Prostate cancer as an environmental disease: An ecological study in the French Caribbean islands, Martinique and Guadeloupe

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Abstract. Using a transdisciplinary methodological approach we have conducted a multifactorial analysis in Martinique and Guadeloupe in order to elucidate the aetiology of prostate cancer. In 2002, world age standardized rates of prostate cancer were 152 new cases per 100,000 person-years in the two islands; one of the highest worldwide rates and much higher than those reported for other Caribbean islands and metropolitan France. 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. That these curves are not parallel suggests that although a Caribbean genetic susceptibility factor may be involved in carcinogenesis, this factor cannot *per se* account for the observed growing incidence. On the basis of mapping analysis of soil pollution, we further showed that water contamination by pesticides originates from banana plantations. Moreover, we have established retrospectively that general population subjects investigated in 1972 in Martinique for the presence of organochlorinated pesticides in their adipose tissue had been contaminated by extremely high levels of DDT, DDE, α, ß and γHCH, aldrin and dieldrin. Our study leads to the conclusion that the growing incidence of prostate cancer cannot be related either to a modification of ethnographic factors nor to a change in lifestyle and therefore suggests that environmental factors such as the intensive and prolonged exposure to carcinogenic, mutagenic and reproductive toxin pesticides may cause prostate cancer.

Introduction

In Western countries, prostate cancer is the most frequent non-cutaneous cancer and the second cause of cancer death in men. Each year, there are presently ~300,000 and 218,000 new cases, respectively in Europe and the USA (1,2). Although the recent use of screening detection in addition to therapeutic progress may have contributed to a decrease in mortality (3), this cancer is still responsible for the yearly death of ~68,000 men in Europe and of 30,000 men in the USA (1,2). In most countries, the mean age at diagnosis is 65-70 years and the late discovery of this cancer, often combined with a slow rate of progression results in most patients dying from other causes. Nevertheless, currently, 10 to 20% of prostate cancer patients still die of their cancer, regardless of treatment (2,4).

Although prostate cancer is now the most commonly diagnosed cancer in men in Western countries, its aetiology remains unclear. The most consistent risk factors are advancing age, family history and ethnic origin (5,6). However, risk factors are not necessarily cancer causing agents, i.e. agents directly involved in the carcinogenesis process, but are most often factors that contribute to genetic susceptibility and/or to exposure to carcinogens. Moreover, although environmental factors have not yet been clearly established (5,7), prostate cancer, as it is generally the case for any cancer, is believed to result from a multifactorial process involving both genetic and environmental components (8).

Prostate cancer has become very frequent in Martinique and Guadeloupe and these two places are presently regarded as having one of the highest world age standardized incidence rates (9,10). Martinique and Guadeloupe are two tropical islands in the French West Indies. Their relative geographical isolation, their limited land surface (1080 km^2 for Martinique and 1703 km^2 for Guadeloupe), the low number of inhabitants (393,000 for Martinique and 450,000 for Guadeloupe), a similar health care system and medical practice as in metropolitan France, the possibility of determining environment- and/or lifestyle-related factors and their time-related modifications; all these factors explain why Martinique and Guadeloupe constitutes a particularly relevant model for the investigation of prostate cancer causing agents.

Based on a transdisciplinary approach, our multifactorial study had three interdependent objectives: to evaluate the incidence rates of prostate cancer in Martinique and Guadeloupe, during the last 25 years and to compare their

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evolution with metropolitan France; analyze the geographical distribution of incidence rates, in order to determine whether local environment-related risk factors can be highlighted; and to carry out a retrospective analysis of the agricultural use of pesticides and of the resulting contamination of populations in order to determine whether pesticides may be involved in prostate carcinogenesis.

Materials and methods

Data collection. Data on which this study is based come from available official documents, scientific publications and specific investigations. For the determination of incidence rates, all prostate cancer cases diagnosed between 1995 and 2002 in Guadeloupe and between 1983 and 2002 in Martinique, i.e. 2104 cases and 4613 cases respectively have been included. For Martinique, we used data from the French Institute of Sanitary Control (Institut national de Veille Sanitaire, InVS). These data have been derived from the Martinique cancer registry held by AMREC, the Martinique Association for Epidemiological Research on Cancer (11). In the absence of a cancer registry for Guadeloupe, we considered data published by urologists of the University Hospital of Pointe-a-Pitre in Guadeloupe (9). Although the evolution of incidence rates for prostate cancer in Guadeloupe tends to be similar to the one in Martinique, we could not use published data from Guadeloupe for comparison, because these data were established without using the standardized procedures and criteria set up by the French National Cancer Registry (12). In addition, because all official data were not available, we were obliged to restrict our analysis to the period 1983-2002 for Martinique and to 1978-2002 for metropolitan France.

All incidence rates have been standardized to the world standard population of 1976. For comparison with metropolitan France, we used data from the French National Cancer Registry, which provides incidence rates from 11 metropolitan departmental registries. These registries are those from which the national extrapolated incidence rates of prostate cancer in metropolitan France are based on. For international comparison, we used incidence rates from the Globocan 2002 database of the International Agency for Research on Cancer (IARC) (13). Mapping of prostate cancer incidence rates according to case residence has been obtained from the cancer registry of AMREC for Martinique, whilst for Guadeloupe a similar investigation was carried out using data collected by the department of medical informatics of the University Hospital of Pointe-a-Pitre. Moreover, in order to correlate the localization of prostate cancer with that of banana plantations on the two islands, we used mapping as determined by the bureau of geological and mining resources (Bureau des resources géologiques et minières, BRGM) which is the leading French public institution for the sustainable management of natural resources and surface/subsurface risks. Also, in order to interprete the geographical distribution of prostate cancer incidence rates in Martinique, we analyzed specifically water supply conditions since 1944, using information available from the French Institute for Environment (Institut français de l'environnement, IFEN) and from the Regional Department for Environment (Direction Regionale de l'Environnement, DIREN), two French organisations involved in the control of environmental pollutants.

The amount, time trends and types of pesticides used in Martinique have been determined from official documents and published data (14) and by the means of a specific investigation conducted by one of us in 1972 (15). Concentrations of 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT), its metabolite, 1, 1-dichloro-2, 2-bis (p-chlorophenyl)-ethylene (DDE), α, ß and γ isomers of hexachlorocyclohexane (HCH), aldrin and dieldrin were measured in the adipose tissue of 36 subjects hospitalized for benign diseases in Martinique. There were 25 females and 11 males of whom, 28 were adults (20-68 years old) and 8 were children (11-16 years old). Mean age was 34 years. The 36 subjects tested were from all parts of the islands. Benign diseases included appendicitis, salpingitis, hernia, fractures and benign ovary or kidney cystis. Fat samples of 3 to 5 cm^3 were taken from the abdominal subcutaneous region and the intra-abdominal tissues of 17 and 19 subjects respectively. Samples were collected, under aseptic conditions stored in -20˚C and analyzed using high pressure gas chromatography.

Data processing and statistical analysis. We used a 3 step methodology. In the first step, we compared the evolution of prostate cancer incidence rates in Martinique with that of metropolitan France, based on data obtained from the 11 afore-mentioned metropolitan departmental registries. Hence, the overall incidence curve for Martinique was compared to the one extrapolated for overall metropolitan France.

Furthermore, in order to determine the best model fitting incidence growth curves, we checked for growth homogeneity for each of the 11 metropolitan departmental registries and for the registry of Martinique. For modelisation, we used a linear regression analysis and determined curve equations according to the best value obtained for the determination coefficient (R^2). For comparison, we used rights instead of exponential curves and calculated the slope of incidence growth curves for each registry.

Statistical analysis consisted in the calculation of the standard deviation, based on real values obtained from the 11 departmental registries, while for Martinique, real values were compared with their corresponding values in the curve.

In the second step, we searched for a possible geographical correlation between the distribution of standardized incidence ratios (SIR) of prostate cancer and the agricultural use of pesticides. Indeed, in Martinique and Guadeloupe the tropical climate, while being suitable for crop growth also favours pests. This situation results in the use of large amounts of numerous pesticides on banana plantations. We thus undertook a specific mapping analysis, comparing the soil pollution distribution by several pesticides including ßHCH and chlordecone, with the local distribution of prostate cancer incidence rates according to SIR. Since water is a vehicle for pesticides, we also examined precisely the water distribution in Martinique.

Finally, in the third step, using available data, we undertook a retrospective analysis of the amount and types of pesticides used in the two islands. We took into consideration, as chronological indicator, the results that we obtained in

Table I. Incidence of prostate cancer in 2002 in Caribbean, metropolitan France, Sweden, USA, Martinique and Guadeloupe.

Region	Prostate cancer incidence[a]	Life expectancy at birth (males)[b]
Caribbean		
Cuba	28.2	75
Haiti	38.1	53
Jamaica	42.4	70
Trinidad and Tobago	60.5	67
Bahamas	65.3	70
Dominican Republic	85.3	65
Barbados	99.7	71
Porto Rico	100.1	-
Metropolitan France	75.3	77
Metropolitan departments		
Bas-Rhin	69.34	75
Calvados	72.12	74.5
Doubs	47.53	75.6
Isère	70.70	76.3
Somme	52.26	73.3
Tarn	80.77	76.4
Sweden	90.9	79
USA	124.8	75
Martinique	152.7	75.3
Guadeloupe	152.3	74.3

[a]World standardized rates per 100,000; data source obtained from Globocan 2002 (13). [b]Data source obtained from Score santé (46) (year 1999) for Guadeloupe, Martinique and the other French departments and from WHO Statistical Information System (47) (year 2005) for the other Caribbean countries, Sweden and USA.

1972, which revealed the presence of pesticide residues in the adipose tissue of Martinicans.

Results

The growing incidence of prostate cancer

Comparison with metropolitan France and other countries. As indicated in Table I, the world age standardized incidence rate of prostate cancer in 2002 in Guadeloupe is similar to that obtained in Martinique: 152 per 100,000. The incidence rates for Martinique and Guadeloupe appear to be much higher than those reported by IARC for other Caribbean countries. Moreover, incidence rates in the two islands reached values twice the ones obtained from metropolitan France (152 vs. 75/100,000) and are much higher than the ones in Sweden, which has the highest incidence rate of prostate cancer in Europe (13). Prostate cancer incidence rates in the two French Carribean islands are even higher than the ones in the USA (all races included), but tends to be similar to incidence rates observed in black Americans living in the USA and in first generation black Caribbeans and black Africans living in the UK (16).

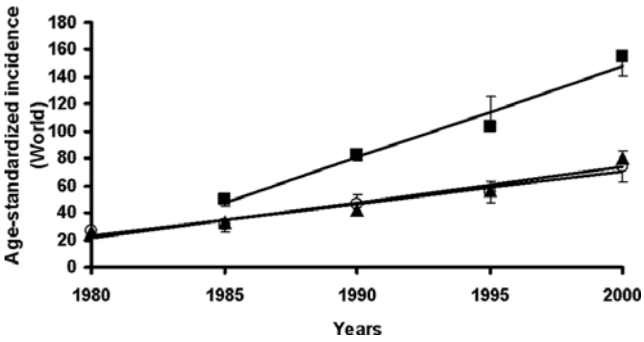

Figure 1. Evolution of the incidence rates of prostate cancer in Martinique ■ in comparison with the ones in 11 metropolitan departmental registries ○ and overall metropolitan France ▲. Although the best modelisation was found to fit exponential growth equations (see text), we evaluated the divergence of the different incidence growth curves, by using rights instead of exponentials. For rights, values of R^2 were 0.9675 for Martinique, 0.9391 for the 11 metropolitan departmental registries and 0.9641 for overall metropolitan France.

Fig. 1 indicates that the growth curve of prostate cancer incidence rates during the period 1983-2002, in Martinique differs significantly from the one observed in metropolitan France, as determined from the 11 metropolitan departmental registries. The latter curve fits in perfectly with the extrapolated curve for overall metropolitan France. We found that the rise in incidence might be at constantly increasing rates. Using a linear regression analysis, we found values of R^2 of 0.9779 for Martinique, of 0.9816 for the 11 metropolitan departmental registries and of 0.9928 for overall metropolitan France for the exponential model. However, although the best modelisation was found to fit exponential growth equations, we considered it more convenient to evaluate rights instead of exponentials to evaluate the divergence of the different incidence growth curves. In this case, growth equations in the simple form of $y=ax+b$ were $y=6.724x-4674.930$ for Martinique, $y=2.373x-4674.931$ for the 11 metropolitan French departments and $y=2,646x-5217.930$ for overall Metropolitan France. As indicated in Fig. 1, the slope of the growth curve of prostate cancer incidence rates in Martinique is significantly diverging since 1985 from the one in the 11 metropolitan French departments and from the one in overall metropolitan France. We found that the slope of the incidence growth curve for Martinique was 6.724 ± 0.871, whereas the mean slope of the incidence growth curve for the 11 metropolitan registries was only 2.373 ± 0.2648.

Geographical distribution of prostate cancer. Accurate mapping of prostate cancer incidence rates in Guadeloupe was unfortunately not possible owing to incomplete data. However, we observed that in Martinique although soil pollution by ßHCH and chlordecone are mostly situated in the North part of the island (Fig. 2A), paradoxally the highest incidence rates of prostate cancer were found to be localized in the South-Western part of the island (Fig. 2B). As indicated in Fig. 2C while the North and the South-East of Martinique

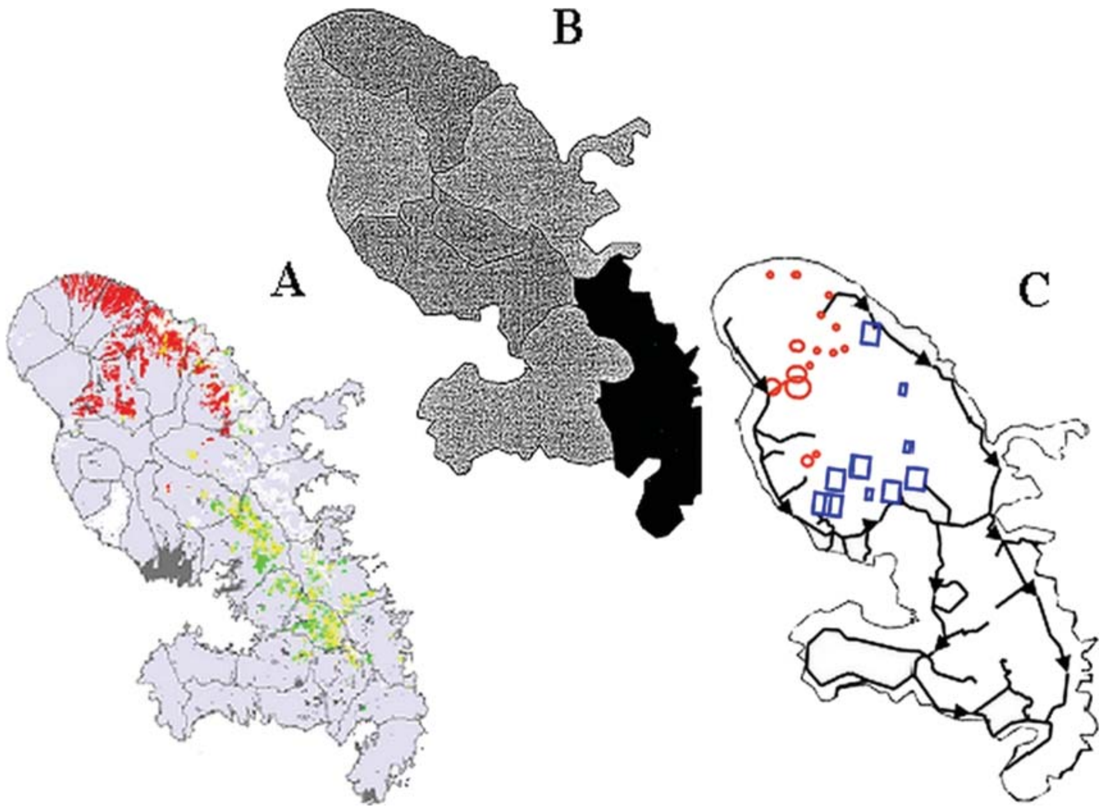

Figure 2. Soil pollution by pesticides (A), distribution of standardized incidence ration (SIR) of prostate cancer (B) in Martinique and fresh water distribution (C). (A) Localization of soil pollution by Chlordecone (mg/kg) according to BRGM. Localisation is similar for Chlordecone. (Grey) <0.1 mg/kg; (green) 0.1-0.5 mg/kg; (yellow) 0.5-1 mg/kg; (red) 1 mg/kg; (white) not studied classes; (dark grey) Urban, Water. (B) Distribution of Standardized Incidence Ratio (SIR) of prostate cancer (grey and black) 0.85-0.95; 0.95-1.05; (dark grey and black) >1.15 according to AMREC. (C) Fresh water distribution according to BRGM. ○ Corresponds specifically to natural water springs coming from mountains (Montagne Pele) □ corresponds specifically to drilling water. Arrows indicate ways of freshwater distribution.

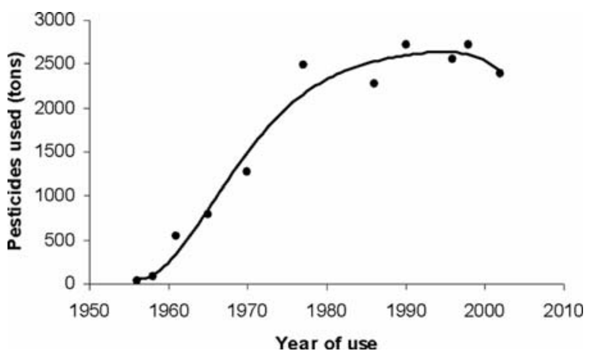

Figure 3. Amounts of pesticides used in Martinique.

were supplied with water coming from other sources, according to official mapping, we further observed fresh water distribution and found that the South-West of Martinique was specifically supplied with water coming from rivers located in the northern part of the island, which is covered by pesticide-contaminated banana plantations, as indicated in Fig. 2A.

Retrospective analysis of pesticides use and human contamination. Fig. 3 shows the total amount of pesticides (in tones) which have been imported to Martinique since 1955. Since banana plantations were introduced to the two islands at the same time period, and as the pesticides used were provided by the same companies in both islands, a similar trend was observed for Guadeloupe (data not shown). Table II shows the carcinogenic, mutagenic and reproductive toxin (CMR) or presumed CMR pesticides most used in Martinique and Guadeloupe on banana plantations and which might be involved in prostate carcinogenesis. All except simazine have been classified as possibly carcinogenic by the IARC. Table III further indicates concentrations of pesticides found in the adipose tissue of 36 Martinicans during the 1972 study. An important finding is that all tested subjects, independently of their place of residence on the island, were shown to be contaminated by extremely high doses of DDT and DDE, with extreme values climbing up to 9 mg/kg of DDT and 16 mg/kg of DDE in adults and 8 mg/kg of DDT and 7 mg/kg of DDE in children aged between 11 and 16 years. Similarly, all three isomers of HCH were detected in all tested subjects, but at relatively weaker concentrations, with extreme values rising up to 0.6 mg/kg for αHCH, 2 mg/kg for ßHCH and 0.2 mg/kg for lindane (γHCH) in adults and up to 0.3 mg/kg for αHCH and 0.6 mg/kg for ßHCH in children. In several subjects, relatively high levels of aldrin and dieldrin were also detected. If individual values of DDT and of its metabolite DDE are added up, in order to estimate the DDT-associated contamination (DDT-AC); and similarly, if individual values of the 3 HCH isomers are summed up in order to estimate the

Table II. CMR and presumed CMR pesticides used since 1955 in Martinique and Guadeloupe.

	On the market	Maximum of use	Withdrawal from the market for agricultural use	Continuation of use	IARC classification
Technical DDT	1939	1960-90	1972		2B
Technical HCH	1940[a]	1950-60	1988	1998	2B
Lindane	1940[a]	1950-60	1992		2B
Aldrin/dieldrin	1950[a]	1960	1972	1992	2B
Chlordecone	1972	1980	1990	1993	2B
Chlordanes	1960[a]				2B
Perchlordecone (mirex)	1977[a]	1980	1990		2B
Simazine	1991[a]		2001		3[b]

[a]Official data not available. [b]Simazine, a non-organochlorinated molecule, is associated with an increased risk of prostate cancer (43). Technical DDT is a mixture of the isomers p,p'-DDT (85%), o,p'-DDT (15%) and o,o'-DDT (<1%) and technical HCH, a mixture of the isomers α, ß and γ. Chlordanes include trans-chlordane, cis-chlordane, trans-nonachlor, cis-nonachlor and heptachlor.

Table III. Mean concentrations and extreme values of organochlorinated pesticides in the adipose tissue of normal subjects in 1972 in Martinique.[a,b]

	DDT	DDE	αHCH	ßHCH	γHCH
16-68 years	2.5	2.66	0.14	0.30	0.10
(28)	(0.7-9)	(0.3-16)	(0.01-0.6)	(0.06-2)	(0.03-0.24)
11-16 years	1.1	2	0.14	0.36	0.2
(6)	(0.8-8)	(1.4-7)	(0.04-0.3)	(0.14-0.6)	-

[a]Values are expressed in mg/kg of lipids extracted from adipose tissue. [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.

HCH-associated contamination (HCH-AC), then in the adipose tissue of all subjects, the mean values obtained are 4.1 mg/kg and 0.44 mg/kg for DDT-AC and HCH-AC, respectively. These mean values represent considerably high levels of human contamination by these two organochlorines.

Discussion

Prostate cancer incidence is steadily increasing in all industrialized countries, where the rise is commonly attributed to improvement in screening detection and to population aging (17). We have previously analysed the effect of these two factors on prostate cancer incidence, concluding that improvement in screening detection by the routine use of Prostate-Specific Antigens (PSA) test cannot *per se* fully account for the currently growing incidence of this cancer (18). Similarly, we have pointed out that increase in life expectancy cannot explain why rising prostate cancer incidence affects all age categories (19), why it is more perceptible in young people than in the elderly (20) and why it occurs at an earlier stage in life (21).

The present study tends to confirm our previous analysis (18,19). A major new finding is that the incidence rates of prostate cancer in Martinique and Guadeloupe are much higher than in metropolitan France (Table I) and that the curves of growing incidence diverge between those areas (Fig. 1). Since medical practice in the two French Caribbean islands such as the routine use of the PSA-based screening test does not differ from that in metropolitan France, it is unlikely that the difference observed in incidence rates is due to improved screening techniques. Similarly, since life expectancy of the population in Martinique and Guadeloupe does not significantly differ from the one in Metropolitan France (Table I), it clearly appears that aging cannot *per se* account for the difference in incidence.

Therefore, as neither screening detection or aging can be set forth to explain the differences in prostate cancer occurrence, we looked for other possible causes.

Prostate cancer is a type of cancer for which family history has been clearly identified. Genetic susceptibility factors have been thus considered first because they appear to be frequently involved (8,22). Unfortunately, search for specific genetic factors has led to the determination of dozens of different loci or genes of hereditary susceptibility (23), so genetic investigations tend to be extremely complex. Ethnographic factors have also been set forth (16,24). The incidence of prostate cancer varies substantially across ethnic groups, with Afro-Americans having the highest rates worldwide, with

Caucasians showing intermediate rates and Asians the lowest rates (25).

An ethnographic factor of genetic susceptibility has been found to be involved in prostate carcinogenesis in subjects with African ancestry. Even though it is probably the same for the Caribbean population (because of its origin), our study leads us to conclude that this factor cannot *per se* account for the current growing incidence of prostate cancer in Martinique and Guadeloupe, for the following reasons: i) The fact that for the period considered (1983 and 2002), incidence growth curves in Martinique and metropolitan France are not parallel but divergent (Fig. 1). This suggests that although a Caribbean genetic susceptibility factor may be involved in the genesis of prostate cancer, it cannot *per se* account for the observed divergence. Indeed, if an ethnographic factor alone had been causally involved, the curve of growing incidence for Martinique would have been parallel with that of metropolitan France. ii) The drastic increase in prostate cancer incidence observed since 1983 in the two islands, over approximately one generation, cannot be explained by an increase in susceptibility due to gene segregation, as the development period is too short. iii) Furthermore, as indicated in Table I, there is a considerable variation in prostate cancer incidence rates among the different Caribbean islands, even though they are associated with similar ethnographic features. This suggests that factors other than genetics are involved. Moreover, prostate cancer incidence rates in Martinique and Guadeloupe are much higher than those observed in the other Caribbean islands while, with the exception of Haiti, the Dominican Republic and Trinidad and Tobago, similar life expectancy is observed (Table I). iv) Finally, in order to explain the growing incidence of prostate cancer in Martinique, the consideration of genetic factors alone cannot account for the concentration of the highest prostate cancer incidence rates in the South-Western area of this island (Fig. 2B).

These different arguments therefore strongly support the hypothesis that in addition to aging specific non-genetic factors must be considered to account for the growing incidence of prostate cancer in the two French islands.

Considering the concept of carcinogenesis, it clearly appears that the older a person is, the longer his/her exposure period to carcinogens is and hence the greater the probability of cancer occurrence will be (26).

Among non-genetic factors are lifestyle-related factors. For >25 years, epidemiological studies have reported imbalanced diets, alcohol consumption and tobacco smoking as being potential risk factors for prostate cancer (27,28). This hypothesis has been mainly based on migration studies which have shown that people moving from countries with low incidence and/or mortality rates of prostate cancer such as China or Japan, to countries with high prostate cancer incidence rates such as the USA - characterized by significantly higher prostate cancer incidence and mortality than people in the countries of origin (29). Moreover, because the rise of prostate cancer incidence in Asian countries was found to be associated with a gradual adoption of westernized lifestyles, it has been postulated that western diet may be implicated in prostate cancer aetiology (28). Research on dietary factors has probably generated the most extensive efforts aiming to clarify the role of lifestyle-related factors in prostate carcinogenesis, because factors, such as high fat diets, and high protein and energy intake (30) are thought to induce significant changes in level of endogenous hormones and their metabolites, thus contributing to prostate carcinogenesis. Hence considering prostate cancer as an hormone-dependent tumor, it has been hypothesized that sex steroid hormones, such as androgens and estrogens, may be regarded as intermediates between dietary factors and molecular targets through the process of carcinogenesis (31). Unfortunately, despite many efforts, the role of dietary factors and other lifestyle-related factors in prostate carcinogenesis still remains elusive (32), with the possible exception of heterocyclic amines related to carbonization of food, among which 2-amino-1-methyl-6-phenylimidazo [4,5-b] pyridine (PhIP) has been the most studied chemical for its carcinogenic properties (33). However, such cooking methods are not common in the two islands and no epidemiological data have clearly pointed out the role of PhIP in the genesis of human prostate cancer. Furthermore, if we consider that a Western diet coming from metropolitan France has been introduced into Martinique and Guadeloupe during the last decades, this new risk factor is not relevant, since it cannot *per se* account for the difference in growing incidence of prostate cancer observed between metropolitan France and the two islands.

We have also previously distinguished environmental factors from lifestyle-related factors (18,19), defining environmental factors as physical, chemical and biological carcinogens or co-carcinogens and listed environmental carcinogens that are presently recognized as such by international cancer research agencies (34).

Several types of chemical agents (including CMRs), acting as endocrine disruptors have been found to be associated with prostate cancer occurrence, but their causal role in prostate carcinogenesis has not yet been proven. Among these substances, organochlorinated pesticides are of major health concern, because they can persist in the environment, concentrate in the food chain and accumulate in the adipose tissue from which they can be released into blood circulation and target peripheral tissues during carcinogenesis (35). Many, but not all epidemiological studies, have shown that chronic exposure to some pesticides or to some pesticide cocktails is associated with a significant increase in prostate cancer risk (36,37).

Our retrospective analysis leads to the conclusion that several types of CMR or presumed CMR pesticides, including DDT, HCH, chlordanes, aldrin, dieldrin, chlordecone and simazine (Table II) have been used in great quantities since 1955 in Martinique and Guadeloupe (14,38) and that several of them, used between 1955 and 1970, have been detected in the adipose tissue of all the subjects tested in our 1972 study (Table III). Subjects then showed similar considerably high levels (up to several mg/kg), as in other studies (39). Other authors have reported that exposure to organochlorinated pesticides is associated with an increased risk of prostate cancer (40,41) and that among the different pesticides used intensively in Martinique and Guadeloupe, DDT and DDE (42,41), lindane (43), aldrin and dieldrin (41), chlordane (41), heptachlor (41,43), oxychlordane (40,44) and simazine (43) have been found to be associated with a significantly increased risk of prostate cancer and/or have been detected at significantly higher levels in prostate cancer patients than in non-cancer patients. Moreover, the increased prostate cancer risk associated with many of the afore-mentioned pesticides has been observed mostly in subjects with a family history of prostate cancer (41), a finding which suggests that exposure to pesticides in genetically susceptible subjects increases the risk of prostate cancer. Although our data suggest that several pesticide types, including DDT and HCH, may have been implicated in the genesis of prostate cancer in Martinique and Guadeloupe, we cannot exclude that other CMR substances, including other types of pesticides, polychlorobiphenyls (40,44) and polychlorinated aromatic hydrocarbons (45) may also have been involved.

The role of such other factors might be suggested by our paradoxal observation showing that in Martinique most banana plantations are located in the Northern part of the islands, while the highest prostate cancer incidence rates were found in the South-Western part of the island (Fig. 2A and B). However, analysing official data did not suggest any specific local factors, such as farming, road traffic or industrial activities, which could have accounted for the higher increase in prostate cancer incidence in the South-Western Martinique (data not shown). By contrast, a retrospective inquiry on the history of fresh water distribution for the Southern Martinique, pointed out that since 1944, fresh water distributed specifically to the South-West of the Martinique was directly issued from polluted rivers located in banana plantation areas. Consequently, our interpretation is that people living in South-Western Martinique may have been permanently contaminated by high pesticide levels coming from banana plantations. As for people living in the other parts of the Island, their use of a different fresh water source would have been less contaminated by pesticides (Fig. 2C).

This interpretation is reinforced by the fact that the different pesticides used in banana plantations that have been detected in 1972 at very high concentration in the adipose tissue of Martinicans, concerned people living in the South as well as in the North of the island. Indeed, this finding can be easily explained by the fact that the main source of pesticide exposure is from diet, that local food may be contaminated by multiple pesticide residues, and that in general, islands may be characterized by a faster and wider diffusion of chemical pollutants as compared to continental countries such as metropolitan France, which may be associated with more efficient detoxifying ecosystems.

Therefore, on the basis of the afore-mentioned data, we hypothesize that some pesticides, such as those indicated in Table II or some pesticide cocktails may have been implicated in the growing incidence of prostate cancer in Martinique and Guadeloupe, and more generally that pesticides may cause prostate cancer.

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References

1. Ferlay J, Autier P, Boniol M, Heanue M, Colombet M and Boyle P: Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 18: 581-592, 2007.
2. Jemal A, Siegel R, Ward E, Murray T, Xu J and Thun MJ: Cancer statistics, 2007. CA Cancer J Clin 57: 43-66, 2007.
3. Collin SM, Martin RM, Metcalfe C, Gunnell D, Albertsen PC, Neal D, *et al*: Prostate-cancer mortality in the USA and UK in 1975-2004: an ecological study. Lancet Oncol 9: 445-452, 2008.
4. Kvale R, Auvinen A, Adami HO, Klint A, Hernes E, Moller B, *et al*: Interpreting trends in prostate cancer incidence and mortality in the five Nordic countries. J Natl Cancer Inst 99: 1881-1887, 2007.
5. Grönberg H: Prostate cancer epidemiology. Lancet 361: 859-864, 2003.
6. Nelson WG, De Marzo AM and Isaacs WB: Prostate cancer. N Engl J Med 349: 366-381, 2003.
7. Crawford ED: Epidemiology of prostate cancer. Urology 62 (Suppl 1): 3-12, 2003.
8. Schaid DJ: The complex genetic epidemiology of prostate cancer. Hum Mol Genet 13: R103-R121, 2004.
9. Mallick S, Blanchet P and Multigner L: Prostate cancer incidence in guadeloupe, a French Caribbean archipelago. Eur Urol 47: 769-772, 2005.
10. Dieye M, Veronique-Baudin J, Draganescu C and Azaloux H: Cancer incidence in Martinique: a model of epidemiological transition. Eur J Cancer Prev 16: 95-101, 2007.
11. AMREC: L'incidence et la mortalité par cancer en Martinique de 1996 à 2000; Monographie du Registre des Cancers de la Martinique pp137-143, 2004.
12. Remontet L, Buemi A, Velten M, Jougla E and Esteve J: Evolution de l'incidence et de la mortalité par cancer en France de 1978 à 2000. InVS, 2003.
13. Ferlay J, Bray F and Pisani DM: GLOBOCAN 2002. Cancer Incidence, Mortality and Prevalence Worldwide. IARC press, Lyon. Available at: http://www-dep.iarc.fr/ [accessed 1 April 2008].
14. Bocquene G and Franco A: Pesticide contamination of the coastline of Martinique. Mar Pollut Bull 51: 612-619, 2005.
15. Martin M: Les pesticides Organochlorés. Recherches des résidus dans le tissu adipeux. humain et animal en Martinique. PhD Medical Thesis, INRA Antilles-Guyane, 1973.
16. Ben-Shlomo Y and Kuh D: A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Int J Epidemiol 31: 285-293, 2002.
17. Hankey BF, Feuer EJ, Clegg LX, Hayes RB, Legler JM, Prorok PC, Ries LA, *et al*: Cancer surveillance series: interpreting trends in prostate cancer - part I: Evidence of the effects of screening in recent prostate cancer incidence, mortality, and survival rates. J Natl Cancer Inst 91: 1017-1024, 1999.
18. Belpomme D, Irigaray P, Sasco AJ, Newby JA, Howard V, Clapp R, *et al*: The growing incidence of cancer: role of lifestyle and screening detection (Review). Int J Oncol 30: 1037-1049, 2007.
19. Irigaray P, Newby JA, Clapp R, Hardell L, Howard V, Montagnier L, *et al*: Lifestyle-related factors and environmental agents causing cancer: an overview. Biomed Pharmacother 61: 640-658, 2007.
20. Post PN, Stockton D, Davies TW and Coebergh JW: Striking increase in incidence of prostate cancer in men aged <60 years without improvement in prognosis. Br J Cancer 79: 13-17, 1999.
21. Newby JA, Busby CC, Howard CV and Platt MJ: The cancer incidence temporality index: an index to show temporal changes in the age of onset of overall and specific cancer (England and Wales, 1971-1999). Biomed Pharmacother 61: 623-630, 2007.
22. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, *et al*: Environmental and heritable factors in the causation of cancer - analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 343: 78-85, 2000.
23. Eeles RA, Kote-Jarai Z, Giles GG, Olama AA, Guy M, Jugurnauth SK, *et al*: Multiple newly identified loci associated with prostate cancer susceptibility. Nat Genet 40: 316-321, 2008.

24. Robbins AS, Whittemore AS and Van Den Eeden SK: Race, prostate cancer survival, and membership in a large health organization. J Natl Cancer Inst 90: 986-990, 1998.
25. Miller BA, Kolonel LN, Bernstein L, Young JL, Swanson GM Jr, West D, *et al*: Racial/Ethnic Patterns of Cancer in the United States 1988-1992, National Cancer Institute, NIH Publ. No. 96-4104, Bethesda, MD, 1996.
26. Armitage P and Doll R: The age distribution of cancer and a multi-stage theory of carcinogenesis. 1954. Int J Epidemiol 33: 1174-1179, 2004.
27. Kolonel LN: Fat, meat, and prostate cancer. Epidemiol Rev 23: 72-81, 2001.
28. Shirai T, Asamoto M, Takahashi S and Imaida K: Diet and prostate cancer. Toxicology 181-182: 89-94, 2002.
29. Cook LS, Goldoft M, Schwartz SM and Weiss NS: Incidence of adenocarcinoma of the prostate in Asian immigrants to the United States and their descendants. J Urol 161: 152-155, 1999.
30. Kolonel LN, Nomura AM and Cooney RV: Dietary fat and prostate cancer: current status. J Natl Cancer Inst 91: 414-428, 1999.
31. Carruba G: Estrogen and prostate cancer: an eclipsed truth in an androgen-dominated scenario. J Cell Biochem 102: 899-911, 2007.
32. Park SY, Murphy SP, Wilkens LR, Henderson BE and Kolonel LN: Fat and meat intake and prostate cancer risk: the multiethnic cohort study. Int J Cancer 121: 1339-1345, 2007.
33. Stuart GR, Holcroft J, de Boer JG and Glickman BW: Prostate mutations in rats induced by the suspected human carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine. Cancer Res 60: 266-268, 2000.
34. Belpomme D, Irigaray P, Hardell L, Clapp R, Montagnier L, Epstein S, *et al*: The multitude and diversity of environmental carcinogens. Environ Res 105: 414-429, 2007.
35. Irigaray P, Newby JA, Lacomme S and Belpomme D: Overweight/obesity and cancer genesis: more than a biological link. Biomed Pharmacother 61: 665-678, 2007.
36. Van Maele-Fabry G and Willems JL: Prostate cancer among pesticide applicators: a meta-analysis. Int Arch Occup Environ Health 77: 559-570, 2004.
37. Bassil KL, Vakil C, Sanborn M, Cole DC, Kaur JS and Kerr KJ: Cancer health effects of pesticides: systematic review. Can Fam Physician 53: 1704-1711, 2007.
38. IFEN (Institut Français de l'Environnement). Les pesticides dans les eaux. Données 2005. nº9, 2007.
39. Waliszewski SM, Aguirre AA, Infanzon RM, Silva CS and Siliceo J: Organochlorine pesticide levels in maternal adipose tissue, maternal blood serum, umbilical blood serum, and milk from inhabitants of Veracruz, Mexico. Arch Environ Contam Toxicol 2001: 432-438, 2001.
40. Ritchie JM, Vial SL, Fuortes LJ, Guo H, Reedy VE and Smith EM: Organochlorines and risk of prostate cancer. J Occup Environ Med 45: 692-702, 2003.
41. Alavanja MC, Samanic C, Dosemeci M, Lubin J, Tarone R, Lynch CF, *et al*: Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort. Am J Epidemiol 157: 800-814, 2003.
42. Settimi L, Masina A, Andrion A and Axelson O: Prostate cancer and exposure to pesticides in agricultural settings. Int J Cancer 104: 458-461, 2003.
43. Mills PK and Yang R: Prostate cancer risk in California farm workers. J Occup Environ Med 45: 249-258, 2003.
44. Hardell L, Andersson SO, Carlberg M, Bohr L, van Bavel B, Lindström G, *et al*: Adipose tissue concentrations of persistent organic pollutants and the risk of prostate cancer. J Occup Environ Med 48: 700-707, 2006.
45. Rybicki BA, Nock NL, Savera AT, Tang D and Rundle A: Polycyclic aromatic hydrocarbon-DNA adduct formation in prostate carcinogenesis. Cancer Lett 239: 157-167, 2006.
46. Score santé for French Caribbean and other department. Available: http://www.fnors.org/scoreprod/ synthesefinalenrfr.aspx?lib=chk_o41-01-01-11-01%2c
47. WHO Statistical Information System (WHOSIS), Core Health Indicators Available: http://www.who.int/whosis/database/core/core_select.cfm?strISO3_select=SWE&strIndicator_select=LEX0Male&intYear_select=latest&language=english.