RESEARCH ARTICLE

# Differentiated Thyroid Carcinoma Risk Factors in French Polynesia

**Constance Xhaard[1,2,3], Yan Ren[1,2,3], Enora Clero[1,2,3], Stephane Maillard[1,2,3], Pauline Brindel[1,2,3], Frederique Rachedi[4], Jean-Louis Boissin[5], Joseph Sebbag[5], Larrys Shan[5], Frederique Bost-Bezeaud[4], Patrick Petitdidier[6], Vladimir Drozdovitch[7,8], Francoise Doyon[1,2,3], Carole Rubino[1,2,3], Florent de Vathaire[1,2,3]***

## Abstract

**Background: To investigate differentiated thyroid cancer risk factors in natives of French Polynesia is of interest because of the very high incidence of this cancer in the archipelago. Materials and Methods: To assess the role of various potential risk factors of thyroid cancer in the natives of French Polynesia we performed a case-control study. The study included almost all the French Polynesians diagnosed with differentiated thyroid carcinoma between 1981 and 2003 (n=229) and 373 French Polynesian control individuals from the general population without cancer. Results: Thyroid radiation dose received from nuclear fallout before the age of 15, a personal history of neck or/and head medical irradiation, obesity, tallness, large number of children, an artificial menopause, a familial history of thyroid cancer, a low dietary iodine intake, and having a spring as the main source of drinking water were found to be significant risk factors. No roles of smoking habits, alcohol consumption, iodine containing drugs, and exposure to pesticides were evidenced. Conclusions: Except for smoking, differentiated thyroid carcinoma risk factors in natives of French Polynesia are similar to those in other populations. Our finding on the role of having a spring as a drinking water origin is coherent with some other studies and could be due to geological factors.**

**Keywords:** Differentiated thyroid carcinoma - nuclear test - French Polynesia - radiation induced cancer

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## Introduction

Substantial variations in thyroid cancer incidence in the world strongly implicate environmental factors in the etiology of this cancer. The highest thyroid cancer incidence rates are observed in the Pacific populations (Henderson et al.,1982; Curado et al., 2007), but only few publications have investigated the reasons for these high rates.

Thyroid cancer mortality (de Vathaire and Le Vu, 1996) and incidence (Le Vu et al., 2000; de Vathaire et al., 2000) in French Polynesia was reported to be the highest in the world, in particular among natives of this set of archipelago (Gleize et al., 2000). To investigate the reasons for this level of incidence and the potential role of atmospheric fallout from nuclear tests performed by France between 1966 and 1974, we conducted between 2002 and 2005 a population-based case-control study among natives of French Polynesia including most of the thyroid cancer patients diagnosed between 1981 and 2003, who were aged 55 years or less and still alive. Previously, we reported that a low level of education (Brindel et al., 2008), tallness and a high body mass index (Brindel et al., 2009), a family history of thyroid cancer (Brindel et al., 2010), and, in women, a large number of pregnancies (Brindel et al., 2008) were associated with an increased risk of thyroid cancer in this population. We also estimated the radiation doses received by the study subjects during the atmospheric nuclear tests (Drozdovitch et al., 2008) and concluded that nuclear radiation fallout played a small but significant role in the high incidence of thyroid cancer in French Polynesia (de Vathaire et al., 2010). Lastly, we estimated that traditional Polynesian dietary pattern was associated with a lower thyroid cancer incidence than western pattern (Clero et al., 2012a). French Polynesia is a mild iodine deficiency area in which a higher consumption of food from the sea and a higher dietary iodine intake are significantly associated with a decreased risk of thyroid cancer (Clero et al., 2012b).

In this report we investigated the potential risk factors

*[1]Inserm, Centre for Research in Epidemiology and Population Health (CESP), U1018, Radiation Epidemiology Group, [2]Gustave Roussy, [3]University Paris XI, Villejuif, [7]International Agency for Research on Cancer, Lyon, France, [4]Territorial Hospital Taaone, [5]Endocrinologist, [6]Laboratoire Boz, Papeete, French Polynesia, [8]Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, Bethesda, USA *For correspondence: florent.devathaire@gustaveroussy.fr*

that have not been previously reported.

## Materials and Methods

*Study population*

Between 1980 and 1984 two partial registries maintained by clinicians and pathologists were in operation. The cancer incidence registry of French Polynesia was officially created in 1984. Between 1996 and 1998, we investigated the exhaustiveness of the registry and identified 539 new cancers after having examined all the medical transport files, insurance records, and hospital and pathological laboratory files available in French Polynesia. An additional survey limited to thyroid cancer was also performed in 2002–2005, to complete registry data with incident cases diagnosed up to 2002 in data from medical insurance files, and records from the four endocrinologists in Tahiti.

The methodology and practical realization of the case-control study can be found elsewhere (de Vathaire et al., 2010). Briefly, 229 of the of 255 patients diagnosed with differentiated thyroid carcinoma between 1981 and 2003 at the age of 55 or less, and born and residing in French Polynesia at time of diagnosis, as well as 373 population controls matched on sex and birth date extracted from the French Polynesian birth registry were included in the study. Due to errors in inclusion, some patients aged between 56 and 62 were included and kept in this analysis. The study subjects were interviewed face to face by trained Maori interviewers. Information on ethnic group, education, occupation, places of residence, weight history, personal and familial history of thyroid disease and cancer, gynecologic and reproductive history, medical X-ray exposure, and diet at the time of the interview and in childhood was collected during the personal interview.

**Table 1. Description of Thyroid Cancer Cases, French Polynesia**

| Characteristics | | Cases (N=229) | |
|---|---|---|---|
| | | N | % |
| Sex | Men | 26 | 11.4 |
| | Women | 203 | 88.6 |
| Age at time of first test (years) | 15+ | 61 | 26.6 |
| | 0-14 | 124 | 54.2 |
| | Born during tests | 33 | 14.4 |
| | Born after tests | 11 | 4.8 |
| Age at diagnosis (years) | 10-19 | 8 | 3.5 |
| | 20-29 | 39 | 17 |
| | 30-39 | 76 | 33.2 |
| | 40-49 | 63 | 27.5 |
| | 50-62 | 43 | 18.8 |
| Histology | Papillary | 176 | 76.9 |
| | Follicular | 53 | 23.1 |
| Tumour size (mm) | ≤ 10 | 106 | 52.2 |
| | 11-40 | 75 | 37.0 |
| | >40 | 22 | 10.8 |
| | Unknown | 26 | - |
| Multifocal tumour | No | 128 | 61 |
| | Yes | 82 | 39 |
| | Unknown | 19 | - |
| Extra-thyroidal invasion | No | 191 | 83.4 |
| | Yes | 38 | 16.6 |

Table 1 describes the 229 cases included in the study, and Table 2 summarizes the main findings previously published.

*Estimation of radiation thyroid doses*

Radiation doses to the thyroids of the study subjects were assessed based on available annual reports published by France on the radiological situation in French Polynesia, including measurements of the radioactivity in the air, vegetables, milk, and fish, and on meteorological data including daily precipitation and wind speed and direction. Dietary consumption data concerning childhood and information on the source of drinking water collected during the personal interviews were also used to estimate individual radiation doses to the thyroid. Dose reconstruction was conducted without knowledge of the case or control status of the subject. The methodology used to estimate thyroid doses to the study subjects and results can be found elsewhere (Drozdovitch et al., 2008).

*Statistical analysis*

Data were analyzed using conditional logistic regression (Breslow and Day, 1987) with the Epicure epidemiological software (Preston et al., 1993) and SAS® V9.2. To investigate the relationship between the radiation dose to the thyroid and the risk of thyroid cancer, we compared nested models using likelihood-ratio tests (Moolgavkar and Venzon, 1987). Tests for linear trend (Breslow and Day, 1987) were also performed.

## Results

Only 17 study subjects reported use of traditional Polynesian medicine, a practice that did not significantly modify the risk of thyroid cancer. The use of Colchimax or Amiodarone, which are drugs containing iodine, did not significantly modify the risk of thyroid carcinoma. Only 11 cases and 18 controls were or had been farmers. This

**Table 3. Risk factors for Thyroid Cancer in French Polynesia**

| | Cases (n=229) | | Controls (n=373) | | OR (95%CI)* | p value** |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | | |
| Traditional Polynesian medicine (Raau Tahiti). | | | | | | |
| No | 222 | 97 | 363 | 97 | 1* | |
| Yes | 7 | 3 | 10 | 3 | 0.6 (0.2-1.9) | 0.4 |
| Colchimax or Amiodarone (drug containing iodine) | | | | | | |
| No | 212 | 93 | 342 | 92 | 1* | |
| Yes | 17 | 7 | 31 | 8 | 0.9 (0.4-1.8) | 0.8 |
| Farmer as occupation | | | | | | |
| No | 218 | 95 | 355 | 95 | 1* | |
| Yes | 11 | 5 | 18 | 5 | 1.0 (0.4-2.3) | 1 |
| Domestic or professional use of pesticides | | | | | | |
| No | 127 | 55 | 163 | 44 | 1* | |
| Yes | 102 | 45 | 210 | 56 | 1.0 (0.6-1.5) | 1 |
| Report of regular alcohol consumption | | | | | | |
| No | 222 | 97 | 361 | 97 | 1* | |
| Yes | 7 | 3 | 10 | 3 | 1.2 (0.3-4.5) | 0.8 |
| Current smoker | | | | | | |
| No | 101 | 44 | 197 | 53 | 1* | |
| Yes | 128 | 56 | 176 | 47 | 1.1 (0.8-1.7) | 0.8 |

*OR: odds ratio, CI: confidence interval; **Multivariate conditional logistic regression, taking into account all other factors in Table 2

**Table 2. Risk Factors for Thyroid Cancer in French Polynesia**

| | | Cases (n=229) | | Controls (n=373) | | OR (95%CI)* | p value** |
|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | | |
| Maximal Body Mass Index (kg/m²) | ≤ 22.5 | 12 | 5 | 49 | 13 | 1* | |
| | 22.6-26.3 | 36 | 16 | 91 | 24 | 1.1 (0.5-2.5) | <0.0005 |
| | 26.4-31.6 | 62 | 27 | 103 | 28 | 1.8 (0.8-3.9) | |
| | ≥ 31.7 | 119 | 52 | 130 | 35 | 2.8 (1.3-5.8) | |
| Height (m) (Female) (Males) | (<1.60) (<1.70) | 32 | 14 | 80 | 22 | 1* | |
| | (1.60-1.64) (1.70-1.74) | 64 | 28 | 101 | 27 | 1.6 (0.9-2.8) | <0.05 |
| | (1.65-1.69) (1.75-1.79) | 72 | 31 | 103 | 28 | 1.7 (1.0-3.1) | |
| | (≥1.70) (≥1.80) | 61 | 27 | 89 | 24 | 1.9 (1.0-3.4) | |
| Women: number of pregnancies | 0 | 25 | 12 | 49 | 15 | 1* | |
| | 1-Feb | 38 | 19 | 84 | 26 | 1.2 (0.5-2.7) | |
| | 3-Apr | 53 | 26 | 84 | 26 | 1.5 (0.6-3.3) | <0.05 |
| | 5-Jun | 35 | 17 | 48 | 15 | 1.9 (0.8-4.5) | |
| | 7 or more | 52 | 26 | 61 | 19 | 2.3 (1.0-5.2) | |
| Women: menopausal status | Premenstrual | 1 | 1 | 2 | 1 | | |
| | Still menstruated | 161 | 81 | 277 | 87 | 1* | |
| | Natural menopause | 17 | 8 | 26 | 8 | 1.9 (0.7-5.0) | |
| | Artificial menopause | 19 | 10 | 11 | 4 | 4.5 (1.5-12.0) | 0.02 |
| Nuclear worker during atmospheric test | No | 219 | 96 | 361 | 97 | 1* | |
| | Yes | 10 | 4 | 12 | 3 | 1.0 (0.3-3.3) | 0.9 |
| Atmospheric tests nuclear radiation fallout : thyroid dose before age 15 | | | | | | | |
| | <1 mGy | 156 | 68 | 250 | 67 | 1* | |
| | 1-9.9 mGy | 61 | 27 | 111 | 30 | 1.0 (0.5-2.0) | |
| | 10-19.9 mGy | 7 | 3 | 9 | 2 | 3.9 (0.9-17) | <0.05 |
| | 20-39 mGy | 5 | 2 | 3 | 1 | 7.0 (0.9-53) | |
| First degree familial history of thyroid cancer | No | 205 | 90 | 362 | 97 | 1* | |
| | Yes | 24 | 10 | 11 | 3 | 4.5 (1.9-10.6) | 0.01 |
| Total food from sea consumption (g/day) | ≤45 | 112 | 49 | 136 | 37 | 1* | |
| | 46-90 | 58 | 25 | 115 | 31 | 0.5 (0.3-0.9) | 0.0002 |
| | ≥91 | 59 | 26 | 120 | 32 | 0.4 (0.3-0.8) | |
| Parents ethnic group | Both Polynesian | 122 | 53 | 206 | 55 | 1* | |
| | Poly-Asian | 37 | 16 | 63 | 17 | 1.3 (0.8-2.3) | 0.6 |
| | Poly-European | 46 | 20 | 75 | 20 | 1.3 (0.7-2.2) | 0.9 |
| | Mixed | 23 | 10 | 29 | 8 | 2.2 (1.1-4.5) | 0.08 |
| | Missing | 1 | | | | | |
| Educational level | No diploma | 101 | 44 | 138 | 37 | 1* | |
| | Primary leaving certificate | 53 | 23 | 84 | 23 | 0.9 (0.5-1.4) | <0.02 |
| | Middle school degree | 24 | 11 | 31 | 8 | 1.5 (0.8-3.3) | |
| | Vocational training certificate | 32 | 14 | 49 | 13 | 0.8 (0.4-1.5) | |
| | Technical school certificate | 10 | 4 | 18 | 5 | 0.7 (0.3-1.8) | |
| | High school diploma | 9 | 4 | 53 | 14 | 0.2 (0.1-0.6) | |
| Medical or therapeutic irradiation of the neck | No | 191 | 83 | 331 | 89 | 1* | |
| | Yes | 38 | 17 | 42 | 11 | 1.9 (1.1-3.4) | 0.02 |

*OR: odds ratio, CI: confidence interval; **Multivariate conditional logistic regression, taking into account all other factors in the Table

**Table 4. Origin of Drinking Water and Thyroid Cancer in French Polynesia**

| | | Cases (n=229) | | Controls (n=373) | | OR (95%CI)* | |
|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | | p value** |
| Spring as main drinking water origin | | | | | | | |
| No | | 179 | 78 | 321 | 86 | 1* | |
| Yes | | 50 | 22 | 52 | 14 | 1.7 (1.1-2.9) | 0.03 |
| Yes in Tahiti or Moorea | | 4 | 2 | 2 | 2 | 1.1 (0.3-4.5) | 0.9 |
| Yes in other Société islands | | 5 | 2 | 3 | 1 | 3.8 (0.3-4.5) | 0.1 |
| Yes in Australes | | 16 | 7 | 13 | 3 | 2.7 (1.1-6.6) | 0.03 |
| Yes in Marquises | | 23 | 10 | 29 | 8 | 1.2 (0.6-2.7) | 0.6 |
| Yes in atolls of Tuamotu-Gambier | | 4 | 1 | 2 | 2 | 2.4 (0.4-13.1) | 0.3 |
| Spring as main drinking water origin before the age of 15 | No | 192 | 84 | 339 | 91 | 1* | |
| | Yes | 37 | 16 | 34 | 9 | 2.5 (1.4-4.7) | 0.003 |
| Personal cistern as main drinking water origin | No | 188 | 82 | 315 | 84 | 1* | |
| | Yes | 41 | 18 | 58 | 16 | 1.0 (0.6-1.7) | 0.9 |
| Public cistern as main drinking water origin | No | 215 | 94 | 354 | 95 | 1* | |
| | Yes | 14 | 6 | 19 | 5 | 1.0 (0.5-2.1) | 0.9 |

*OR: odds ratio, CI: confidence interval; **Multivariate conditional logistic regression, taking into account all other factors listed in Table 2

occupation did not significantly modify the risk of thyroid carcinoma. Reported domestic occupational exposure to pesticides was not found to be significantly linked to thyroid carcinoma risk (Table 3).

Only 7 cases and 10 controls reported regularly drinking alcohol. We did not find evidence of any significant relation between reported alcohol consumption or smoking habits and thyroid carcinoma risk (Table 3).

Fifty cases and 52 controls declared having or having had a spring as main source of drinking water in at least

one of their places of residence, mainly in Australes and Marquises Islands. Having or having had a spring as main origin of drinking water was associated with a significantly increased risk of thyroid cancer, in particular at age less than 15 years old. Among 102 subjects who have had a spring as a main source of drinking water, 3 (2.9%) had received 10 mGy or more to the thyroid during atmospheric tests, as compared with 21 (4.2%) of the 500 subjects who never had such source of drinking water. Adjusting for spring as origin of drinking water did not modify the relation between thyroid radiation dose estimate and thyroid cancer risk. No relation between other sources of water, public or private rainwater cisterns, and thyroid cancer risk was found (Table 4).

## Discussion

This case-control study aimed to identify lifestyle and environmental risk factors, specific to French Polynesia, which could explain the high differentiated thyroid carcinoma incidence observed in these archipelagos. The study identifies having a spring as origin of drinking water as a risk factor, but the low frequency of this risk factor (14% in controls and 22% in cases) does not permit it to play an important role, its population attributable fraction being about 9%. On the other hand, we failed to evidence the role of smoking habits, alcohol consumption, iodine containing drugs, and exposure to pesticides.

The description of general strength and weaknesses of this case-control study can be found elsewhere (Brindel et al., 2008; de Vathaire et al., 2010; Clero et al., 2012b). In brief, the weaknesses of this study are the traditional ones of case-control studies in general population in which exposure assessment is based on self-reported data, i.e. potential bias of anamnesis and uncertainties in exposure assessment. Its strengths are those arising from the small size of the French Polynesian population (it is still possible to localize the current living place of any person when knowing only name, first name, and birth date) and its geographic isolation up to the 1990s (traditional Polynesian food was the rule in all Polynesian islands except Tahiti, until very recently).

As regards the potential risk factors specifically investigated in this article, the most important weakness concerns the weight of religious prohibitions and is illustrated by the unrealistically low (3%) proportion of cases and controls who declared drinking alcohol, as compared with what is known about alcoholic epidemics in French Polynesia (Bertrand and Berry, 2013). This strong limitation means that our study is unable to investigate alcohol role, which in fact may be inhibitory (de Menezes et al., 2013). Similar limitation probably does not exist for smoking habits, the self-reported current smoker proportion in controls (47%) being similar to what is expected in a French Polynesian population of the same age (Rasanathan and Tukuitonga, 2007), and an over-reporting of tobacco in cases being improbable. Nevertheless, smoking has been seen as negatively associated with thyroid carcinoma incidence in several studies (Hershman, 2012; Kabat et al., 2012; Kitahara et al., 2012; Zivaljevic et al., 2013), and additional data are needed to interpret the lack of association in our study (OR=1.1, 95%CI: 0.8 to 1.7) as a specificity of the French Polynesia population, rather than being due to hazard or to low power.

An interesting result of this study is the association between the effect of having or having had a private spring, rather than private or public cisterns collecting rainwater or public drinking water distribution networks, as main drinking water origin, and the risk of developing thyroid cancer. This result is coherent with recent results concerning fertilizers and incidence of cancer and exposure to fertilizer (Ward, 2009), and in particular with those of a cohort study which evidenced an increased risk of developing thyroid cancer in subjects having artesian well as drinking water origin (Ward et al., 2010). Nitrate concentration could be higher in water from artesian wells and personal untreated springs than in water from public water networks. Another explanation could be the occurrence of metals or other elements in water from artesian wells and personal springs. Indeed, the high incidence of thyroid cancer observed in islands, in particular in volcanic areas of some islands such as Sicily (Pellegriti et al., 2009), has been associated with a high concentration of metals in the drinking water (Malandrino et al., 2013). If such elements are in higher concentrations in artesian wells and personal spring water than in the public water networks, these findings could explain our results.

Thyroid cancer risk factors in French Polynesia were similar to those observed in other populations of the Asia and Pacific area. Some discrepancies, nevertheless, have to be noted.

The most controverted putative differentiated thyroid cancer risk factor is parity. Despite two case-control studies performed in China (Preston-Martin et al., 1993) and New-Caledonia (Truong et al., 2005) evidenced, as we did, an increased risk in women who were ever-pregnant, two cohort studies, performed in China (Wong et al., 2006) and Japan (Pham et al., 2009), did not evidence such an increased risk, and another performed in Thailand, although based on 17 cases showed a decreased risk (Sungwalee et al., 2013). Results in other populations are heterogeneous (Peterson et al., 2012) and this heterogeneity does not seem to be attributable only to differences in number of children between studied populations. As an example, no relation between number of pregnancies and risk of thyroid cancer was found in a large scale cohort study in which each woman had on average more than three children (Schonfeld et al., 2011). This heterogeneity remains to be explored and was observed both between recent studies (Schonfeld et al., 2011; Peterson et al., 2012) and between studies performed more than 20 years ago (La Vecchia et al., 1999). An explanation of this heterogeneity could come from cofactors. Indeed, the need for additional thyroid hormones during pregnancy leads to a multiplication of thyroid cells (Glinoer et al., 1990; Manole et al., 2001; Sack, 2013), and this multiplication could act by promoting carcinogens involved in cancer initiation. In our study, a positive significant (p=0.03) interaction was evidenced between nuclear fallout exposure and

pregnancy number: the increase in thyroid cancer risk when increasing thyroid radiation dose was limited to women having had four pregnancies or more (de Vathaire et al., 2010).

In comparison, body size, i.e., BMI (Renehan et al., 2008) and tallness (Engeland et al., 2006; Rinaldi et al., 2012), are established for thyroid cancer, and have been confirmed in Asian populations (Dal Maso et al., 2000; Suzuki et al., 2008; Kim et al., 2012).

Except for smoking, differentiated thyroid carcinoma risk factors in natives of French Polynesia are similar to those in other populations. Our finding on the role of having a spring as a drinking water origin is coherent with some other studies and could be due to geological factors.

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