Evidence of increased chromosomal abnormalities in French Polynesian thyroid cancer patients

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Abstract. *Purpose:* The aim of this study was to evaluate the frequency of chromosomal abnormalities in thyroid cancer patients before and after radioactive iodine administration in order to assess cytogenetic particularity in Polynesian thyroid cancer patients. *Methods:* Chromosomal abnormalities were studied in 30 Polynesian patients with differentiated thyroid cancer, prior to and 4 days after ^{131}I administration. Unstable chromosomal abnormalities were counted in peripheral blood lymphocytes using a conventional cytogenetic method. Peripheral blood was irradiated in vitro at different doses (0.5, 1 and 2 Gy) in order to establish the dose-response of the lymphocytes. Control groups were composed of 50 European thyroid cancer patients before and after first administration of ^{131}I, and of ten European healthy donors. In addition, in vitro irradiation assays were performed at different doses (0.5, 1 and 2 Gy). *Results:* The relative risk of spontaneous dicentrics before any radiation treatment was 2.9 (95% CI 1.7–5.1) times higher among Polynesian thyroid patients than among European thyroid cancer patients. After in vitro irradiation, the rise in frequency of dicentrics was similar in the Polynesian thyroid cancer group and the European thyroid patients and healthy donors. Four days after administration of 3.7 GBq ^{131}I, the relative risk for a dicentric per cell was 1.3 (95% CI 1.0–1.5) times higher in Polynesian than in European patients. This can be explained by higher ^{131}I retention in Polynesian compared with European patients. The results obtained revealed an increased frequency of cytogenetic abnormalities in Polynesian thyroid cancer patients compared with European control patients. *Conclusion:* These preliminary findings are compatible with possible previous environmental aggression and therefore imply a need for further investigations on larger series including, in particular, French Polynesian healthy donors. In addition to French Polynesians, Maori and Hawaiian control groups could be useful.

Keywords: Polynesian – Thyroid cancer – Chromosomal abnormalities – Dicentrics – Biological dosimetry

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Introduction

Epidemiological studies have shown a high risk of thyroid cancer in the French Polynesian population compared with Hawaiian and New Zealand populations [1]. This increase could be attributed to various genetic and/or environmental factors [2]. However, attention has been focussed on the atmospheric nuclear weapon tests carried out in French Polynesia. In view of this particular environmental situation in French Polynesia, the aim of this study was to evaluate the frequency of chromosomal abnormalities in thyroid cancer patients before any radiation therapy and 4 days after ^{131}I administration, in order to assess cytogenetic particularity in Polynesian thyroid cancer patients. We also compared, before treatment, the dose-response obtained after in vitro irradiation of blood lymphocytes of Polynesian thyroid cancer patients and of the control population.

Materials and methods

Patients and controls

The study group consisted of 30 native Polynesian patients with differentiated thyroid carcinoma treated in the Department of Nuclear Medicine at Institut Gustave Roussy. Most of them were living in Tahiti. There were two males and 28 females with a mean age of 46 years (range 21–68).

A control group was composed of 50 thyroid cancer patients from European countries who were undergoing the same treatment at Institut Gustave Roussy. There were eight males and 42 females, with a mean age of 46 years (range 25–78 years). Our inquiry did not demonstrate a risk of irradiation by the Chernobyl accident fallout for these thyroid cancer controls [3]. However, it must be noted that fallout areas are not very well established, that the personal history of the patients was complex and, moreover, that these patients could have been irradiated in other ways. For this reason, another control group of ten healthy controls born and living in the Paris area (France), free from abnormal irradiation, was also introduced. This latter group was composed of four females and six males with a mean age of 40 years (range 27–58 years).

In vitro irradiation assays were carried out on blood samples from 21 of the 30 patients in the Polynesian patient group, from ten of the 50 European control patients and from all ten European healthy donors.

All thyroid cancer patients had undergone subtotal or total thyroidectomy. Thyroid hormone treatment was withdrawn 4–6 weeks before ^{131}I administration and all patients were hypothyroid. None of the thyroid cancer patients or the controls was known to have been previously exposed to ionising radiation (either accidental, diagnostic or therapeutic). Apart from ionising radiation exposure, cancer history and treatment, no other lifestyle data were collected at the time of study.

Twenty Polynesian and 50 European thyroid cancer patients provided a blood sample before treatment and on day 4 after administration of 3.7 GBq of ^{131}I. A total body scan was performed 4 days after administration of ^{131}I using a home-made digitised whole-body rectilinear scanner. Polynesian patients, European thyroid patients and the healthy controls were sampled over the same period (1997–1999) at Institut Gustave Roussy, so any possible effect due to year and seasons was equivalent in all groups [4].

This study was conducted in accordance with local ethical rules, and all patients and healthy donors signed informed written consent (CCPPRB 97–56).

Method

In vitro irradiation procedure, lymphocyte culture and chromosome preparation

Blood samples of patients and controls were irradiated in vitro with ^{60}Co at different doses (0.5, 1 and 2 Gy). Five millilitres of medium were added to 0.5 ml of blood and incubated. The medium consisted of: 5 ml RPMI 1640 supplemented with 10% foetal calf serum, 0.1 ml phytohaemagglutinin M (GIBCO/BRL, Grand Island, USA), 1% glutamine, 1 m*M* sodium pyruvate, 5 μg ml^{-1} BrDU and antibiotics (penicillin and streptomycin). Colcemid (0.1 μg ml^{-1}) was added 2 h before harvesting, and slides with chromosomes in metaphases were prepared following the standard methanol/acetic acid (3/1, v/v) fixation method. The slides were stored at –20°C until use.

Conventional cytogenetics

Fluorescent plus Giemsa staining was applied to the slides on which metaphases were spread. Only complete metaphases (46 centromeres) were scored for dicentrics and acentric fragments under a light microscope. Counting of unstable chromosomal abnormalities in peripheral blood lymphocytes, in particular dicentrics, is considered the most reliable method in biological dosimetry by reference to dose-response curves [5–13].

Statistical analysis

The primary endpoint was the frequency of chromosomal aberrations in the different populations. Statistical analysis was performed with SAS Version 8.0 software package (SAS Institute, Inc., NC, USA). Comparison between the frequencies of chromosomal aberrations in different populations was performed using a logistic regression model for grouped data [14]. Such analysis takes into account the number of cells and the number of chromosomal aberrations for each individual. This model was used to estimate the relative risk associated with a given patient's characteristics, origins, cancer and irradiation status, age category and gender. Ninety-five percent confidence intervals (95% CI) for relative risk were estimated using maximum likelihood methods [15].

Results

Increased frequency of spontaneous chromosomal abnormalities in Polynesian thyroid cancer patients before treatment

The corresponding relative risk of unstable chromosomal abnormalities for Polynesian patients, as referenced to the risk for European control patients, was 2.9 (95% CI 1.7–5.1, p=0.0002 for dicentrics and 1.9 (95% CI 1.2–3.0, p=0.004) for acentric fragments (Table 1). When controlling for sex and age, dicentrics and acentric fragments were about twice as frequent in cells of patients aged over 45 years than in younger patients for both European and Polynesian populations. Such conclusions were not possible concerning gender owing to the low number of males, particularly amongst the Polynesian cancer patients.

Polynesian and European thyroid cancer patients exhibit a similar increasing trend in the frequency of dicentrics after in vitro ionising radiation

As expected, European thyroid patients and healthy donors exhibited similar dicentric frequencies before and after in vitro irradiation (this validates the European group as an effective control as regards Polynesian cancers). The mean frequencies and relative risk for dicentrics among Polynesian and European thyroid cancer patients before treatment, and among European healthy donors, are shown in Table 2. Although the frequency of dicentrics was approximately three times higher in Polynesian patients than in European patients before any ionising radiation treatment, no difference in the rate of dicentrics according to X-ray dose was evidenced between the two population groups after submitting their blood lymphocytes to in vitro radiation exposure.

In both ethnic groups, results were not modified by age at test (test for interaction: p=0.7 for Polynesians and

Table 1. Frequency and relative risk for unstable chromosomal abnormalities among Polynesian and European thyroid cancer patients, before treatment by ^{131}I (57 dicentrics and 81 acentric fragments among 11,862 metaphases). For each sample, 50–280 metaphases (median 200) were counted per sample in Polynesian patients, compared with 150–200 (median 180) in European patients

Category	No. of patients	Dicentrics			Acentric fragments		
		N(×100)/cell (s.e.m.)	Relative risk[a] for a dicentric per cell (95% CI)	*p* Value	*N*(×100)/cell (s.e.m.)	Relative risk[a] for a fragment per cell (95% CI)	*p* Value
Ethnic group							
European	50	0.25 (0.08)	1[b]	0.0002	0.51 (0.18)	1[b]	0.004
Polynesian	30	0.72 (0.14)	2.9 (1.7–5.1)		0.98 (0.29)	1.9 (1.2–3.0)	
Sex							
Male	10	0.35 (0.21)	1[b]	0.6	0.65 (0.47)	1[b]	0.2
Female	70	0.43 (0.08)	1.3 (0.5–3.7)		0.68 (0.17)	0.7 (0.4–1.3)	
Age							
≤45 yr	46	0.31 (0.08)	1[b]	0.007	0.55 (0.20)	1[b]	0.02
>45 yr	34	0.57 (0.13)	2.1 (1.2–3.7)		0.85 (0.26)	1.7 (1.1–2.7)	

N(×100)/cell mean number of chromosomal abnormalities per cell, *s.e.m.* standard error of the mean
[a] Multivariate analysis including origin, sex and age
[b] Reference category

Table 2. Frequency and relative risks for dicentrics among Polynesian and European thyroid cancer patients, before treatment by ^{131}I, and among European healthy donors, according to the dose of in vitro ionising radiation

Category	No. of patients	Dicentrics		
		N(×100)/cell (s.e.m.)	Relative risk[a] for a dicentric per cell (95% CI)	*p* Value
Polynesian thyroid cancer patients				
After irradiation, 50–250 metaphases were scored for each sample (median: 200 for 0.5 Gy, 200 for 1 Gy, 121.5 for 2 Gy)				
No rx	21	0.87 (0.2)	1[b]	
0.5 Gy	21	3.4 (0.4)	4.8 (3.3–7.2)	<0.0001
1.0 Gy	21	6.6 (0.9)	11 (7.4–16)	<0.0001
2.0 Gy	21	19 (1.3)	30 (21–44)	<0.0001
European healthy donors				
200 metaphases scored per sample				
No rx	10	0.17 (0.1)	1[b]	
0.5 Gy	10	3.3 (0.3)	26 (8.2–84)	<0.0001
1.0 Gy	10	7.8 (0.3)	61 (23–249)	<0.0001
2.0 Gy	10	21 (0.9)	194 (74–784)	<0.0001
European thyroid cancer patients				
150–200 metaphases scored per sample				
No rx	10	0.17 (0.1)	1[b]	
0.5 Gy	10	3.2 (0.3)	15 (5.4–42)	<0.0001
1.0 Gy	10	9.4 (0.4)	44 (16–120)	<0.0001
2.0 Gy	10	21 (0.9)	114 (43–308)	<0.0001

N(×100)/cell mean number of dicentrics per cell, *s.e.m.* standard error of the mean
[a] Adjusted for sex and age
[b] Reference category

Table 3. Frequency and relative risk of unstable chromosomal abnormalities among Polynesian and European thyroid cancer patients, 4 days after administration of 3.7 GBq of ^{131}I (411 dicentrics and 305 acentric fragments among 11,059 metaphases). Two hundred to 250 metaphases were scored in each European cancer sample, and 29–300 metaphases per sample (median 200) in Polynesian patients

Category	No. of patients	Dicentrics			Acentric fragments		
		N(×100)/cell (s.e.m.)	Relative risk[a] for a dicentric per cell (95% CI)	*p* Value	*N*(×100)/cell (s.e.m.)	Relative risk[a] for a fragment per cell (95% CI)	*p* Value
Ethnic group							
European	50	3.6 (0.2)	1[b]	0.03	1.4 (2.5)	1[b]	<0.0001
Polynesian	20	4.8 (1.0)	1.3 (1.0–1.5)		6.6 (4.7)	4.9 (3.9–6.9)	
Sex							
Male	10	4.5 (0.7)	1[b]	0.1	2.6 (3.5)	1[b]	0.7
Female	60	3.9 (0.4)	0.8 (0.6–1.1)		2.9 (4.1)	0.9 (0.7–1.3)	
Age							
≤45 yr	39	3.9 (0.5)	1[b]	0.2	2.8 (4.4)	1[b]	0.4
>45 yr	31	4.1 (0.4)	1.1 (0.9–1.4)		3.0 (3.6)	0.9 (0.7–1.1)	

N(×100)/cell mean number of chromosomal abnormalities per cell, *s.e.m.* standard error of the mean
[a]Multivariate analysis including origin, sex and age
[b]Reference category

0.3 for Europeans), or by gender (test for interaction: p=0.3 for Europeans).

Increased frequency of chromosomal abnormalities in Polynesian thyroid cancer patients 4 days after the first ^{131}I administration

^{131}I retention on day 4, as measured by total body scan, ranged from 1% to 23% of the administered activity in European thyroid cancer patients and from 2% to 34% in Polynesian thyroid cancer patients.

The mean frequencies and relative risk of unstable chromosomal abnormalities for Polynesian and European thyroid cancer patients after administration of 3.7 GBq of ^{131}I treatment are shown in Table 3.

Four days after the first administration of 3.7 GBq of ^{131}I, a significant increase in chromosomal aberrations was observed in peripheral blood lymphocytes of both European and Polynesian thyroid cancer patients. The mean frequency of dicentrics per 100 cells was 4.8 (s.e.m. 1.0) in Polynesian thyroid cancer patients and 3.6 (s.e.m. 0.2) in European thyroid cancer patients. According to the dicentric frequency before ^{131}I administration, this corresponded to a relative risk for a dicentric per cell 1.3 (95% CI 1.0–1.5) times higher in Polynesian than in European thyroid cancer patients (p=0.03). When controlling for age and sex, no significant difference was evidenced between Polynesian and European patients. In Polynesian patients, after ^{131}I treatment the relative risk for a fragment per cell reached a very high level.

When the number of dicentrics in peripheral blood lymphocytes of patients 4 days after administration of 3.7 GBq (Table 2) was plotted on their dose-response curve, the mean dosimetric index was 0.65 Gy (95% CI 0.32–1.03 Gy) in Polynesian thyroid cancer patients and 0.53 Gy (95% CI 0.3–0.7 Gy) in European thyroid cancer patients.

Discussion

The most striking observation concerning the Polynesian thyroid cancer patients was an increased rate of unstable chromosomal abnormalities before any radiation treatment, compared with that in European patients of the same age and sex. The spontaneous dicentric frequencies vary between both populations and laboratories; however, taking uncertainties into account, the mean values of 2.5×10^{-3} and 1.7×10^{-3} dicentrics/cell obtained for our European thyroid patients before treatment and for European healthy controls, respectively, are within the range of background frequency of dicentrics per cell reported in previous studies [16]. The background frequency of chromosomal abnormalities for the Polynesian population is unknown. Nevertheless, compared with the level of dicentric chromosomes found in our European controls, the high frequency detected in the Polynesian patients strongly suggests a previous history of exposure to mutagens or carcinogens [6].

Ionising radiation is the most effective factor associated with an increase in the background dicentric chromosome frequency. According to dose-response curves that

we have published previously [5], the mean value of 7.1×10^{-3} dicentrics/cell found for Polynesian thyroid cancer patients would correspond to a radiation dose estimate of 0.20 Gy (95% CI 0.12–0.48). Given that France performed 41 atmospheric nuclear bomb tests on the Mururoa and Fangataufa atolls between 1966 and 1974, it is possible that the Polynesian population was exposed to local fallout during this period. However, these results must be discussed in the light of genetic and epigenetic considerations.

Concerning genetic considerations, the high level of chromosomal aberrations exhibited by our patients could reflect an inherent susceptibility to cancer in the French Polynesian population. However, such susceptibility most often occurs concomitantly with DNA repair deficiency; the fact that we observed similar in vitro responses to ionising radiation in Polynesian cancer patients and in controls therefore renders it improbable that there is a Polynesian genetic hypersusceptibility to cancer [17–19]. Thus, the aforementioned hypothesis appears unlikely to be correct, at least on the basis of our protocol.

Some epigenetic considerations can contribute in explaining our findings. As they can induce dicentric chromosomes [20] and are widely used in French Polynesia, pesticides must be considered as the most suspect of these factors. Indeed, exposure to genotoxic chemicals, such as pesticides, could have a deleterious effect on DNA in the Polynesian rural population. Moreover, their use can coincide with smoking habits [21]. Vijayalaxmi and Evans [22] and Littlefield and Joiner [23] reported that the incidence of sister chromatid exchange in blood lymphocytes of heavy cigarette smokers is significantly greater, by a factor of approximately 50%, than that in non-smokers. Wang et al. [24] reported a higher frequency of spontaneous and induced breaks in irradiated lymphocytes in smokers than in lymphocytes of non-smokers. Drinking, caffeine intake, contraceptive pills and even copper contained in contraceptive devices have been suspected of DNA alteration [3]. These lifestyle factors were not taken into account in this pilot study conducted in metropolitan France. All of these factors, and indeed all Polynesian environmental factors, should be considered in future investigations.

This study confirms the results of our previous study, conducted on a larger series of patients [25], by showing (a) that thyroid cancer patients are hypothyroid at the time of ^{131}I administration and (b) that this hypothyroid status decreases renal clearance of radioiodine, thus increasing whole-body irradiation. The excess of unstable aberrations following ^{131}I administration in Polynesian patients, compared with European patients, could be explained by higher ^{131}I retention in Polynesian patients, suggesting modulation by thyroid equilibrium, individual factors and extent of surgery.

This study is the first report to assess a statistically significant increase in the frequency of spontaneous unstable chromosomal abnormalities in Polynesian compared with European thyroid cancer patients [1]. It strongly supports the hypothesis of previous exposure. However, the existence of hypersusceptibility to cancer in French Polynesians cannot definitively be ruled out by our protocol. Therefore, this work is considered a first step towards future investigations both on healthy Polynesian people not exposed to radiation and on thyroid cancer patients with similar genetic/ethnic background and environmental lifestyle characteristics. Besides the French Polynesian population, Maori and Hawaiian control subjects should be used.

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