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A time trend analysis of papillary and follicular cancers as a function of tumour size: A study of data from six cancer registries in France (1983–2000)

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ABSTRACT

The incidence of thyroid cancers, and in particular the papillary forms, has been increasing sharply for many years in Western countries. However, the factors explaining this increase have not been clearly established. Some studies mention the effects of radioactive fallout, particularly after the accident in Chernobyl. Another probable cause is related to progress in medical practice, and particularly in diagnosis. In this article, we describe time trends in the incidence of papillary and follicular cancers, taking into account the size of the tumour at the time of diagnosis. The analysis was carried out on cases from six French cancer registries for the period 1983–2000. Anatomopathological reports concerning 3381 cancer cases were systematically recoded and centralised, following ICDO-3 rules. Over the whole period, the annual percent change of the incidence of papillary cancers was +8.13% and +8.98%, respectively in men and in women. For micropapillary carcinomas (⩽10 mm), this increase was respectively +12.05% and +12.85%. There is no significant effect of period apart from micropapillary carcinomas in women. However, a birth cohort effect exists for some groups. This effect corresponds to an acceleration in the risk for people born after the 1930s. For the most recent period (1998–2000), half the cases of papillary cancer were micropapillary carcinomas, and for one third of these, the tumour was ⩽5 mm. Our description of a time trend of incidence as a function of tumour size supports the hypothesis of the role of medical practice in a context of high prevalence. Obviously, these findings do not exclude the possible role of other factors.

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1. Introduction

Many epidemiological studies have described an increase in the incidence of thyroid cancers. This increase is observed both for earlier periods[1–5] and for more recent periods.[6–13] This increase does not involve all histological types; the incidence of papillary cancer only is increasing, while the incidence of other histological types either remains stable or decreases. Since exposure to ionising radiation has been shown to be a risk factor for papillary cancers, a doubt still exists about the possible role of radioactive fallout related to the accident in the Chernobyl nuclear plant. However, the fallout was relatively low in Western Europe.[14] Advances in diagnostic practices can also lead to a mechanical increase in the number of cancers detected.[11,15,16] Also, a further element to take into consideration in analysing the time trends in the incidence of papillary cancers is the effect of 'tumour classification'. The application of the 1988 WHO classification of differentiated thyroid carcinomas probably had the effect of transferring some diagnoses of follicular carcinomas or atypical adenomas into the category of follicular variants of papillary carcinomas.[11,16] The general description of the changes in thyroid cancer incidence in France has been summarised in a descriptive analysis.[9]

Our aim in this article is to study changes in the incidence of papillary and follicular thyroid cancers, and also the effect of tumour size. If the increase was found to be mainly in small papillary cancers, this would be a further argument to indicate the major role of advances in both diagnostic and therapeutic practices in the increase in incidence of thyroid cancers.

2. Material and methods

2.1. Cancer cases

The cases of cancer diagnosed during the 1983–2000 period in seven French administrative areas (*départements*) (Ardennes, Bas-Rhin, Calvados, Isère, Marne, Somme and Tarn) are based on a total general population of 4.6 million inhabitants (2000 census). These data were collected by six cancer registries, since the Ardennes and the Marne were covered by a single specialised registry for thyroid tumour. The observations from Calvados cover the period 1983–1999.

So as to describe the time changes in incidence using the homogenous definitions for the whole study period, all the anatomopathological case reports were centralised and coded using CIM-O 3 definitions and rules.[17] Based on these reports, the size of tumours on operative specimen, or by default, the post-operative T (33 cases) were colligated. Three size categories were defined:[18] tumours measuring 10 mm or less (microcarcinoma), tumours measuring 40 mm or less and tumours larger than 40 mm. All cases for which the size is unknown are put into the same category, whatever the reason for the absence of information. Papillary microcarcinomas are also placed in two sub-categories: tumours $\leqslant 5$ mm, and tumours >5 mm and $\leqslant 10$ mm. Only 21 microcarcinomas, indicated by pT only, could not be included in this detailed analysis.

2.2. Statistical method

The incidence data were analysed by standardising over the world population to estimate standardised rates; by using Poisson regression to estimate the annual rate percent change of the incidence; by using smoothing splines to determine the existence of a curvature in the change of incidence rate, either by period or by cohort. Smoothing spline functions of respectively the period effect and the cohort effect were estimated using a 'penalised deviance' criterion, which is a compromise between goodness-of-fit to the data and the complexity of the function sought.[19] In other words, spline functions are constructed between the only nodes – corresponding either to a period or to a cohort – giving sufficient information to characterise the curvature. In order to do this, the adjustment criterion (least squares) is increased – penalised – by information measuring the importance of the curvature at each of the curve. The Poisson regression and the smoothing spline models modelling the logarithm of the incidence took account of age, period and birth cohort by year.

3. Results

3.1. Cancer cases

For the 1983–2000 period, 3590 cases of differentiated thyroid cancers were recorded. There were 2901 papillary cancers (81%), 480 follicular cancers (13%) and 209 medullary cancers (6%). Only the papillary and follicular cancers were studied, i.e. 3381 cases. The anatomopathological report of the operative specimen was found for 3194 cases (95% of cases). For the remaining cases, 35 patients were not operated on (1%) and the report was not available for 152 cases (4.5%).

3.2. General characteristics of the cases studied

The median age of cases at the time of diagnosis is 47 years for papillary cancers (range: 15–94) and 52 years for follicular cancers (range: 16–90). Eighty percent of all cases are women. The histological type most frequently encountered is papillary cancers, covering 84% of cases in men and 86% of cases in women (Table 1). For follicular cancers, the majority of tumours measure between 10 and 40 mm in both sexes. This category is the most numerous for papillary cancers in men, whereas papillary cancers measuring less than 10 mm are most frequent in women, representing 45% of the total. Very small tumours ($\leqslant 5$ mm) are the most numerous papillary microcarcinomas (61% of men and women together), for both sexes (Table 2).

3.3. Changing trends according to histological type and size

This trend is described in terms of annual percent change for the 1993–2000 period (Table 3) and in terms of standardised rates by comparing the rates for 1983–1986 with those for 1995–2000 (Table 4). Over the whole of the 1983–2000 period, follicular cancers decreased slightly in men, dropping from 0.25 per 100,000 in 1983–1988 to 0.16 in 1995–2000, and were

Table 1 – Distribution of cases by histological type, sex and tumour size

	⩽10 mm		[10–40]		>40 mm		Unspecified		Total
	Cases	%	Cases	%	Cases	%	Cases	%	Cases
Papillary									
Men	197	34.2	263	45.7	58	10.1	58	10.1	576
Women	1040	44.7	986	42.4	152	6.5	147	6.3	2325
Follicular									
Men	5	4.5	52	46.4	33	29.5	22	19.6	112
Women	30	8.2	206	56.0	73	19.8	59	16.0	368

Table 2 – Distribution of cases by sex and tumour size (micropapillary cancers)

	⩽5 mm		[5–10]		Total
	Cases	%	Cases	%	Cases
Men	114	58.5	81	41.5	195
Women	626	61.3	395	38.7	1021

Table 3 – Annual percent change of incidence (with 95% confidence intervals) by histological type, sex and tumour size

	Annual percent change	95% lower	95% upper
Papillary, Men	8.13	6.32	9.97
Papillary, Women	8.98	8.06	9.90
Follicular, Men	−2.24	−5.70	1.34
Follicular, Women	−0.47	−2.43	1.52
Papillary depending on size			
Papillary ⩽10 mm, Men	12.05	8.68	15.53
Papillary ⩽10 mm, Women	12.85	11.35	14.38
Papillary [10–40 mm], Men	7.99	5.33	10.71
Papillary [10–40 mm], Women	8.80	7.40	10.22
Papillary >40 mm, Men	8.86	3.18	14.85
Papillary >40 mm, Women	2.42	−0.72	5.66
Papillary, Size unknown, Men	−2.73	−7.48	2.26
Papillary, Size unknown, Women	−5.12	−8.10	−2.05
Micropapillary			
Papillary, ⩽5 mm, Men	13.44	8.88	18.20
Papillary, ⩽5 mm, Women	14.64	12.61	16.70
Papillary, [5–10 mm], Men	10.61	5.58	15.89
Papillary, [5–10 mm], Women	11.23	8.89	13.62

stable in women, remaining at 0.72 per 100,000 (Tables 3 and 4) with annual percent changes of −2.24% and −0.47%, respectively. The analysis by size for this histological type showed no time trend except for a decrease in the incidence of cases of unknown size (results not reported). The increase in papillary cancers is high for both sexes. In women it rose from 2.65 per 100,000 in 1983–1988 to 7.5 in 1995–2000, which is an annual percent change of 8.98%. In men, it rose from 0.78 to 1.82 per 100,000, which is a mean variation of 8.13%. For these cancers, the study by size shows that the sharpest increase was observed for cancers smaller than 10 mm, with a yearly progression of over 12% in men and women, which corresponds to a 4-fold increase in the incidence rate. In this group, tumours measuring 5 mm or less increased annually by 13% in men and 14% in women. Tumours measuring over 40 mm are increasing in men, but are stable in women. The number of cancers for which the size is unknown is decreasing, particularly in women.

3.4. *Description of the shape of the trend*

In order to specify the shape of the progression of the incidence in papillary cancers, we tested the statistical significance of both a non-linear period effect, and of a non-linear birth cohort effect for the logarithm of the incidence. The results of the tests given in Table 5 present additional information concerning the relative risks according to period (Figs. 1–4) with the year 1990 as reference and according to birth cohort (Figs. 5–8) with the birth year 1940 as reference.

What is primarily apparent is that the linear model for the logarithm of the incidence correctly represents the period effect, except for micropapillary cancers (⩽10 mm) in women with an acceleration of the risk in recent years. The fluctuations in trend, particularly according to size for small papillary cancers in men, are not significant. Contrary to what is observed for the period, the linear model is not sufficient to describe correctly the birth cohort effect in women, whatever the size of the tumour, nor in men for small tumours (⩽10 mm). However, the linearity cannot be excluded for papillary cancers measuring 5 mm or less.

Thus for all papillary cancers, an acceleration in trend is observed according to birth cohort starting with cohorts born in 1935–1940, and this acceleration is more marked in women

Table 4 – World age-standardised incidence rates (with 95% confidence intervals) and number of observed cases by histological type, sex, period and tumour size

Histological type	Period	Men				Women			
		Cases	WASR[a]	Lower	Upper	Cases	WASR[a]	Lower	Upper
Papillary	1983–1988	110	0.78	0.63	0.93	388	2.65	2.38	2.92
	1995–2000	292	1.82	1.61	2.03	1218	7.5	7.07	7.93
Follicular	1983–1988	38	0.25	0.17	0.32	110	0.72	0.58	0.86
	1995–2000	27	0.16	0.1	0.22	123	0.72	0.59	0.85
Papillary [0–10 mm]	1983–1988	26	0.18	0.11	0.26	120	0.85	0.7	1.01
	1995–2000	116	0.71	0.58	0.85	602	3.71	3.41	4.01
Papillary [10–40 mm]	1983–1988	52	0.38	0.27	0.48	160	1.12	0.95	1.3
	1995–2000	131	0.83	0.69	0.98	519	3.23	2.95	3.52
Papillary >40 mm	1983–1988	8	0.05	0.02	0.09	45	0.24	0.16	0.31
	1995–2000	29	0.17	0.11	0.24	63	0.36	0.27	0.46
Papillary, unspecified size	1983–1988	24	0.16	0.1	0.23	63	0.44	0.33	0.55
	1995–2000	16	0.1	0.05	0.15	34	0.2	0.13	0.27
Papillary [0–5 mm]	1983–1988	15	0.11	0.05	0.17	64	0.44	0.33	0.55
	1995–2000	71	0.28	0.2	0.36	382	2.35	2.11	2.59
Papillary [5–10 mm]	1983–1988	11	0.07	0.03	0.12	51	0.37	0.27	0.48
	1995–2000	45	0.28	0.2	0.36	217	1.33	1.15	1.52

a WASR: world age standardised rates.

Table 5 – *p-Values corresponding to curvature test (period spline and cohort)*

	Effect of cohort		Effect of period	
	Men	Women	Men	Women
Papillary	<0.001	<0.001	NS	NS
Follicular	NS	0.03	NS	NS
Papillary [0–10 mm]	<0.01	<0.001	NS	<0.05
Papillary [10–40 mm]	NS	<0.001	NS	NS
Papillary >40 mm	NS	<0.001	NS	NS
Papillary, unspecified size	<0.05	<0.001	NS	NS
Papillary [0–5 mm]	NS	<0.001	NS	NS
Papillary [5–10 mm]	<0.01	<0.001	NS	NS

NS: not significant.

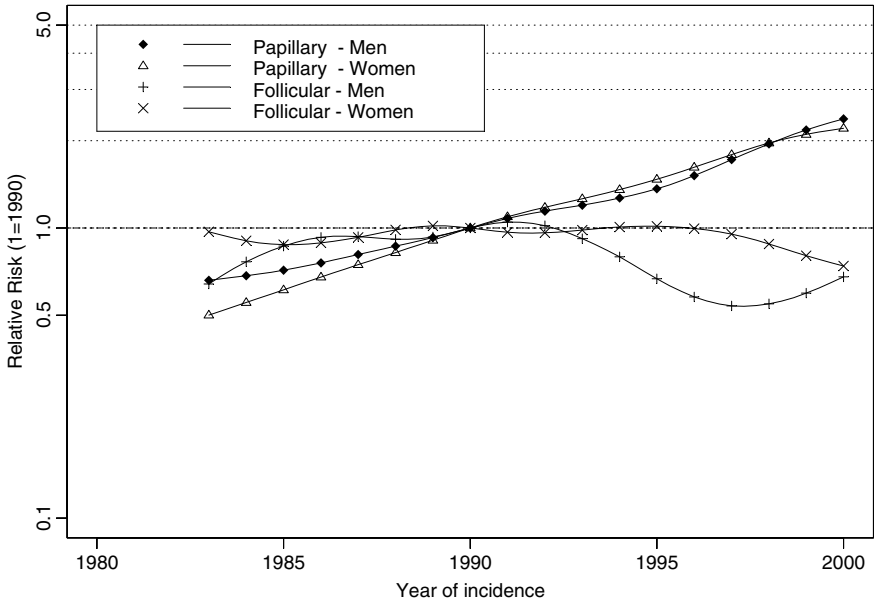

Fig. 1 – Relative risks of incidence according to period by histological type and sex.

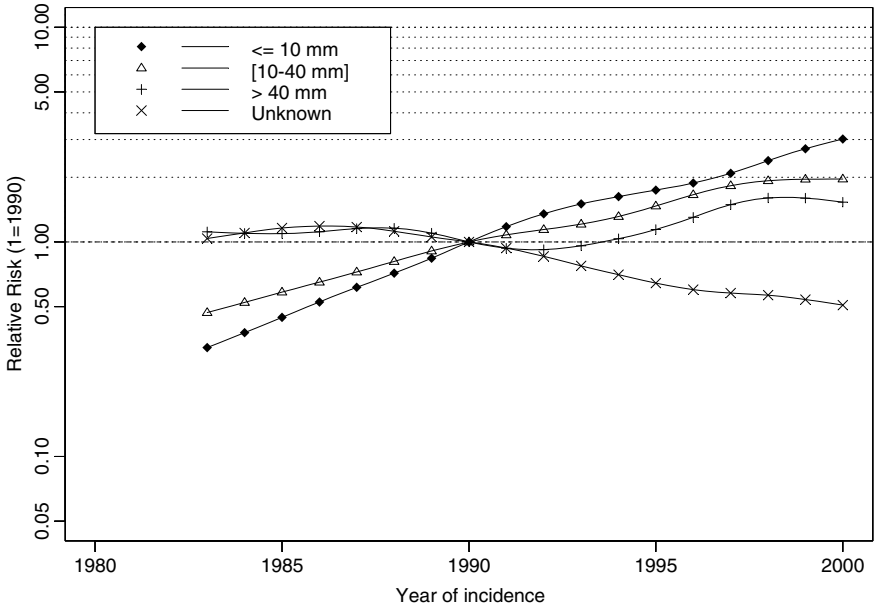

Fig. 2 – Relative risks of incidence according to period by tumour size – papillary cancers, women.

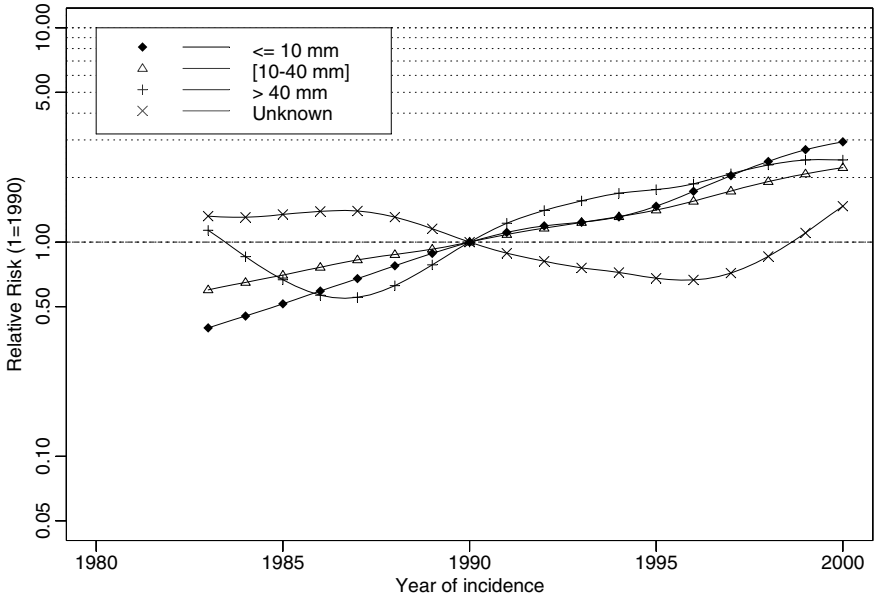

Fig. 3 – Relative risks of incidence according to period by tumour size – papillary cancers, men.

than in men. The risk for women born in 1975 is 12.5 times greater than for women born in 1940. For men, the corresponding relative risk is 9.

The progression according to birth cohort of the incidence of papillary cancer tumours as a function of tumour size in women shows a change in trend beginning with the 1930–1935 cohorts. The sharpest acceleration is observed for small tumours ($\leqslant$10 mm), whereas the acceleration is smallest for tumours >40 mm. The relative risk for women in the 1975 cohort compared with those in the 1940 cohort is 27 for tumours $\leqslant$10 mm, 13.5 for tumours measuring 10–40 mm and 7 for tumours >40 mm. The increase in relative risk is continuous for tumours of 40 mm or less, whereas the increase in tumours of over 40 mm concerns only women born in or after 1940. The relative risk of tumours of unknown size is decreasing constantly.

The trend according to birth cohort in men taking the size of papillary cancers into account is harder to describe since there is no statistical significance for certain categories. However, there are certain similarities with the trend observed for women: a trend break for cohorts born between 1930 and 1935, although these breaks are not statistically significant for medium to large tumours, and a decrease in relative risk for tumours of unspecified size for recent cohorts. Nevertheless, the relative risks according to birth cohort are lower than those observed for women, which is

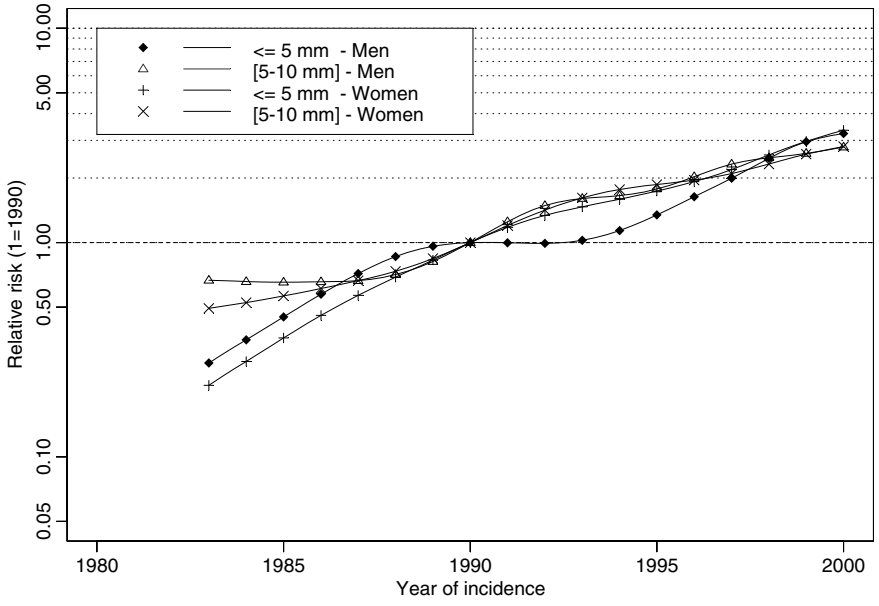

Fig. 4 – Relative risks of incidence according to period by tumour size and sex – micropapillary cancers.

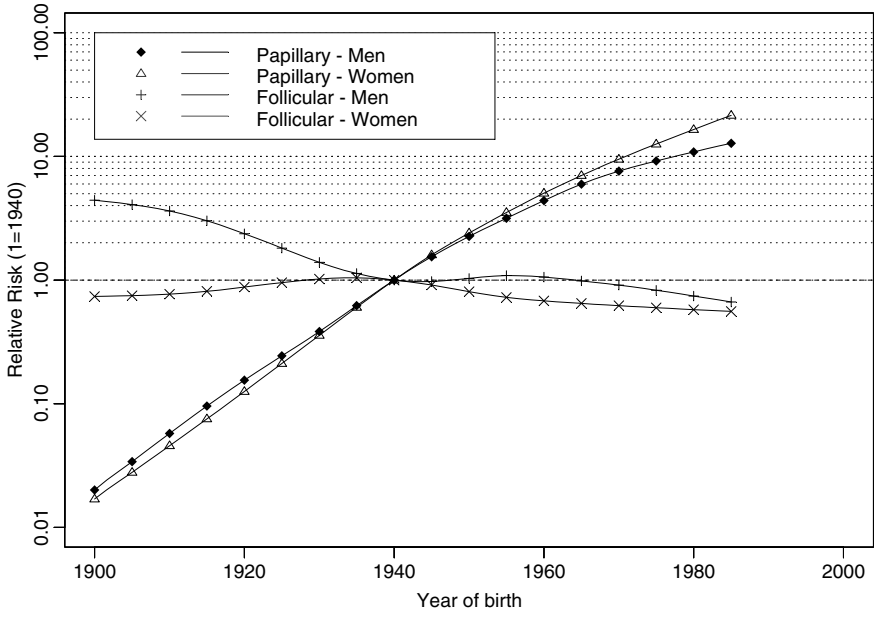

Fig. 5 – Relative risks of incidence according to cohort by histological type and sex.

interpreted as a slower acceleration by cohort: the estimated relative risk of the 1975 cohort compared with the 1940 cohort is 17 for tumours of 10 mm or less, and 11 for tumours measuring between 10 and 40 mm and tumours of over 40 mm. It is also noticeable that the incidence of large tumours has a similar type of progression to that of the intermediate sized tumours, which was not the case for women. Obviously this statement needs to be qualified by taking account of the number of papillary cancers occurring in men. A third difference from the trend observed for women concerns the relative risks curve for small tumours, which shows a recent slowing of the increase of relative risk according to birth cohort.

For papillary microcarcinomas, it is noted that the increase in relative risk by cohort accelerates from year of birth 1935, although this break is not significant for men. The relative risks of the 1975 cohort compared with the 1940 cohort are 95 for women and 65 for men for tumours of 5 mm or less, and 27 for women and 7 for men for 5–10 mm tumours. The relative risk curve shows a slowing of the increase of 5–10 mm tumours in men, although the curvature test is not statistically significant.

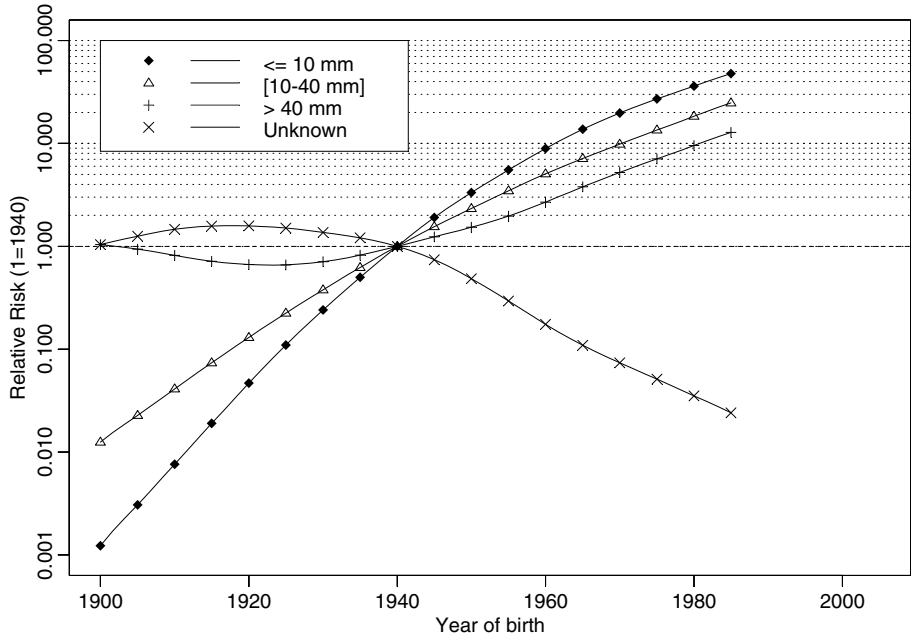

Fig. 6 – Relative risks of incidence according to cohort by tumour size – papillary cancers, women.

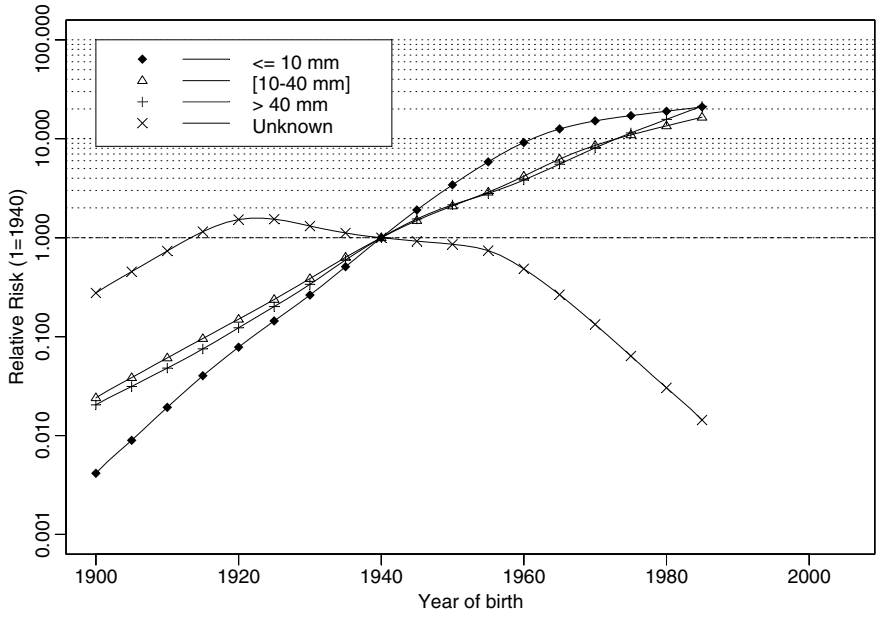

Fig. 7 – Relative risks of incidence according to cohort by tumour size – papillary cancers, men.

4. Discussion

4.1. *Confirming the hypothesis of the increase of small tumours*

Our study's description of the change in incidence trends confirms the hypothesis about the major increase in small papillary tumours, which was the hypothesis that had already been put forward to explain the time trend of thyroid cancer incidence in France.[9] These results are particularly robust because they concern a cohort including a large number of cases – over 3000 cases – diagnosed in a population of over 4.6 million inhabitants. The interest and scope of the study are also reinforced by the systematic recovery of anatomopathological reports with centralised recoding of histological type according to ICDO-3[17] including data on the size of the tumour. This systematic recoding frees the study from the effects of the 1988 WHO classification of thyroid tumours, which were clearly shown in the study by Verkooijen and colleagues (436 thyroid cancers diagnosed in the Geneva Canton in Switzerland for the 1970–1998 period).[11]

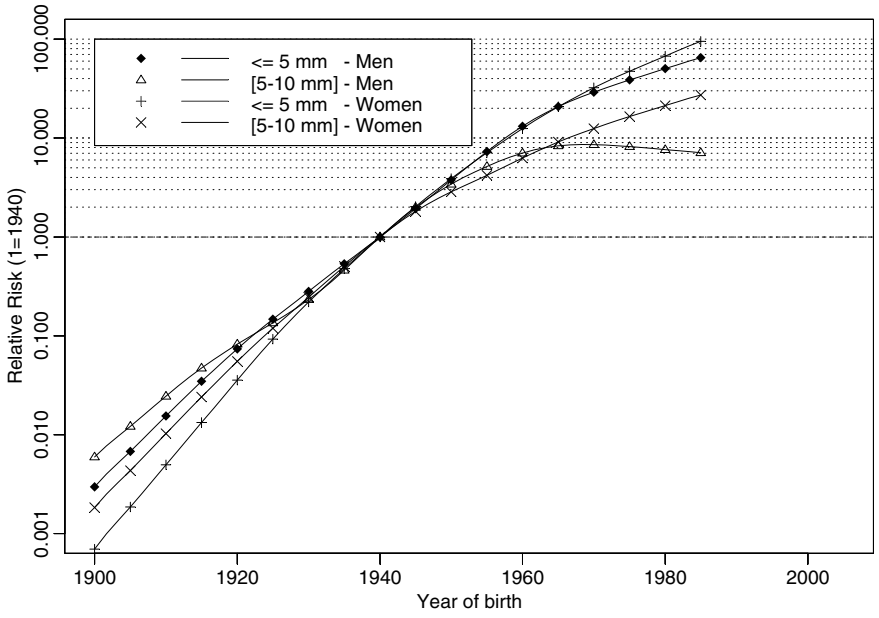

Fig. 8 – Relative risks of incidence according to cohort by tumour size and sex – micropapillary cancers.

4.2. *Details about the increase in the number of cases according to tumour size*

The smaller the tumour, the greater the increase in the incidence of papillary cancers: half the papillary tumours diagnosed during the 1998–2000 period were micropapillary (⩽10 mm), and a third measured 5 mm or less. Over the same period, the number of cases of unspecified tumour size decreased sharply. This decrease cannot explain the increase in the number of small tumours. The lack of size information does not depend so much on the tumour size as on the practice of certain anatomopathological structures. The number of cases of tumours of unspecified size decreased between the years 1983–1985 and 1998–2000, whereas the number of tumours ⩽10 mm increased 9-fold over the same periods. Thus there is a real differential increase according to size. Few publications exist describing, in the general population, either the recent situation, or the increase in papillary cancers as a function of tumour size. In France, a specific study in the Marne and Ardennes *départements* showed an increase in the proportion of micropapillary carcinomas between the 1983–1987 period (18% of papillary carcinomas were micropapillary) and the 1998–2001 period (43% of papillary carcinomas were micropapillary).[20] This is a similar proportion to the data from all French registries under consideration, since our study found a proportion of 47% of microcarcinomas among papillary cancers for the 1995–2000 period. A change in the distribution of the size of papillary cancers has also been described in the USA,[21] where the estimated proportion of micropapillary cancers within papillary cancers was 27% in 1996. In Switzerland, an increase was observed in thyroid microcarcinomas, mainly of the papillary type, which rose from 17% for the 1970–1979 period to 24% for the 1990–1998 period.[11]

4.3. *Increased incidence rate: medical practices as an explanatory factor*

One of the characteristics highlighted in our work is the increase in incidence for the whole period of observation, with a birth cohort effect. Although trend changes by cohort are sometimes difficult to determine accurately, particularly in men, overall there is a noticeable acceleration in the increase in trend, starting with cohorts born between 1930 and 1935, when the cohort born in 1940 is taken as a reference.

Since our study is purely descriptive, it is not possible to give an answer in terms of association between a potential risk factor (or factors) and the observed increase in incidence. However, it is possible to verify the plausibility of certain explanatory hypotheses.

The mechanism of the change that we observe corresponds to an increase in the incidence that is inversely proportional to tumour size, which adds weight to the hypothesis of a diagnostic effect. The emergence of a risk factor would give rise to a similar increase for all tumour sizes. It is well known that medical practices have evolved over the last 20 years[15,16] with the introduction of thyroid ultrasonography and fine-needle aspiration biopsy (FNA), and with greater awareness of thyroid pathology both in practitioners and in the general public. Thyroid surgery is constantly increasing, with more systematic use of total thyroidectomy even for benign pathologies, which makes it easier to detect microcarcinomas. And this advance in practices is occurring in a context of high prevalence of the disease in the population. Different autopsy series have shown the high proportion of occult thyroid carcinomas, even though the prevalence observed fluctuates according to the series. Most of these occult carcinomas correspond to very small papillary cancers. The prevalence of occult papillary cancers has been shown to be 2%,[22] 7.3%,[23] 11.3%,[24] and

35.6%.[25] Francilla and colleagues[26] mention a prevalence of 14% in an autopsy series in children and young adults. Kovacs and colleagues[27] estimate that the presence of thyroid microcarcinomas in the autopsy series is between 100 and 1000 times greater than what was detected clinically. This great divergence between prevalence and incidence, associated with advances in medical practice, fits with an increased incidence rate of cancers, particularly those involving small tumours.

The fact that there is a greater increase in incidence in women than in men supports the hypothesis of the role of medical practice. This is due to two things: women take up medical care and preventive measures more readily than men; and there is a greater prevalence of benign thyroid pathologies in women than in men.[9] A recent case-control study showed that reproductive and hormonal factor may contribute to the risk of thyroid cancer among women.[28] Lastly, the observed cohort effect is compatible with the hypothesis of the change in consumer behaviour of younger generations concerning medical care.

4.4. *Increased incidence rate: ionising radiation*

Ionising radiation is a known risk factor for papillary cancers. The hypothesis of an effect due to increased ambient radiation from atmospheric nuclear tests at the end of the 1950s, posited by Akslen[2] for Norway and Petterson[1] for Sweden, and more recently for both countries by Lund,[29] is not confirmed by our observations on cohorts. The ionising radiation effect should have been maximal on cohorts born during the period 1945–1965 and exposed during childhood, given that it is mainly exposure during childhood that is known to increase the risk. However, for papillary cancers, we observed an increase in risk for all cohorts, even if an acceleration was noted starting with the cohort born at the end of the 1930s.

A second potential source of radiation is linked to the exposure of the population to diagnostic X-rays, particularly for dental examinations, which is constantly increasing. However, no research has convincingly shown an increase in risk associated with X-ray examinations during childhood. This absence of proof is related to the methodological difficulties involved in retrospective studies. As well as exposure during examinations, there is the possibility of an effect of the use of radiation therapy for benign conditions of the head and neck in children. This risk factor was posited by Zheng and colleagues[4] in a study of a cohort of children from Connecticut born between 1930 and 1940. It seems that this medical practice was used relatively rarely in Europe.[2,3,11]

Finally, a third source of exposure to be taken into consideration is the effects of radioactive fallout after the Chernobyl accident in 1986. In a recent study, Montanaro and colleagues[13] raises the question of the effect on the incidence of thyroid cancers based on the observation of an increased risk among recent cohorts in Switzerland. However, these authors underline the important variability of the estimates in these cohorts for which the number of observed cases is low. We cannot confirm this observation from our results. Our results show a strong linear effect of the time trend over the whole period for papillary cancers, however the trend shows curvatures on the cohorts' scale. These curvatures are seen for cohorts born in the 1930s, a generation less concerned by a possible Chernobyl effect than recent cohorts, in our case the 1971–1986 cohorts. As Montanaro and colleagues emphasise, post-Chernobyl monitoring is needed to be able to validate and interpret the time trend.

5. Conclusion

It is important to highlight factors that explain the increase in papillary cancer. Our observations are a contribution to the idea of a role of medical practice in the increase and acceleration of the incidence rate. This is extremely important, because any wrong interpretation of the causes of the increase can have negative consequences. For example, knowing the link between excess iodine and the frequency of these cancers,[30] the increase in the incidence of papillary cancers should not be used as a basis for reducing iodine supplementation as practiced in European countries with iodine deficiency.[31]

Also, our findings emphasise the issues involved in medical practice, because highlighting the stage as a favourable prognostic factor for thyroid cancer[32] should not hide the compromise that needs to be found between over-diagnosis and beneficial early screening.

Conflict of interest statement

None declared.

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REFERENCES

1. Pettersson B, Adami H, Wilander E, Coleman M. Trends in thyroid cancer incidence in Sweden, 1958-1981, by histopathologic type. *Int J Cancer* 1991;**48**:28–33.
2. Akslen L, Haldorsen T, Thorensen S, Glattre E. Incidence pattern of thyroid cancer in Norway: influence of birth cohort and time period. *Int J Cancer* 1993;**53**:183–7.
3. Dos Santos I, Swerdlow A. Thyroid cancer epidemiology in England and Wales: time trends and geographical distribution. *Br J Cancer* 1993;**67**:330–40.

4. Zheng T, Holford T, Chen Y, et al. Time trend and age-period-cohort effect on incidence of thyroid cancer in Connecticut, 1935-1992. *Int J Cancer* 1996;**67**:504–9.
5. Lundgren CI, Hall P, Ekbom A, Frisel J, Zedenius J, Dickman P. Incidence and survival of Swedish patients with differentiated thyroid cancer. *Int J Cancer* 2003;**106**:569–73.
6. Haselkorn T, Bernstein L, Preston-Marin S, Cozen W, Mack WJ. Descriptive epidemiology of thyroid cancer in Los Angeles County, 1972–1995. *Cancer Causes and Control* 2000;**11**:163–70.
7. Liu S, Semenciw R, Ugnat AM, Mao Y. Increasing thyroid cancer in Canada, 1970–1996: time trends and age-period-cohort effects. *Br J Cancer* 2001;**85**:1335–9.
8. Burgess JR. Time trends for thyroid carcinoma in Australia: an increasing incidence of papillary thyroid carcinoma. *Thyroid* 2002;**12**:141–9.
9. Colonna M, Grosclaude P, Remontet L, et al. Incidence of thyroid cancer in adults recorded by French cancer registries (1978–1997). *Eur J Cancer* 2002;**38**:1762–8.
10. Reynolds R, Weir J, Stockton D, Brewstert D, Sandeep TC, Strachan M. Changing trends in incidence and mortality of thyroid cancer in Scotland. *Clinical Endocrinology* 2005;**62**:156–62.
11. Verkooijen HM, Fioretta G, Pache JC, et al. Diagnostic changes as a reason for the increase in papillary thyroid cancer incidence in Geneva, Switzerland. *Cancer Causes and Control* 2003;**14**:13–7.
12. Crocetti E, Capocaccia R, Casella C, et al. Population-based incidence and mortality cancer trends (1986–1997) from the network of Italian cancer registries. *Eur J Cancer Prevention* 2004;**13**:287–95.
13. Montanaro F, Pury P, Bordoni A, Lutz JM and the Swiss Cancer Registries Network. Unexpected additional increase in the incidence of thyroid cancer among a recent birth cohort in Switzerland. *Eur J Cancer Prevention* 2006;**15**:178–86.
14. Cardis E, Krewski D, Boniol M, et al. Estimates of the cancer burden in Europe from radioactive fallout from the Chernobyl accident. *Int J Cancer* 2006;**119**:1224–35.
15. Leenhardt L, Bernier MO, Boin-Pineau MH, et al. Advances in diagnosis practices affect thyroid cancer incidence in France. *Eur Journl Endocrinol* 2004;**150**:133–9.
16. Leenhardt L, Grosclaude P, Chérié-Chlline L. Recommendations pour la mise en place d'un dispositif de surveillance épidémiologique nationale. Institut de Veille Sanitaire, Saint Maurice, Avril 2003 (disponible sur http://www.invs.sante.fr).
17. International Classification of Diseases for Oncology. Edited by A Fritz, C Percy, A Jack, et al. Geneva: WHO, 3rd ed, 2000.
18. UICC. TNM classification of malignant tumors. Edited by LH Sobin and Ch Witterkind. New York: Wiley, 5th ed., 1997, 180–82.
19. Green PJ, Silverman BW. Non parametric regression and generalized linear model: a roughness penalty approach. London: Chapman and Hall; 1994.
20. Leenhardt L, Grosclaude P, Cherie-Challine L. Increased incidence of thyroid carcinoma in France: a true epidemic or thyroid nodule management effects? Report from the French Thyroid Cancer Committee. *Thyroid* 2004;**14**:1056–60.
21. Hundahl SA, Cady B, Cunningham MP, Mazzaferri E, McKee J, Rosai J. Initial results from a prospective cohort study of 5583 cases of thyroid carcinoma treated in the United States during 1996. U.S. and German Thyroid Cancer Study Group. An American College of Surgeons Commission on Cancer Patient Care Evaluation study. *Cancer* 2000;**89**:202–17.
22. Solares CA, Penalonzo MA, Xu M, Orellana E. Occult papillary thyroid carcinoma in postmortem species: prevalence at autopsy. *Am J Otolaryngol* 2005;**26**:87–90.
23. Autelitano F, Spagnoli LG, Santeusanio G, Villaschi S, Autelitano M. Occult carcinoma of the thyroid gland: an epidemiological study of autopsy material. *Ann Ital Chir* 1990;**61**:141–6.
24. Yamamoto Y, Maeda T, Izumi K, Otsuka H. Occult papillary carcinoma of the thyroid. A study of 408 autopsy cases. *Cancer* 1990;**65**:1173–9.
25. Harach HR, Franssila KO, Wasenius VM. Occult papillary carcinoma of the thyroid. A "normal" finding in Finland. A systematic autopsy study. *Cancer* 1985;**56**:531–8.
26. Franssila KO, Harach HR. Occult papillary carcinoma of the thyroid in children and young adults. A systematic autopsy study in Finland. *Cancer* 1986;**58**:715–9.
27. Kovacs GL, Gonda G, Vadasz G, et al. Epidemiology of thyroid microcarcinoma found in autopsy series conducted in areas of different iodine intake. *Thyroid* 2005;**15**:152–7.
28. Memon A, Darif M, As-Saleh K, Suresh A. Epidemiology of reproductive and hormonal factors in thyroid cancer: evidence from a case-control study in the Middle East. *Int J Cancer* 2002;**97**:82–9.
29. Lund E, Galanti M. Incidence of thyroid cancer in Scandinavia following fallout from atomic bomb testing: an analysis of birth cohorts. *Cancer Causes and Control* 1999;**10**:181–7.
30. Ron E. Thyroid cancer. In: Schottenfeld D, Fraumeni JF, editors. *Cancer Epidemiology and Prevention*. New York: Oxford University Press; 1996. p. 1000–21.
31. Delange F, Benker G, Caron P, et al. Thyroid volume and urinary iodine in European schoolchildren: standardization of values for assessment of iodine deficiency. *Eur J Endocrinol* 1997;**136**:180–7.
32. Lundgren CI, Hall P, Dickman PW, Zedenius J. Clinically significant prognostic factors for differentiated thyroid carcinoma. A population-based, nested case-control study. *Cancer* 2006;**106**:524–31.