millennium [5]. Fig. 6 shows the estimated total amount of pesticides (in tons) which has been brought to Martinique since 1955. Initially, most insecticides and nematicides used in banana plantations were organochlorines. In the 1960s, the main compounds were hexachlorobenzene (HCB), which is structurally a cyclic form of HCH; technical DDT; technical HCH and its γ isomere, lindane; chlordanes such as heptachlor and one of its major metabolite, oxychlordane; aldrin and its metabolite dieldrin and endrin. During the 1970s, following DDT, toxaphene was massively used as well as chlorecone, a CMR organochlorine pesticide, may last half a millennium [5]. Fig. 6 shows the estimated total amount of pesticides (in tons) which has been brought to Martinique since 1955. Initially, most insecticides and nematicides used in banana plantations were organochlorines. In the 1960s, the main compounds were hexachlorobenzene (HCB), which is structurally a cyclic form of HCH; technical DDT; technical HCH and its γ isomere, lindane; chlordanes such as heptachlor and one of its major metabolite, oxychlordane; aldrin and its metabolite dieldrin and endrin. During the 1970s, following DDT, toxaphene was massively used as well as chlorecone, a CMR organochlorine pesticide, may last half a millennium [5].

Fig. 5. Evolution of the incidence rates of prostate cancer in Martinique in comparison with the ones for 11 metropolitan departmental registries and with the ones extrapolated for overall metropolitan France. Although the best modelisation was found to fit exponential growth equations, we evaluated the divergence of the different incidence growth curves, by using rights instead of exponentials. Values of $R^2$ were 0.9675 for Martinique, 0.9391 for the 11 metropolitan departmental registries and 0.9641 for overall metropolitan France [1].

Pesticides were replaced in the 1990s by a second generation of apparently less toxic organophosphorous pesticides. In addition, the main herbicides used until recently or still now used are triazines such as simazine, diuron and the quaternary ammoniums, paraquat, diquat and glycophosat. Table 2 shows among many different pesticides, some of the CMR or presumed CMR pesticides marketed since 1933 in metropolitan France and progressively used since 1955 in Martinique mainly for the culture of bananas. Table 3 indicates the concentrations of several organochlorinated CMR pesticides that we have measured in 1972 in the adipose tissue of 34 martinicans operated for benign diseases. An important finding in our study is that all subjects tested, whatever their place of residence in the island, were contaminated by extremely high doses of these organochlorine pesticides [6]. As indicated in Table 3, high mean values of DDT and DDE have been detected in all subjects tested with extreme values up to 9 mg/kg bw of DDT and 16 mg/kg bw of DDE in adults and 8 mg/kg bw of DDT and 7 mg/kg bw of DDE in children aged between 11 and 16 years. Likewise, the three isomers of HCH have been detected in all subjects tested, but at relatively weaker concentrations, with extreme values up to 0.6 mg/kg bw for αHCH, 2 mg/kg bw for βHCH and 0.2 mg/kg bw for lindane (γHCH) in adults and up to 0.3 mg/kg bw for αHCH and 0.6 mg/kg bw for βHCH in children.

4. Search for correlation between pesticide exposure and increasing risk of prostate and breast cancers

All pesticides reported in Table 2 are CMR or presumed CMR substances and, at the exception of simazine, aldrin and dieldrin, and endrin (rated Group 3) and endosulfan (not classified), have been rated as possibly carcinogenic (Group 2B) by the International Agency for Research on Cancer (IARC). All of them have been however directly or indirectly implicated in prostate and/or breast carcinogenesis. Indeed, many but not all epidemiological studies have shown that chronic exposure to these pesticides or to cocktails of them is associated with a significant increase in prostate and/or breast cancer risk.

Several case-control studies have reported that exposure to pesticides and more especially to organochlorine pesticides is
associated with an increased risk of human prostate cancer [7–13]. In particular, a large epidemiological agricultural health study in the USA thanks to a collaboration between the National Cancer Institute, the National Institute of Environmental Health Sciences and the Environmental Protection Agency revealed a direct associative link between exposure to the fungicide methyl-bromide and increased prostate cancer risk [14,15]. Likewise, exposure to chlopyrifos, fonofos, coumaphos, phorate, permethrin and butylate [9,16] has been correlated with an increased prostate cancer risk in men with familial history of prostate cancer, and a suspected action mechanism for chlopyrifos, fonofos, and phorate has been proposed suggesting that they may strongly inhibit CYP1A2 and CYP3A4 cytochrome P450 (CYP) monooxydases, which normally inactivate estradiol, estrone and testosterone [17]. As a consequence of enzymatic inhibition, increase in endogenous natural estrogens and androgens may thus occur. Albeit it is possible, it is not clear whether these pesticides were used in Martinique. However, among pesticides which were certainly intensively used in Martinique (See Table 2), DDT and its metabolite derivative p,p’-DDE [9,18], lindane [19], HCB [20], aldrin and dieldrin [9], chlordanes [9] such as heptachlor [9,19] and oxychlordane [8,20], and simazine [19] have been associated with significantly increased risk of prostate cancer in case-control studies and/or have been detected at significantly higher concentrations in the blood and/or the adipose tissue of prostate cancer patients. Moreover as previously indicated, risk increase of pesticide-associated prostate cancer has been mostly observed in subjects with family history of prostate cancer, meaning that pesticide exposure may increase prostate cancer risk especially in genetically susceptible subjects [9].

Likewise, although not all epidemiological studies were positive [21–24], breast cancer risk has been also associated with the same types of pesticides as those used since 1955 in Martinique (see Table 2). Indeed, it has been shown that pesticides contamination by DDT can induce both early puberty, which is recognized as a breast cancer risk factor [25] and breast cancer increase risk [26]. Also pesticides of the triazine group (to which simazine belongs) and of the chlor dane family have been proved to induce mammary tumors in animals [27], and case-control studies have shown an increased breast cancer risk associated with exposure to toxaphene [28] or pesticides such as those of the triazine group [29]. Also, an increased risk of breast cancer has been found to be associated with exposure to mixture of pesticides, but

<table>
<thead>
<tr>
<th>Table 2</th>
<th>CMR and presumed CMR pesticides used intensively since 1955 in Martinique.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>On the market</td>
</tr>
<tr>
<td>HCB</td>
<td>1933</td>
</tr>
<tr>
<td>Technical DDT\textsuperscript{a}</td>
<td>1939</td>
</tr>
<tr>
<td>Technical HCH\textsuperscript{b}</td>
<td>1940\textsuperscript{c}</td>
</tr>
<tr>
<td>Lindane</td>
<td>1940\textsuperscript{c}</td>
</tr>
<tr>
<td>Toxaphene</td>
<td>1945</td>
</tr>
<tr>
<td>Aldrin/dieldrin</td>
<td>1950\textsuperscript{c}</td>
</tr>
<tr>
<td>Endosulfan</td>
<td>1954\textsuperscript{d}</td>
</tr>
<tr>
<td>Endrin\textsuperscript{d}</td>
<td>1960\textsuperscript{d}</td>
</tr>
<tr>
<td>Chlordanes\textsuperscript{e}</td>
<td>1960\textsuperscript{e}</td>
</tr>
<tr>
<td>Perchlordecone (mirex)\textsuperscript{f}</td>
<td>1977\textsuperscript{g}</td>
</tr>
<tr>
<td>Simazine\textsuperscript{g}</td>
<td>1991\textsuperscript{h}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Technical DDT is a mixture of the isomers p,p’-DDT (85%), o,p’-DDT (15%) and o,o’-DDT (<1%).
\textsuperscript{b} Technical HCH is a mixture of the isomers α, β and γ.
\textsuperscript{c} Official data not available.
\textsuperscript{d} Endrin is a dieldrin stereoisomer.
\textsuperscript{e} Chlordanes include trans-chlordane, cis-chlordane, trans-nonachlor, cis-nonachlor and heptachlor.
\textsuperscript{f} To our knowledge, mirex was not used intensively in Martinique, but in Guadeloupe.
\textsuperscript{g} Simazine, a non organochlorinated molecule, is associated with an increased risk of prostate cancer [19].
\textsuperscript{h} Not classified.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Mean concentrations and extremes values of organochlorinated pesticides dosed in the adipose tissue of normal subjects in 1972 in Martinique.\textsuperscript{a,b}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DDT</td>
</tr>
<tr>
<td>16–68 years</td>
<td></td>
</tr>
<tr>
<td>(28)</td>
<td>2.5</td>
</tr>
<tr>
<td>(0.7–9)</td>
<td>(0.3–16)</td>
</tr>
<tr>
<td>11–16 years</td>
<td></td>
</tr>
<tr>
<td>(6)</td>
<td>1.1</td>
</tr>
<tr>
<td>(0.8–8)</td>
<td>(1.4–7)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Values are expressed in mg/kg of lipids extracted from adipose tissue.
\textsuperscript{b} Detection of aldrin and dieldrin was negative in most subjects but positive in several subjects where concentration mean values were between 0.05 and 0.08 mg/kg.
unfortunately case-control studies could not discriminate which pesticide is implicated [30–33]. However, following the pioneer works of Wassermann et al. [34] and Unger [35,36], pesticides such as those used in Martinique, i.e. DDT [37], p,p’-DDE [38–41], HCB [37,42], Lindane [43], βHCH [44], heptachlor [45], aldrin [43] and dieldrin [46,47] or cocktails of DDT, DDE and poly-chlorobiphenyls (PCBs) [48,49], have been clearly evidenced to be at significantly higher concentration in breast tumors or in the serum and/or the adipose tissue of breast cancer patients [40,50–52]. These data therefore strongly suggest that the aforementioned pesticides may be involved in breast carcinogenesis. In addition, it has been shown that the total effective xenoestrogen burden of mixture of 16 different organochlorine pesticides measured in the adipose tissue of breast cancer women is associated with an increased risk for breast cancer, especially in postmenopausal learner women [43]. Moreover, due to their estrogenic properties, organochlorine pesticides such as DDT and p,p’-DDE, HCB, Lindane, chlordanes, aldrin, dieldrin and endrin, endosulfan and toxaphene are thought to possibly induce human breast cancer through endocrine disruption [50,53–55].

Since due to their endocrine disrupting properties pesticides used in Martinique (see Table 2) have been experimentally shown to cause both prostate and breast cancer types, we hypothesize that these pesticides may account for the growing incidence of both prostate and breast cancers in the island through a common endocrine disruption mechanism.

5. Pesticides as carcinogens and endocrine disruption as a common causal mechanism of prostate and breast exogenous chemical carcinogenesis

Despite the fact that prostate and breast cancers are the most commonly diagnosed cancer in Western countries, their aetiology remains unclear. On the basis of epidemiological data, the most consistent risk factors for prostate cancer are advancing age, family history and ethnic origin [56,57]; while for breast cancer, in addition to advancing age and family history, the most consistent risk factors are radiation exposure after the age of 10, age-dependent hormonal status, such as age at puberty, age at menopause and age at first child, and hormone intake for oral contraception or postmenopausal hormone replacement therapy [58]. All these factors — other than aging, family history and radiation — are interpreted as resulting from estrogen impregnation. In addition, animal fat-rich diet and body weight gain are also suspected to be risk factors for postmenopausal breast cancer, but these risk factors are not evidenced for prostate cancer.

Indeed risk factors as determined through epidemiological studies may contribute to explain no more than 50% of breast cancer cases [59] and this is probably less for prostate cancer. Furthermore, risk factors are not necessarily cancer-causing agents, i.e. carcinogens or cocarcinogens directly involved in the carcinogenic process, but are most often factors indirectly associated with genetic susceptibility and/or exposure to cancer-causing agents. Because epidemiological studies cannot evidence a causal link between cancer-causing agents and cancer, and risk factors are most often not cancer-causing agents, epidemiological studies without the complementary help of toxicology and biology, may therefore lead to unsuspected biases and misinterpretations [60].

Carcinogenesis is indeed an extremely complex and longstanding biological process involving initiation, promotion and progression, which are three individualized steps that chronologically and sequentially contribute to cancer genesis and development through the interplay of a myriad of endogenous and exogenous causal factors [61]. Since prostate and breast cancers are two hormone-dependent cancers, the question is whether their apparently synchronous growing incidence in Martinique, instead of being interpreted as a consequence of the different progresses made in early detection and screening, may in fact be caused by a common set of causally-related factors. More precisely, the question is whether among the numerous man made environmental chemicals that have been brought in Martinique, pesticides, because of their estrogenic properties and carcinogenic potential, may in fact be common causal agents of prostate and breast cancers.

5.1. Pesticides as tumor promoters

Lifetime exposure to endogenous estrogens has been firstly established as a common risk factor for breast cancer in women [62] and for prostate cancer [63]. However, as previously outlined, the growing incidence of these cancers in more recent birth cohorts, i.e. in younger patients [2,64] strongly suggests that environmental xenoestrogens such as pesticides may also be involved. Some xenoestrogens may possess a 1000 times lower affinity for nuclear estrogen receptors (ERs) than estradiol [65], meaning that they could not efficiently combine with and activate or inhibit ERs. However activation or inhibition of ERs is an extremely complex ligand-structure-dependent phenomenon, which also depends on several other factors including cell tumor-specific expression of coactivator/coregulatory proteins, gene promoters and cell environment [66]. More precisely, mechanisms of estrogen activation involve ligand-induced dimerization of ERs, interactions with estrogen responsive elements in target gene promoters and transcriptional activation [67]. ERz and ERβ are two major ER subtypes that have been evidenced in estrogen-dependent tissues. Activation of ERz stimulates cell proliferation and is associated with cancer-causing effects through tumor promotion, whereas activation of ERβ stimulates terminal cell differentiation and may contribute to anti-cancer effects [68]. Many xenoestrogens, especially organochlorine pesticides have been shown to disrupt endocrine processes by acting as agonists on ERz and/or antagonists on ERβ [65] and also possibly as antagonists on androgenic receptors (ARs) [69,70]. Indeed, in addition to the induction of a more or less agonistic effects by interacting with ERz, many pesticides used in Martinique such as chlordane, endosulfan, aldrin, dieldrin and endrin have been shown to be associated with antagonistic effects by activating ERβ, meaning that agonistic effects involving ERz in addition
to antagonistic effects involving ERβ may strongly contribute to the tumor promoting effects of these pesticides [65]. As a result, among organochlorine pesticides used in Martinique, DDT [71–75], βHCH [75–77], lindane [78,79], HCB [80], aldrin and dieldrin [73,78,81] and chlordane [79,81–83], have been shown to possess estrogenic properties in vivo in the uterotrophic assay and/or in vitro, and therefore are tumor promoters. These properties are thought to occur in humans since estrogen-dependent human tissues contain both ERα and ERβ. Note that chlordane, which was used extensively between 1970 and 1993 and caused severe and persistent contamination of soil, water, and food in the French West Indies [5] is as potent as the endogenous estrogen 17βestradiol in the uterotrophic assay and is a stronger in vitro estrogenic agonist for ERα relatively to other pesticides [82,83].

In addition, several of the aforementioned pesticides used in Martinique or their metabolites have been shown to exhibit antiandrogenic effects by binding to ARs and competing with endogenous androgens, a property that reinforce their estrogenic effect. This is particularly true for p,p'-DDE [84–87], HCH [87], dieldrin [88] and chlordane [84,87]. Until recently, endocrine disruption involving interferences with synthesis, metabolism, transport and clearance of steroid hormones have received little attention in comparison with steroid receptor interactions, although many pesticides may also disrupt endocrine processes by modifying the activity of key enzymes involved in steroid synthesis and metabolism [89].

Because prostate and breast tissues and also adipose tissue are equipped with many key enzymes of steroid metabolism, and particularly with the CYP19 α- aromatase that converts testosterone to 17βestradiol and androstenedione to estrone, we propose that as a consequence of α- aromatase induction [90], pesticides which stimulate α- aromatase such as those used in Martinique, more precisely p,p'-DDE [91], chlordanes, aldrin and dieldrin [92], toxaphene [93] and atrazine [89,92] may also indirectly contribute to prostate and breast cancer promotion by increasing concentration of endogenous natural estrogens in peripheral tissues as well as in the intratumoral milieu.

For breast cancer, a basic observation is that due to their agonistic effect on ERα, natural estrogens stimulate the growth of hormone-dependent target tissues — mainly the mammary gland and the endometrium and therefore are endogenous tumor promoters. However, on the basis of the aforementioned data, pesticides may also act as exogenous tumor promoters not only through direct and/or indirect promoting effect on ERα- and ERβ-containing tissues but also by activating α- aromatase.

A similar but more complex picture deals with the tumor promotion effects of estrogens in prostate carcinogenesis. An intriguing question is how xenoestrogens such as pesticides could enhance prostate carcinogenesis. Because the normal development of the prostate gland depends on the production and recognition of androgens — particularly of the active metabolite of testosterone, dihydrotestosterone (DHT)—, and prostate cancer retains a dependence on the androgen pathway [94], it is indeed widely accepted that androgens are prostate cancer promoters. However the concept that neither androgens nor estrogens have a sexual specificity has been developed [95], leading to recognize that prostate tissue can express in addition to ARs, both ERα and ERβ as breast tissue [96]. And because of this finding it has been hypothesized that estrogens may also be involved in prostate carcinogenesis as tumor promoters. Indeed, a major observation based on rat experiments is that, when estradiol is added to testosterone [97], prostate cancer incidence markedly increases [98]. A basic finding which could account for this experimental data may relate to the high complexity of the steroid-induced AR-ERβ-Erc complex that triggers prostate cancer cell proliferation [99]. Also, it has been shown in vitro that p,p'-DDE at high concentrations could function as an inhibitor of 5α-reductase, an intraprostatic enzyme that converts testosterone to DHT [100]. However because it cannot be aromatized to estrogen, DHT hardly induces prostate cancer, suggesting that in addition to androgens, estrogens may play locally a major critical role in prostate carcinogenesis [101]. On the basis of these findings, it has been thus proposed that estrogens could create an appropriate estrogenic intraprostatic milieu capable of promoting prostate cancer genesis by inducing transition of precancerous prostate intraneoplastic (PIN) lesions into prostate carcinoma [102].

Consequently, several hypothetic models have been so far proposed, based on the presumed complementary role both of endogenous androgens and estrogens in prostate carcinogenesis [63,98,103]. However, these are purely endogenous-cause models, and because our previous study in Martinique clearly revealed that environmental factors may play a critical role in prostate carcinogenesis [1], we strongly suggest that xenocchemicals such as organochlorine pesticides may also causally contribute to prostate cancer genesis, as is suggested for breast cancer.

5.2. Pesticides as tumor initiators

In addition to tumor promotion-induced endocrine disruption mechanisms, pesticides may be directly or indirectly mutagenic through free radical production [45] and may cause both tumor initiation and subsequent tumor promotion by inhibiting Gap junctional intercellular communication (GJIC) [104]. Inhibition of GJIC has clearly been shown in normal epithelial breast tissue exposed to relatively high concentrations of organochlorine pesticides such as those used in Martinique. Indeed DDT, dieldrin, toxaphene or mixtures of one of these pesticides with HCB [104] have been shown to inhibit GJIC and therefore may contribute to carcinogenesis through this mechanism. Indeed, during tumor initiation, blockage of GJIC between normal and neoplastic cells consequently create an appropriate intratissue microenvironment leading initiated cells to escape growth control from normal surrounding cells and therefore indirectly contribute to tumor promotion [105,106]. This may also be the case for several non organochlorine pesticides more recently used in Martinique, such as the quinonoid herbicide Paraquat [107], which has been proved to block GJIC in mouse hepatocytes.
6. Carcinogenic low-dose effects of chronic exposure to pesticides. Adipose tissue as a reservoir for lipophilic organic pesticides

Contrary to some unfounded claims [132], cancer is a disease that may basically be caused by chronic exposure to low-dose chemical carcinogens [110,133]. Indeed as for ionizing radiation, there is no clearly demonstrated threshold for chemical mutagens. This may also apply to both endogenous and exogenous tumor promoters, since as for endogenous natural hormones, tumor promotion caused by endocrine disrupting chemicals may also depend on the sensitivity of receptors. Indeed, as for endogenous hormones, there is a non-monotonic U or inverted U-shape dose—response relationship, indicating a lack of threshold-dependant dose effect for endocrine disruptors [125,134]. Accordingly, pesticides, be they mutagens or tumor promoters, can in fact be carcinogenic at doses lower than those at which no effect level is observed in classical rodent tests [133]. Moreover, since many environmental organic pollutants, such as organochlorine pesticides are lipophilic molecules which bioaccumulate in the adipose tissue as we have shown, this tissue may function as a transit reservoir for organic pollutants [133,135]. As previously indicated, following perinatal exposure, and/or adulthood exposure, pesticides such as DDT and DDE [128] or HCB [129] has been shown to increase the risk of overweight/obesity during childhood or at puberty. In addition to carcinogenic endocrine disrupting properties, DDT, DDE and HCB [129] (as we have demonstrated for benzo[a]pyrene [136]) can increase the adipose tissue mass, thus indirectly contributing to carcinogenesis by increasing the capacity of this tissue to bioaccumulate other carcinogenic pollutants [135]. Moreover, following bioaccumulation in adipose tissue, pesticides can be steadily released in the organism at doses which do not correspond to those found in the environment [134,135] and thus may be carcinogenic at environmental extremely low doses. Moreover, occurrence of fasting episodes or pregnancy stimulates release of organic pollutants from the adipose tissue to the blood circulation [134,135], and this phenomenon may explain why breast cancer risk may increase in postmenopausal learner women [43] and why due to foetal contamination during pregnancy, cancer initiation, as showed in animal models [122] might occur in utero.

Low-dose carcinogenesis is indeed clearly evidenced for the foetus, for which interactions between exogenous chemicals and receptors (be they hormonal receptors or enzymes) can trigger biological response at extremely low-dose of chemicals [137]. This may especially account for the extreme susceptibility of foetus to many xenochemicals. Moreover, according to the

[105,108] and thus possibly contribute to carcinogenesis through this mechanism.

In addition to non-endocrine tumor initiation-associated mechanisms involving mature tissues, pesticide-induced tumor initiation may also concern foetal and/or neonatal tissues. The different window susceptibility periods of the organism to endocrine disruptors and especially the specific vulnerability of foetus and children to endocrine disruption shall be discussed [109]. It has been fully established in animal models that gestational exposure of normal foetal prostate tissues to low-dose xenoestrogens [110—112] or postnatally exposure of normal newborn prostate tissues to higher dose xenoestrogens [113], — a process referred in both cases as “estrogen imprinting” — may increase susceptibility to carcinogenesis [114,115], cause permanent alterations of prostate development [116] and result in precancerous PIN lesions and genesis of prostate or breast adulthood cancers [113,117,118]. Likewise, in several animal models [119] it has been shown that following perinatal exposure to xenoestrogens, estrogen sensitivity of the mammary gland increases, and that following gestational or neonatal exposure to low dose or higher dose xenoestrogens respectively, preneoplastic lesions and mammary tumors occur [120,121], meaning that due to estrogenic imprinting, initiation of breast cancer may started in the womb [122], as it may also be the case for prostate cancer. Estrogenic imprinting has been clearly evidenced in animal models not only for estradiol but also for synthetic xenoestrogens such as diethylstilbestrol [110,123] and bisphenol A (BPA) [118,124,125] and also for pesticides such as DDT and DDE following in utero exposure [126]. In humans, it has been confirmed that the prenatal period constitutes an important window of vulnerability not only for cancer but also for obesity [127]. Prenatal exposure to several organochlorine pesticides such as DDT and DDE [128] or HCB [129] has been shown to increase the risk of overweight/obesity during childhood or at puberty. In addition to carcinogenic endocrine disrupting properties, DDT, DDE and HCB might therefore be also indirectly carcinogenic through adipose tissue mass increase, see section 6. Furthermore, a retrospective analysis of sera coming from females exposed early in life to p,p'-DDT revealed that high levels of p,p'-DDT before the age of 14 can predict a statistically significant 5-fold increased risk of adulthood breast cancer [26]. These data which suggest a tumor initiating effect of pesticides early in life of women with breast cancer may also apply for prostate cancer, since animal experiments showed that exposure to pesticides in the very early period of life can initiate prostate cancer as well. In Martinique, the median age of patients at which prostate and breast cancers are diagnosed is between 65—70 and 50—54 years respectively (see Figs. 3 and 4). If we extrapolate the animal data to humans, the mean time scale of human prostate and breast carcinogenesis would span approximately 65—70 and 50—54 years respectively before clinical occurrence.

Given that pesticide use started in 1955 in Martinique, our hypothesis is that for prostate cancer, pesticide exposure may have mostly contributed to promotion rather than initiation; while for breast cancer due to a shorter latency period, it might have contributed to both initiation and promotion. For prostate cancer, our hypothesis is further supported by previous pathological observations of frequent preneoplastic lesions in Asiatic people suggesting that exogenous promotion may account for the higher prostate cancer incidence rates in the American people living in the US in comparison with the low prostate cancer incidence rates in Asiatic people living in their countries [130] and for the subsequent rise of prostate cancer incidence in first generation Asiatic people having migrated in the US [131].
classical concept of carcinogenesis, duration of exposure rather than dose intensity alone must be considered, i.e. the longer the exposure period to carcinogens is, the greater probability of mutations and hence of cancer genesis [138].

These biological considerations therefore led us to conceive that in Martinique chronic exposure to environmental cocktails of low-dose potentially carcinogenic pesticides may have been and continue to be a major contributing cause of cancer.

7. Arguments for a causal relationship between pesticide exposure and the growing incidence of prostate and breast cancers in Martinique. Compliance to Bradford Hill criteria

The causal implication of pesticides used since 1955 in Martinique in prostate and breast cancer genesis is based on the following arguments:

1. In our previous ecological study, we showed that the growing incidence of prostate cancer in Martinique cannot be explained by genetic (ethnographic) factors, but instead may be caused by environmental factors.
2. Many pesticides used in Martinique since 1955 are CMR or presumed CMR molecules, which at the exception of simazine, aldrin and dieldrin, and endrin have been rated as possible carcinogens (group 2B) by IARC.
3. Despite the fact that some case-control studies were negative, many pesticides or cocktails of pesticides such as those used in Martinique have been shown to be associated with an excess of prostate and/or breast cancer risk in careful epidemiological studies. This is particularly true for studies having correlated cancer risk with levels of pesticides in tumor, blood and/or adipose tissue.
4. Although exposure to carcinogenic endocrine disrupters such as PCBs, BPA and other marketed man-made chemicals, might be involved both in prostate and breast carcinogenesis, there is clearly no reason to believe that at the difference of pesticides, the use of other imported xenochemicals have quantitatively differed from metropolitan France. We however cannot exclude a role for PCBs, BPA and other marketed man-made chemicals since additional exposure to pesticides may produce cocktail effects.
5. In Martinique, we observed a temporal relationship between the intensive use of pesticides and the rise in incidence of prostate and breast cancers.
6. Experimentally low-dose environmental pollution by pesticides may cause cancer, since due to their lipophilicity, pesticides can enter cells and especially bioaccumulate in the adipose tissue from which they may be steadily released in the blood circulation at doses which do not correspond to those found in the environment and therefore may target peripheral tissue at adequate dose for carcinogenesis.
7. Martinique’s rise of incidence rates of prostate and of breast cancers approximately started approximately at the same time, i.e. between 1985 and 1990. In addition to or alternatively to progresses in cancer detection, this synchronous rise in incidence suggests a common etiological mechanism.
8. Both prostate and breast cancer are hormone-dependent tumors.
9. Experimentally all pesticides used in Martinique can cause prostate and breast cancers through a common endocrine disruption mechanism leading to tumor promotion. Moreover endocrine disrupters such as pesticides may also cause tumor initiation through direct or indirect mutagenesis, especially through foetal and/or neonatal hormonal imprinting and/or tissue disorganization of prostate or mammary glands.
10. Since the use of pesticides started in 1955 in Martinique, the presently observed growing incidence of prostate cancer may mostly be due to tumor promotion rather than tumor initiation, while for breast cancer, because the whole process of carcinogenesis may last a shorter time period, tumor promotion as well as tumor initiation may be involved.
11. As pesticide soil retention and consequently fresh water pollution will persist during a very long time, contamination of food and all living organisms may unfortunately continue. Given that carcinogenesis is a long latency process, cancers that are presently detected may result from environmental exposure that started probably several decades ago. Unfortunately, we therefore expect that the growing incidence of prostate and breast cancers will continue because of persisting environmental pollution of the island, and as much as the intensive use of CMR or presumed CMR pesticides is still not forbidden. That prostate and breast carcinogenesis definitely involve both pesticide-induced tumor initiation and tumor promotion suggests that in the future the process will progressively enhance.
12. Chlordecone, a CMR pesticide presently rated as 2B carcinogen by IARC is an extremely toxic endocrine disruptor, due to strong estrogenic and antiandrogenic properties. This presumably explains why despite its categorization as 2B carcinogen, chlordecone is thought to have higher carcinogenic potential relatively to other endocrine disruptors. In addition, because chlordecone has 12 chlorine atoms, and there is at present no means of soil remediation, andosol soil type pollution by chlordecone may unfortunately last half a millennium, meaning that contamination will concern at least 20 generations of Antilleans. Albeit there is at present no data showing a causal relationship between chlordecone exposure and human prostate and breast cancer genesis, we cannot exclude this possibility, even if future epidemiological case-control studies are negative. Since chlordecone use reached a maximum in 1980 and rise in incidence of prostate cancer started 5 years later, we believe that the estimated preclinical latency period is too short to implicate chlordecone in the presently observed growing incidence of prostate and breast cancers, although we cannot exclude that in addition to the earlier use of other pesticides, chlordecone may have already contributed to the genesis of a few cases through cocktail effects.
Our present hypothesis is based on the 12 aforementioned arguments that fit in perfectly with Bradford Hill criteria 1,2,3,4,5 and 9 for causation and partially with criteria 6,7 and 8 [139]. That is, our hypothesis fully met temporal sequence, experimental evidence, biological plausibility, reasoning by analogy, coherence with biological background and previous knowledge and analogy (1,2,3,4,5 and 9 respectively); while biological gradient, strength of association and specificity (criteria 6,7 and 8) are partially met.

8. Public health consequences

On the basis of our previous ecological study [1] and of this review on key mechanisms of pesticide-induced cancer, we strongly suggest that pesticides may be causally involved in the growing incidence of prostate and breast cancers in Martinique through a common carcinogenic endocrine disruption mechanism. Drastic public health measures of primary precaution and prevention should be therefore urgently taken in order to stop the cancer epidemic observed in Martinique and more generally in the French West Indies. Individual protection from pesticide exposure is compulsory, but unfortunately it may be insufficient because of persistent toxic pollution. However, since foetuses and children are extremely susceptible to pesticide exposure, drastic protection of pregnant women and children should be immediately set up and carried out, in order to avoid further occurrence of adulthood cancer as well as other pesticide-related diseases. To this end, mobilisation of general practitioners, gynaecologists, obstetricians, paediatricians and urologists is an urgent necessary step to set up and carry out a set of precautionary and preventive medical recommendations. Also, science-based public health measures should be urgently taken, in close collaboration with medical professionals. Drastic policy measures should also be urgently taken to suppress the use of all CMR or presumed CMR pesticides as islands are especially extremely vulnerable to any forms of chemical pollution, due to limited resources of fresh water and arable land. Consequently, pesticide pollution-caused diseases such as prostate and breast cancers may constitute a public health disaster on islands such as Martinique and of course elsewhere, until public health and policy measures are actually applied.

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