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Incidence of thyroid cancer in adults recorded by French cancer registries (1978–1997)

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Abstract

This article analyses time trends and geographical variations of thyroid cancer by histological type. Incidence data were provided by 8 French cancer registries over the period 1978–1997, with 3853 adult cases reported. To assess the effects of age, period, cohort and area on incidence, log-linear Poisson regression models were used. Thyroid cancer increased exponentially from the cohort born in 1925. This increase was essentially due to papillary cancer, which increased by 6.2% per year in men and 8.1% per year in women over the entire period (1978–1997). In women, the recent trends were significantly different between the studied geographical areas. The analysis shows that the increase in thyroid cancer, essentially of the papillary type, is not recent. It may be attributed to a possible screening effect or to an increase in the number of "incidentally" discovered cases linked to the use of modern diagnostic tools.

Keywords: Thyroid cancer; Incidence; Time trends; Cohort effect

1. Introduction

In 1995, the incidence of thyroid cancer represented approximately 1% of all cancer cases in France [1], i.e. around 2600 cases. In areas covered by a cancer registry, a steady increase has been recorded since the mid-1970s. Different publications have described thyroid cancer time trends, confirming that thyroid incidence has been increasing in many countries. Pettersson and colleagues [2] describe an increase in papillary thyroid cancer in Sweden over the period 1958–1981, especially in women. These authors also mention a smaller increase for follicular cancer and a decrease in the incidence of anaplastic cancer. Akslen and colleagues [3] studied time trends for all histological types of thyroid cancer in Norway for the period 1955–1989. An increase in incidence with a cohort effect was observed. Dos Santos and colleagues [4] have published the trends in the incidence of thyroid cancer in England and Wales from 1962 to 1984. An increase in incidence among people under 45 years of age was observed. Zheng and colleagues [5] studied time trends in thyroid incidence in Connecticut from 1935 to 1992. An increase was observed, essentially for papillary cancer.

We used data on the incidence of thyroid cancer collected in 8 French cancer registries. This article consists of three parts. The first part studies time trends over 20 years (1978–1997) using data from 5 registries whose cancer registration covers the whole period. The second part evaluates the geographical variation in incidence

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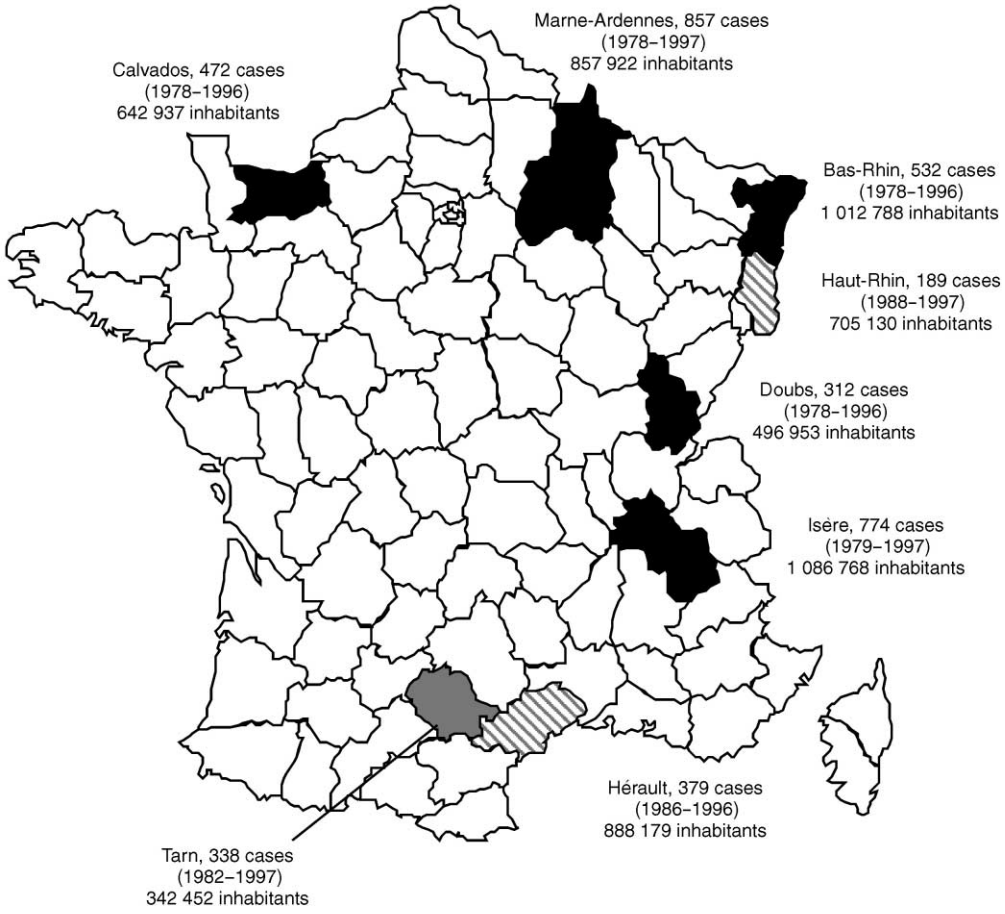

Fig. 1. Map of French cancer registries.

for the period 1988–1996, using data from the 8 cancer registries. Finally, using data provided by 6 cancer registries from 1982 to 1996, we studied how recent trends have changed with geographical area.

2. Patients and methods

2.1. Materials

The data used covered 20 years of registration of thyroid cancer cases, referenced by code 193 of the International Classification of Diseases—Oncology (ICD-O I, 1980). Tumours are classified in 4 groups: papillary cancer (histological codes 80503, 82603 and 83403), follicular cancer (histological codes 83303, 83313 and 83323), medullary cancer (histological codes 85103 and 85113) and anaplastic cancer (histological codes 80203 to 80413). All thyroid cancers are referred to as ''all histological types''.

Data were provided by 8 population-based cancer registries, using the same active search procedure (hospital and pathologist visits). Invasive carcinomas are included, but microcarcinomas could not be distinguished because stage at diagnosis is not recorded by the French cancer registries. Neither autopsy reports nor death certificates are used in French cancer registries. These registries cover 9 administratives areas (''départements''). These areas, the number of observed cases, the period covered and the number of inhabitants in 1997 are reported on a map (Fig. 1). Time trend analysis for the period 1978–1997 used data from 5 cancer registries (black coloured areas). The geographical variation study for the period 1988–1996 involved data from the initial 8 cancer registries. The spatio-temporal analysis for the period 1982–1996 concerned data from 6 cancer registries (black and grey coloured areas). We did not take into consideration cancers diagnosed in children (under 15 years of age), i.e. 23 cases (or 0.6% of the total number of cases).

2.2. Statistical methods

The data analysis was based on Poisson regression [6]. In short:

$$\mu(X) = E[k(X)] = e^{\beta X} m(X)$$
$$K(X) \sim \text{Poisson}(\mu(X))$$

Table 1
World age standardised rates[a] (per 100 000 person-years) and distribution of cases per histological type

	Papillary		Follicular		Anaplastic		Medullary		All	
	Rate	%	Rate	%	Rate	%	Rate	%	Rate	%
1978–1982	1.02	42.7	0.53	22.3	0.21	10.5	0.09	3.7	2.26	100
1983–1987	1.37	48.5	0.67	23.1	0.13	5.5	0.18	5.6	2.69	100
1988–1992	2.17	58.7	0.66	18.6	0.16	4.5	0.30	6.0	3.50	100
1993–1997	3.07	68.2	0.71	13.9	0.11	2.7	0.23	3.5	4.52	100
15–39 years	2.09	70.9	0.50	17.0	0.01	0.2	0.13	4.5	2.94	100
40–59 years	4.53	65.1	1.23	17.6	0.15	2.2	0.33	4.8	6.96	100
60+	2.77	38.7	1.42	19.9	0.86	12.0	0.35	4.9	7.14	100
Men	0.81	53.2	0.29	18.0	0.13	6.7	0.16	7.8	1.53	100
Women	3.05	59.8	0.98	18.2	0.16	4.2	0.24	3.8	4.96	100

[a] The rates in the 3 age groups were not standardised.

Where $K(X)$ and $m(X)$ are the number of cases and of person-years, respectively, corresponding to the set of covariates values defined by the (column) vector X. The (line) vector β is, therefore, the set of log(*relative rate*) comparing the incidence rate for a particular category of a given covariate to that of the corresponding reference category.

The 20-year time trend was analysed using an age-cohort model [7,8] where the cohort effect was modelled with a smoothing spline. The log(*relative rate*) for a cohort c, $\beta(c)$ was obtained by minimising a penalised deviance criterion that provides the best compromise between goodness of fit and smoothing level. The latter defined the equivalent degree of freedom used to fit the non-linear part of the model, which can then be tested for significance [9]. This method is an efficient way to describe the non-linear cohort effect. The available data were classified by histological type, 5-year age groups from 15 to 85+ years and 5-year periods from 1978 to 1997. This classification provides data for 18, 5-year birth cohorts born between 1893 and 1978.

The geographical analysis was carried out separately for each histological type using age and registry as categorical covariates. An age-standardised incidence ratio was then obtained comparing each registry with the Champagne–Ardennes registry, which recorded the largest number of cases. The comparison of time-trends between registries was carried out by testing the significance of an interaction term (registry-period) added to the linear period model [6]. We used world age-standardised rates in the description of our data.

3. Results

In Table 1, we present world age-standardised incidence rates and the distribution of cancer cases according to period, histological type, age and sex. Papillary cancer represented almost 70% of the cases for the period from 1993 to 1997, while these cases represented less than half of the cases for the period 1978–1982. In addition, the standardised incidence rate for papillary cancer was three times greater during the period 1993–1997 than during the period 1978–1982. The proportion of papillary cancers in people younger than 40 years old was high (70.9% of cases). Cancer incidence was over three times greater in women than in men except for medullary and anaplastic cancers where this ratio was less than 2. We observed a decrease in the incidence of anaplastic cancers and a dramatic increase in the incidence of papillary, follicular and the all histological type categories.

3.1. Time trends (1978–1997)

Temporal variations in the incidence rates were analysed using age-cohort models for papillary and follicular cancers and all histological types (Figs. 2 and 3), because the observed number of cases was high in these groups. A non-linear significant cohort effect was found for the group "all histological types" for both males and females. In this group, the increase of thyroid cancer became exponential (linear on the logarithmic scale) for cohort born after 1925, this exponential increase being higher in women than in men. The non-linearity of the logarithm of the incidence was significant ($P = 0.045$) for men and women. In women, the function describing the increase of thyroid cancer presented a weaker curvature than in men. For both men and women, we estimated an approximately 10-fold increase in the rate of thyroid cancer for those born in 1928 compared with those born in 1978. In Fig. 2 (men), we can see that there was some curvature in the follicular cancer trend (non significant). In women (Fig. 3), the incidence of follicular cancer increased slightly, but steadily. In both sexes, an exponential increase was found in papillary cancer from the first generation available. The annual rates of increase of papillary cancer incidence were 6.2 and 8.1% in men and women, respectively. Except for the "all histological type" group, the non-linear part of the models was not statistically significant. In other words, the most adequate description was a constant rate of increase since the cohorts born in 1925. There was no change in the rate of increase of radiation-induced cancer for the younger generations.

3.2. Geographical variations

Age-standardised incidence ratio (SIR) are reported according to sex and histological type (in Table 2), with the Marne–Ardennes areas used as a standard. The analysis was not performed for medullary and anaplastic cancers because the observed number of cases in each

geographical area was very low. The hypothesis of geographical homogeneity of the incidence rates in the eight areas was rejected for each histological type, with the exception of follicular cancers in men. The discrepancies among the areas were wider for women (range greater than 3-fold) than for men (range less than 2-fold). The highest incidence rates were observed in Tarn, except for follicular cancers. The highest incidence rates for "other histological type" in women were found in Calvados.

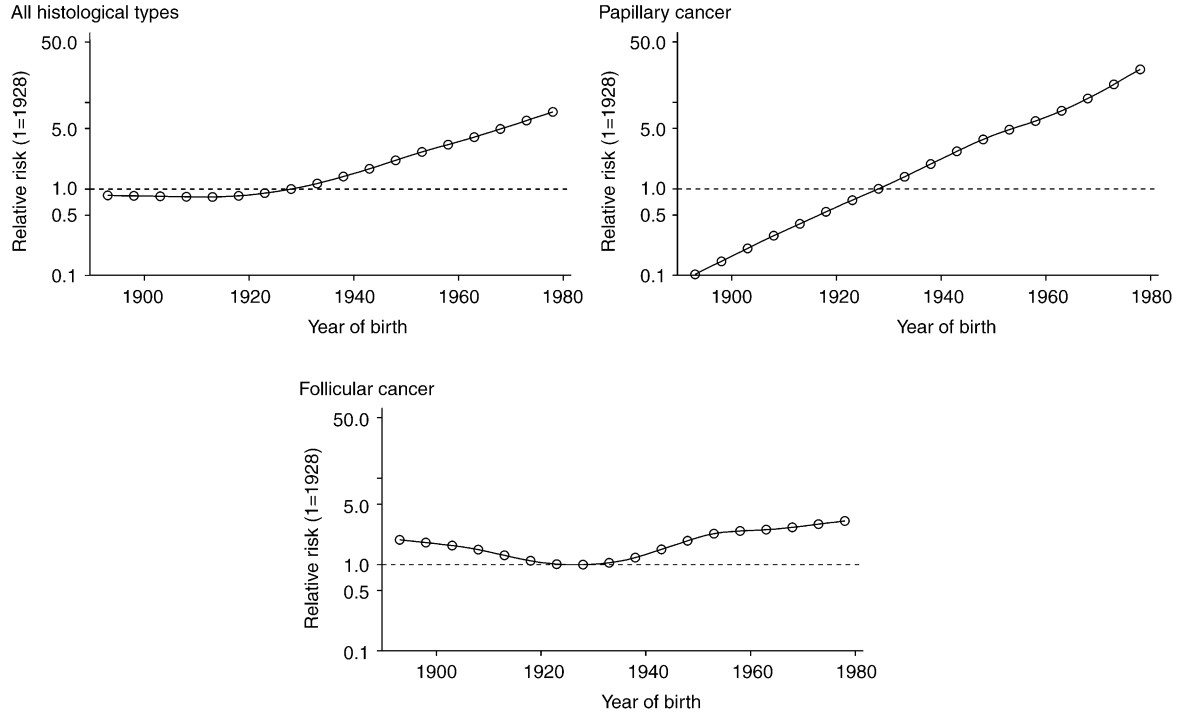

Fig. 2. Time trend analysis by histological type in men (5 cancer registries).

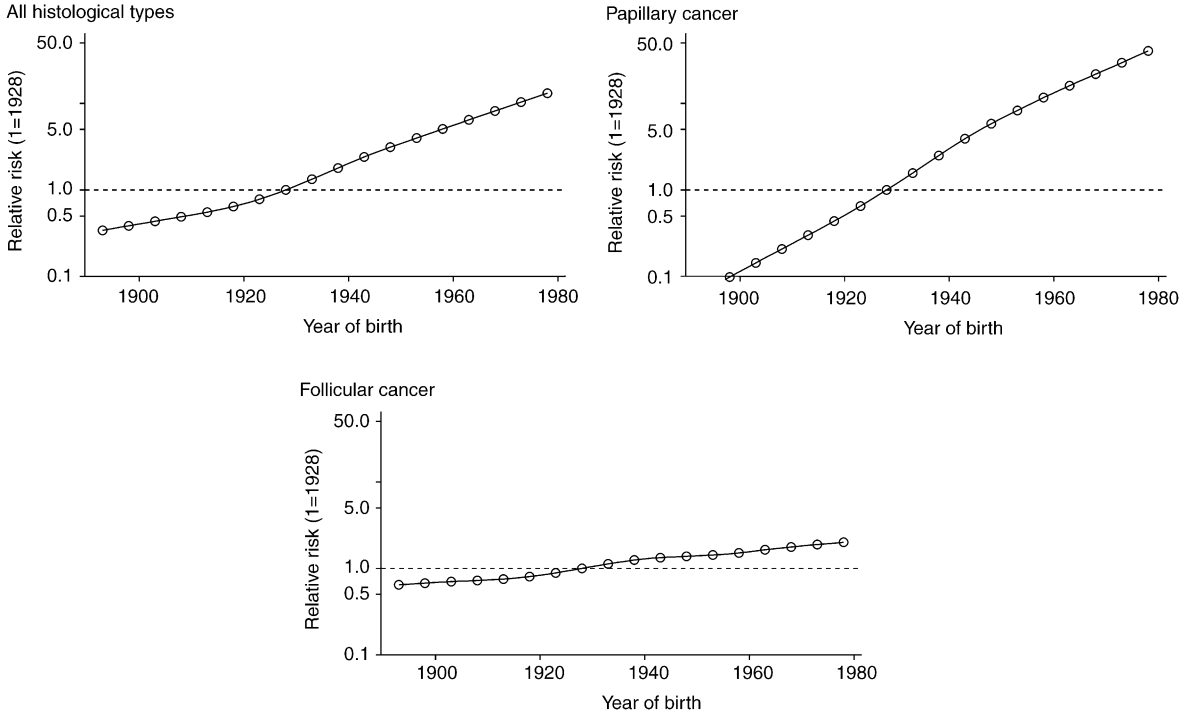

Fig. 3. Time trend analysis by histological type in women (5 cancer registries).

Table 2
. Geographical variation of thyroid cancer by sex and histological type

	Papillary SIR[a] (95% CI)[b]	Follicular SIR (95% CI)	Both SIR (95% CI)	Other SIR (95% CI)	All SIR (95% CI)
Women					
Marne–Ardennes	1	1	1	1	1
Calvados	1.01 (0.83–1.21)	1.07 (0.73–1.56)	1.02 (0.86–1.21)	1.67 (1.14–2.45)	1.10 (0.95–1.29)
Doubs	0.71 (0.56–0.89)	1.11 (0.74–1.67)	0.78 (0.64–0.96)	1.03 (0.64–1.65)	0.82 (0.68–0.98)
Hérault	0.63 (0.51–0.76)	0.60 (0.40–0.89)	0.62 (0.52–0.74)	0.85 (0.56–1.28)	0.65 (0.55–0.76)
Isère	0.73 (0.61–0.87)	0.68 (0.46–0.99)	0.72 (0.61–0.84)	0.99 (0.67–1.46)	0.75 (0.65–0.87)
Bas–Rhin	0.37 (0.30–0.46)	0.53 (0.35–0.79)	0.40 (0.33–0.49)	0.97 (0.66–1.44)	0.48 (0.40–0.57)
Haut–Rhin	0.33 (0.25–0.43)	0.33 (0.19–0.56)	0.33 (0.26–0.42)	0.88 (0.57–1.37)	0.40 (0.33–0.49)
Tarn	1.42 (1.16–1.74)	0.88 (0.54–1.41)	1.31 (1.09–1.58)	1.14 (0.71–1.83)	1.28 (1.07–1.52)
Men					
Marne–Ardennes	1	1	1	1	1
Calvados	0.88 (0.57–1.37)	0.38 (0.14–1.03)	0.75 (0.51–1.12)	0.46 (0.22–0.99)	0.67 (0.48–0.95)
Doubs	0.57 (0.33–0.98)	0.87 (0.39–1.94)	0.64 (0.41–1.01)	0.39 (0.16–0.95)	0.57 (0.38–0.86)
Hérault	0.89 (0.60–1.32)	0.97 (0.51–1.87)	0.91 (0.65–1.28)	0.62 (0.34–1.11)	0.83 (0.62–1.11)
Isère	1.00 (0.69–1.44)	0.95 (0.51–1.78)	0.99 (0.72–1.35)	0.50 (0.27–0.92)	0.85 (0.64–1.12)
Bas–Rhin	0.65 (0.43–0.98)	0.68 (0.34–1.37)	0.66 (0.46–0.94)	0.98 (0.58–1.66)	0.74 (0.55–1.00)
Haut–Rhin	0.75 (0.48–1.16)	0.47 (0.20–1.14)	0.68 (0.46–1.00)	0.90 (0.50–1.62)	0.74 (0.53–1.02)
Tarn	1.33 (0.85–2.09)	0.61 (0.23–1.66)	1.14 (0.76–1.72)	0.70 (0.34–1.45)	1.01 (0.71–1.44)

[a] SIR, age-standardised incidence ratio.
[b] 95% CI, 95% Confidence Interval.

3.3. Analysis and geographical comparison of recent time trends

Time trends were compared for the period 1982–1996 within three histological groups: "all histological type", papillary cancers, papillary and follicular cancers. We have fitted an overall log-linear model and a log-linear model with a different trend for each area (Table 3). The comparison of the deviances of these two models provides a test for trend homogeneity. Time trends were homogenous in the geographical areas for thyroid cancer among men, whereas we observed discrepancies among women. Table 4 shows this geographical heterogeneity in terms of the annual change in incidence rates.

Table 3
Assessment of the recent rate of increase and geographical homogeneity by sex and histological type

Histological type	Sex	Model[a]	Deviance	d.f.	*P* value
Papillary	Women	+ Time	197.24	1	<0.01
		+ Time×registry	21.53	5	<0.01
	Men	+ Time	20.44	1	<0.01
		+ Time×registry	9.03	5	NS
Papillary + follicular	Women	+ Time	162.12	1	<0.01
		+ Time×registry	30.43	5	<0.01
	Men	+ Time	17.03	1	<0.01
		+ Time×registry	6.32	5	NS
All	Women	+ Time	130.81	1	<0.01
		+ Time×registry	40.5	5	<0.01
	Men	+ Time	9.06	1	<0.01
		+ Time×registry	3.33	5	NS

NS, non significant. d.f., Degrees of freedom.
[a] All models include age group (15 d.f.) and registry (5 d.f.).

4. Discussion

Our results showed an increase in the past in thyroid cancer. We can see this increase from the beginning of the study period, which corresponds to the end of the 1970s. It is highly likely that there was already an increase earlier as shown in the Marne–Ardennes specialised registry, where registration started in 1975 [10]. Thus, this increase cannot be attributed to a possible "Chernobyl effect". Geographical variations in incidence and their spatial-temporal trends support this theory. The regions currently with the highest incidence are located in the Western part of France, hence less exposed to the radioactive fallout due to the 1986 Chernobyl accident.

Potential artefacts need to be considered before interpreting these results. Cancer registration may be more thorough in registries that have a higher incidence. There is no precise information available regarding the thoroughness of the thyroid cancer registration, but using comparative indicators there were no differences between registries [11].

The increase in incidence of thyroid cancer always corresponded to an increase in the papillary forms.

Table 4
Estimation of the annual rate of increase by histological type in women (1982–1996)

Histological type	Registry	Annual rate of increase	95% CI
Papillary	Marne–Ardennes	6.9	4.1 ; 9.8
	Calvados	15.3	11.1 ; 19.7
	Doubs	10.7	5.8 ; 15.8
	Isère	10.9	7.5 ; 14.5
	Bas–Rhin	7.5	3.3 ; 11.9
	Tarn	17.8	12.9 ; 22.9
Papillary + follicular	Marne–Ardennes	5.5	3.1 ; 8.0
	Calvados	14.3	10.7 ; 18.1
	Doubs	8.5	4.5 ; 12.6
	Isère	6.1	3.4 ; 8.9
	Bas–Rhin	5.2	1.7 ; 8.7
	Tarn	14.8	10.6 ; 19.2
All	Marne–Ardennes	3.9	1.8 ; 6.1
	Calvados	12.6	9.5 ; 15.8
	Doubs	8.1	4.5 ; 11.8
	Isère	4.4	2.0 ; 6.8
	Bas–Rhin	2.6	−0.2 ; 5.5
	Tarn	12.1	8.5 ; 15.9

Incidence of other types was either stable or had decreased. When we looked for environmental risk factors in the literature, this trend and its geographical heterogeneity are difficult to understand. Until the 1950s, there was probably an iodine deficiency in the mountain areas far from the sea, which may explain the high incidence in Tarn. However, it is difficult to explain the low incidence observed in other areas in the Eastern part of France. Thyroid cancer is related to dietary habits [12,13], however, differences in diet cannot explain the geographical heterogeneity we observed. The hypothesis regarding the effect of environmental contamination linked to atmospheric atomic weapon tests at the end of the 1950s suggested by Akslen for Norway and Petterson for Sweden, and more recently by Lund and colleagues [14] for both countries, does not agree with our observations regarding cohort effects. Radiation should have had a maximal effect on the cohorts born during the period 1945–1965 and exposed during childhood, since it is mainly exposure during early childhood that leads to an increase in risk [19].

For the differentiated types of cancer (essentially papillary carcinoma), we observed a steady increase in risk with date of birth for all cohorts. Taking into account all types of thyroid cancer, it seems that the increase started for people born after 1925, but this effect is only due to the decrease in the incidence of anaplastic cancer in the oldest cohorts. The most plausible explanation for the observed evolution is related to the evolution of medical attitudes regarding screening of thyroid problems, as well as monitoring and cure of benign thyroid conditions, which have led to a strong increase in incidental diagnosis and the discovery of less aggressive tumours. The fact that the observed increase is only related to differentiated cancers, essentially papillary cancers, supports this theory. Unfortunately, data on tumour size were not available for the whole study period. Because they have the most indolent clinical course, these differentiated cancers represent the largest group of occult cancers and thus are the most sensitive to more intensive diagnostic activity. The observation of a linear cohort effect is compatible with the hypothesis regarding the progression in referral to health-care in younger generations. This also applies to the greater increase in women, who are the major consumers of health-care and also because the prevalence of benign thyroid conditions is greater in women. It may also explain the regional discrepancies because practices differ greatly in France. Nevertheless, there is no indicator to precisely measure the use of techniques such as fine-needle biopsy, radioisotope thyroid scanning or indications for the surgical removal of a solitary thyroid nodule in the different regions of France. This hypothesis cannot be verified, but we have shown in previous studies (regarding prostate and lung cancers) marked differences in the use of surgery, that are more often employed in Tarn than in the other regions [15,16]. This difference is probably due to the higher density of physicians associated with the high proportion of private sector care in this area. Franceschi and colleagues [17] suggest a similar hypothesis for regional differences in the incidence of thyroid cancer in Italy.

The small increase in the incidence of follicular cancer is surprising because improvements in diagnostic practices should also affect the incidence of this type of cancer. This can possibly be explained by changes that have occurred in histological definitions. The World Health Organization (WHO)'s rules for the histological typing of the thyroid from 1988 [18] specify that all follicular cancers presenting a papillary component must be considered as papillary cancers. These rules have been progressively adopted at the end of the 1980s and the beginning of the 1990s. A large proportion of cancers, which would previously have been considered as follicular carcinomas or mixed papillary follicular adenocarcinomas (ICD-O M 8340/3), because of their architectural appearance or due to the fact that there is a small cellular portion presenting characteristic images on the nucleus, are now considered as papillary cancers. These cases, that were considered as benign (and not included in incidence calculation), are now classified as (malignant) papillary. The disappearance of iodine deficiency may also have led to a specific decrease in the number of cases of follicular cancers.

Finally, the decrease in rates of the anaplastic types of cancer can be explained by improved medical practices,

particularly earlier treatment of follicular tumours, which can now be diagnosed and treated before they develop into undifferentiated forms. In addition to the explanation provided by the changes in diagnostic practices, the influence of radiotherapy must be considered. Since the beginning of the century, exposure to X-rays used for diagnostic purposes has increased, mainly dental X-rays. However, for methodological problems, no study has convincingly shown an increased risk linked to radiological examinations in children. In contrast, there is some evidence that radiation therapy for benign conditions of the head and neck in children increases the risk of thyroid cancer, as shown, by Zheng [5] using data from Connecticut for children born between 1930 and 1950. Such treatment was not used in Great Britain [4] nor in Norway [3]. The general belief is that it was not routinely used in Europe and was only applied for skin problems, scalp ringworm or angioma until the early 1980s. In the absence of reliable data for France, it cannot be ruled out that it had some small effect on the risk of thyroid cancer.

In conclusion, our data show that the incidence pattern in recent decades may support the hypothesis of an exponential increase in papillary cancer in men and women from the first generation for whom data are available and this increase has remained at stable levels in the youngest cohorts. As in many countries, the increasing number of diagnostic investigations over time can be proposed as an explanation for the upward trends in the incidence of thyroid cancer. The exposure to radiation therapy for benign conditions in early childhood might explain a small part of this increase. Our analysis showed that there was no change in the recent trends in thyroid cancer following the Chernobyl accident. It does not exclude that such changes will occur later when the children who were possibly exposed in 1986 might develop the disease after a long latent period.

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