Geographical correlation between incidence of benign disease and that of cancer of the thyroid among the population of the Rhône-Alpes région of France

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Abstract

Objective: To analyse, at a population level, the relation between the incidences of benign thyroid disease in patients submitted to surgery and that of thyroid cancers based on their respective geographical distributions.

Methods: The study included 3169 cases (691 cancers, 2478 benign diseases) operated on in 2002 in the Rhône-Alpes region, subdivided into 8 départements and 311 cantons.

Results: The total intervention rate (TIR) was 54.6/100 000 (23.4 and 86.4) and annual cancer incidence was 11.9/100 000 (4.7 and 13.8) for men and women, respectively. The prevalence of cancer among thyroid surgery was 21.8% and that of cancer discovered in goiters increased with age (44% at 60 yrs). Intervention rates varied from department to département. In women the incidence of microcancers was correlated to the rate of intervention for benign diseases (TIBR). In men, the incidence of supracentimetric cancers was related to the TIBR. At the canton level, the relative risk of benign diseases was correlated to that of cancers. TIBR and incidence of cancers were higher in urban cantons than in non urban ones. The density in endocrinologists influenced the prevalence of cancers among all cases submitted to surgery.

Conclusion: In the Rhône-Alpes population with high rates of thyroid cancer incidence and of thyroid surgery, a number of correlations were found according to gender and tumor size. However, the general incidence of cancer was not directly related to surgical activity. Geographical variability may be related to heterogeneous medical and pathological practices.
Introduction

That malignant and benign diseases of the thyroid gland could be interconnected was suggested at the beginning of the 20th century in endemic goiter areas such as the Alps where severe iodine deficiency was common and thyroid cancer morbidity and mortality were high (1, 2). This close geographical relationship was reported by Alexis Carrel in 1901 (1), when he wrote in his thesis (translated from French): “Numbers of benign and malignant tumours oscillate in parallel; where goiter is common, cancer is frequent”. This probably reflected a common view which was later shared by Wegelin commenting on observations in Switzerland (2). More recently, case-control studies performed in Switzerland (3) and Northern Italy (4) highlighting long-term residence in iodine deficient areas with endemic goiter as a risk factor for thyroid cancer provide further evidence for a geographical link between the two. However, despite increasing interest in the geographic distribution of diseases, no recent study has been performed on the relationships between these pathologies. Since the presentation of more than 10% of school age children with thyroid hyperplasia in the Rhône-Alpes in the 1980’s, this région of France has been considered an area of endemic goiter (5). Including around 10% of the French population, this région encompasses areas varying widely in terms of physical and human geography. Analysis of a regional thyroid cancer registry in existence since 1998 has suggested temporal and geographical variations in thyroid cancer incidence (6). By contrast, no recent epidemiological data is available concerning benign thyroid diseases, due to the difficulty in assessing their prevalence at the population level. The sub-population of patients operated on for benign disease is however more easily attainable. Numbers within this population clearly depend on the medical practices leading up to the surgical decision, as is the case for the apparent incidence of thyroid cancer (7).

We hypothesized that the incidence of cancer relates directly to surgical activity. Accordingly, we analysed the relations between incidence of benign thyroid diseases in
patients submitted to surgery and thyroid cancer within one year at the population level in the Rhône-Alpes région of France by comparing their respective geographical distributions.

Materials and methods

Thyroid Cancer:

The Thyroid Cancer Registry of the Rhône-Alpes région is a population-based collection of histologically proven incident cases (6). Cases are transmitted from various sources each assuring satisfactory completeness: pathology reports provided by the 30 histopathology laboratories within the Rhône-Alpes région, card-index of 103 surgical wards, and hospital claims databases as previously reported (8). Cancers found in surgical specimens associated with benign pathology (adenoma or goiter) are recorded as cancers.

A total of 691 incident cases of thyroid cancer were recorded in the year 2002 (169 men and 522 women) (Table 1). Mean age at diagnosis of cancer was 49 y in men and 50 y in women. 4105 incident cases of thyroid cancer were recorded for the period 1998-2004 (966 in men and 3139 in women) and were used for the cantonal geographical distribution

Benign thyroid diseases:

For the year 2002, we studied all surgical interventions related to benign thyroid disease. The procedure was the same as the one used in the case of cancer in terms of collecting pathology reports and controlling for completeness of data collection. Cases were considered as benign after pathological examination. The same methodology and codification were used by all pathology laboratories included in the Rhône-Alpes thyroid Cancer Registry since 1998 allowing also for a homogeneous classification of benign diseases at diagnosis.

In this study we used the following terminology to describe the benign diseases: 1) Solitary adenomas had no hyperplastic surrounding parenchyma. A true adenoma was characterised by an architecture differing from the surrounding normal tissue. Adenomas were classified as micro or macrofollicular, oncocytic or atypic. 2) Benign goiter defined all
multinodular or uninodular goiters; uninodular goiter showed the same architecture as the surrounding tissue which was diffusely hyperplastic. This series contained no cases of simple hyperplastic goiter. 3) Hyperthyroidism corresponded to Grave’s disease, multinodular hyperfonctional goiter and toxic adenoma. 4) Other diagnoses included rare cases of lymphocytic thyroiditis and cysts.

A total of 2478 such patients underwent surgery during 2002 including 486 men and 1992 women. Benign goiters, euthyroid or toxic, represented more than half of the total (Table 1). Mean age at diagnosis of benign diseases was 52.7 y in men and 50.9 y in women.

Data Analyses

Several age-adjusted rates (using the world population age structure) were calculated as numbers of cases vs population: a) total thyroid intervention rate (TIR); b) thyroid intervention for benign pathologies rate (TIBR); c) thyroid intervention for benign goiter rate (TIGR); d) incidence of all cancer rate; e) rate of incidence of microcancers; and f) rate of incidence of supracentimetric cancers. Moreover we calculated the prevalence of cancers in all thyroid surgery (%) and the prevalence of cancers discovered in patients operated on for “clinical goiter” (comprising goiters considered as benign by histopathology and those associated with a cancer)

Geographical distribution

All patients selected for the study lived in the Rhône-Alpes région during the study period and geographical distribution was based on each patient’s place of residence.

Distribution according to département

We firstly analysed the geographical variations of incidence and intervention rates for each of the 8 départements (administrative divisions) in the Rhône-Alpes région with populations ranging from 294,000 to 1,616,500. The following age-adjusted incidence rates (using the world population age structure) were calculated as a function of gender: a) the TIR, b) the TIBR, c) the TIGR and d) the incidence rate of all cancers, and of supracentimetric (>1cm) and of microcancers (≤1cm). The prevalence of cancer among all interventions was
also recorded. The relative risk (RR) within each département of cancer and benign goiter was calculated as the ratio between the values obtained for the département and those for the whole Rhône-Alpes région, considered as the reference. The density of endocrinologists for each département (i.e. the number of endocrinologists per 100,000 inhabitants) was calculated. All correlations were analysed using non-parametric Spearman correlation tests.

Distribution according to canton

There are 311 cantons (electoral districts) in the Rhône-Alpes région of which 56 (18%) are urban and 255 (82%) are rural or semi-rural, according to the Institut National de la Statistique et des Etudes Economiques. For each canton, we calculated the incidence rate of cancer and interventions for benign diseases for both men and women. To obtain sufficient data concerning cancer incidence per canton we considered all cases over the 6 year-period from 1998 to 2004. Geographical analysis was performed using a mixed Poisson model as previously reported (6). The covariates introduced into the model with fixed effects were: age, physician density (i.e. the number of general practitioners per 1,000 inhabitants) and the urban/rural characteristics of the canton. Canton was introduced into the model assuming a random effect and, for each canton, its relative rates (using the whole Rhône-Alpes région as a reference) were estimated using a shrinkage estimator (9) and mapped using the Arcview 3.1 software.

Results

Thyroid surgery was performed in a total of 3169 patients during the year 2002 in the Rhône-Alpes région. Overall, 21.8% (20% in women and 26% in men) of all interventions concerned thyroid cancer. The overall crude TIR was 54.6 /100 000 (23.4 and 86.4 for men and women, respectively). Standardized rates were as follows: TIBR (thyroid intervention for benign pathologies Rate) 13.8 and 55.0/100 000 and TIGR (thyroid intervention for goiter Rate) 6.3 and 27.3 /100 000 for men and women, respectively. Standardized incidence rates of
cancer were 4.7 and 13.8/100 000 in men and women, respectively.

Of the cancers discovered, the percentage of microcancers ≤1 cm was 40.4% (30.7% in men, 44.5% in women) and that of cancers ≤ 0.5 cm was 27%. The mean prevalence of cancers discovered inside a goiter represented 31.7% (23% in men and 34.5% in women), 60% of which were microcancers ≤ 1 cm (65% in women and 59% in men). These percentages differed according to the age groups (Table 2). Four percent of cancers coexisted with hyperthyroidism, and 12% were in the vicinity of benign adenomas in the same patient. Overall, cancers were found in 15% of all patients operated on for “clinical goiter”.

**Distribution according to département**

The TIR, TIBR, TIGR and the incidence of cancers varied widely among the départements but were consistently 3 times higher in women than in men (Figure 1, Table 3). The prevalence of cancers found among the total number surgical interventions for thyroid disease (benign and malignant) was variable ranging from 13% in Haute-Savoie, the département with the highest TIR, to 27% in both the Rhône département, the one with the second highest TIR, and the Loire département, with a low TIR (Table 3). The prevalence of cancers and that of microcancers in all thyroid surgery were strongly correlated (r=0.80; p=0.02)

Figure 2 shows the variability in the incidence rates of supra and infracentimetric cancers between départements. Rates also differed between men and women, with rates of supracentimetric cancers higher to that of microcancers in men in most départements. Incidence rates of infracentimetric cancers are higher in women than in men corresponding to the distribution of microcancers which is globally higher in women than in men. (43% versus 33%).

The relationships between cancer incidence and TIBR, microcancer incidence and TIBR and TIGR, and the supracentimetric cancer incidence and TIGR are shown in Figures 3-5. The prevalence of cancers in all the goiters operated on and the relative risk (RR) of benign
goiter and of cancer are shown in Figure 5. We found no correlation between the incidence rates of all cancers and TIBR in men or in women (Figure 3). A significant correlation was found, however, between the incidence rates of microcancers and TIBR, but only in women (r=0.71 p=0.05) (Figure 4). In men, we found a trend towards a correlation between the incidence of supracentimetric cancers and TIGR (r=0.57 p =0.15) (Figure 5A), that was not found in women (data not shown). A significant correlation was found between the prevalence of cancers discovered in all cases of clinical goiter and TIGR (r=0.71; p=0.05) (figure 5B). The respective risks of benign pathology on one hand and of cancer on the other, calculated as described above, were evaluated with respect to each département. Relative risks of cancer and benign goiter only showed a relation in men. (r= 0.55, p=0.17) (Figure 5C). This correlation was highly significant when the data from Haute-Savoie département were removed (r=0.85, p=0.02).

The density in endocrinologists varied from 0.3 in the Ardèche département to 4.5 / 100 000 in the Rhône. This showed no relation to the various intervention rates but a significant relation, in men, to the prevalence of cancers found in all operations (r=0.68 p<0.05) and to the incidence of supracentimetric cancers (r=0.71, p<0.05). We also found a trend towards a correlation between density in endocrinologists and incidence rates of all cancers in men and women (r=0.52 and 0.56 respectively) but not with the incidence rates of microcancers in men and women.

**Distribution according to canton**

The cantons were divided into urban (41% of the whole regional population) and non urban (rural and semirural) (59% of the whole regional population). Differences between rural and urban were statistically significant. Both cancer incidence and TIBR were higher in urban than non urban cantons (Table 4). Cancer incidence was 28% lower in men (relative rate: 4.3/6=0.72) and 15% lower in women (relative rate 14.4/17=0.85) in rural compared to in urban cantons. The TIBR was 10% lower in rural than in urban cantons [22% in men (relative
rates 15.4/19.8 = 0.78) and 4% in women (relative rate = 66.4/68.8=0.96)].

The Poisson mixed model with adjustment on all covariates confirmed these results. General practitioner density did not appear to have a significant effect on incidence of benign and malignant diseases, whether in men or in women. There was a large variability in the intervention and incidence rates of benign and malignant diseases respectively between the cantons varying from -52% to +110% for TIBR and from -40% to +70% for cancer incidence. Relations between benign pathology and cancers according to canton were evaluated in terms of risk for both. A weak yet significant correlation was found only in men (r= 0.26 p<0.05). We also found a correlation between the risks of benign pathology in both men and women (r=0.35 p<0.05).

Figure 6 shows the variability of incidence rates of cancer and of TIBR in men within each canton after adjustment for men's age and the rural/urban characteristic of the canton.

Discussion

Increasing incidence in thyroid cancer has been reported in various countries (10-15). Increased diagnostic activity leading to an increased incidence of small cancers has been advocated as one of the possible causes of this epidemiologic observation (10, 14). Incidental cancers detected in surgical specimens have recently been reported to represent a third of all cancers (6). This was confirmed in the present study since 30% of cancers were discovered within goiter and 15 % of all cases of “clinical goiter” were found to coexist with a cancer. The prevalence of cancers discovered in goiters increased with age, reaching 41.8% in patients older than 60 years. We have previously reported that the incidence of thyroid cancer dramatically increased with age (6). All these data are in accordance with the well-known effect of age on the incidence of thyroid pathology. In the present study. The prevalence of incidental cancers is probably underestimated since partial thyroidectomy was performed in more than 20% of patients. These data are in keeping with the notion that a personal history of
benign pathology, namely a goiter, is a risk factor for thyroid cancer, as has previously been reported in a number of case control studies (16-23).

The present study used a novel population approach to investigate the relations between benign disease and cancer of the thyroid. We hypothesized that, within a defined geographical area, the incidence of cancer would relate to surgical activity in particular that concerning benign goiter, mostly multinodular.

In 2002, high rates of surgical procedures on the thyroid (54.6 per 100 000 person/year) were reported in the Rhône-Alpes, a région of France with 6 million inhabitants and formerly considered a zone of endemic goiter. This can be attributed to a high incidence of goiter, responsible for 50% of surgery performed on the thyroid for benign disease. In 2002, the incidence of thyroid cancer was 11.9 per 100 000 and the prevalence of cancers found during surgery was 21.8%. These results differ from those reported for the same period in the USA where the total thyroid intervention rate was 19.7/100 000 and the percentage of cancers found was 33% (10, 24). As the cancer incidence rates between the USA and France are comparable (6, 10), differences in the intervention rate for thyroid benign disease could explain these discrepancies. It is to be noted that in the Rhône Alpes region, the incidence of thyroid cancer was stable between 2001 and 2006.(6)

In order to investigate the existence of a link between benign and malignant disease, we studied the geographical distribution of both in administrative areas of varying size i.e. départements and cantons within the Rhône-Alpes région of France.

Differences between départements were found when the prevalence of cancers discovered in all operated cases was considered. This prevalence was higher in university hospitals than in general non-academic ones indicating a preoperative selection directed towards cancer.

Although we found together a high rate of surgical intervention and a high incidence of thyroid cancer, our analysis did not reveal a clear relation between surgical intervention
rates for benign diseases and incidence of cancer. However, some relations could be seen when the results were analysed according to gender and tumor size. Indeed, our results suggest a link between cancer and benign disease in men. At the département level, a significant correlation was found between the prevalence of cancer discovered coexisting with goiter, and the intervention rate for benign goiter. A trend towards a correlation was found between the incidence of supracentimetric cancer and surgery for benign goiter. Concordantly, a weak but significant relation was shown between cancer and benign disease at the canton level. In women, a significant relation was found between surgery for benign disease and the incidence of microcancers, which represent a high proportion (45%) of all cancers, most of which were located within the goiter. Generally, microcancer incidence (or in situ cancer) is commonly considered as a strong indicator of medical intervention. The present study shows a parallel between the incidence of microcancers in women and the rate of thyroidectomy.

The cantonal study revealed no zone of over-incidence of benign and malignant disease occurring concomitantly. The existence of any environmental risk factor(s) common to benign and malignant disease in a particular zone of residence would have induced a strong link in incidences at the canton level. As this was not the case, the strong intervention of any common environmental factor may be excluded and the risks in relation to different environmental factors specific to urban and non urban cantons can be considered as having, if any, a very limited influence. Indeed, the differences in incidence of either class of disease are only significant in men. The modestly lower incidence of both benign and malignant disease in rural zones argues against agricultural products having any noticeable influence. The weak over-incidence in urban cantons could be related to factors other than environmental, namely the proximity to health care services with an increased density in urban compared to rural cantons.

Our data suggested no influence of density in general practitioners at the canton level.
Density in endocrinologists did not influence the total rate of intervention on the thyroid at the département level. It did however relate to the prevalence of cancers found in surgical interventions indicating an effect of selection. Since endocrinologists practise in urban zones, this may explain the weak over-incidence compared to rural zones corresponding to the ease of access, especially for men who consult less often than women and mainly for “clinical” diseases.

This epidemiologic study based on a one-year observation has several limitations. Firstly, the histopathological examinations were performed by a large number of pathologists working in 30 different laboratories. A revision of all specimens by the same pathologist or group of pathologists was unrealistic. Secondly, the differential diagnosis of cancers and adenomas can be difficult. In the Rhône-Alpes région, the most doubtful cases are usually sent for revision to one of us (NDB) which consequently leads to at least some homogeneity. Thirdly, while extensive pathological examination of surgical specimens was performed for any cases of goiter considered as benign, the discovery of microcancers depends highly on the number of slides used which may occasionally differ between laboratories. The strong correlation between the prevalence of cancers and that of microcancers among all thyroid surgeries suggests, however, a reasonable homogeneity in the pathology procedures within the participants to Rhône-Alpes Thyroid Cancer Registry. Nevertheless, pathology practices may clearly influence the prevalence of cancers. Other hypotheses to explain variability of incidence rates and prevalence of cancers between départements may include rurality with less favourable access to specialized care, geographic diversity and iodine supply during childhood.

The choice of the benign disease constitutes the major drawback of this study. It was decided that all cases submitted to surgery and classified as benign by histopathology would constitute the core of this group since it appeared unrealistic to record all consultations for thyroid disease in the region. We worked on the assumption that all cases submitted to
surgery corresponded to the prevalence of all thyroid diseases. On this basis, medical practices are clearly the main determinants of the incidence of cases submitted to surgery. The decision to operate was based on local discomfort, hyperthyroidism in nearly 8% of cases, or suspicion of an associated cancer difficult to eliminate by preoperative examination. To our knowledge there exists no consensus criteria for cases, clinically considered as benign, to be referred for surgery. Decision for surgery depends on the patient (where they live, how their illness is perceived, their consent to operate), the physicians, general practitioner or endocrinologist, and principally the surgeon. However, most surgeons working in our region have been trained in the same academic hospitals and participate to regional meetings chaired by one of us (JLP), a member of the French association of endocrine surgery. The role of the type of medical practice has been mentioned above. We were unable to identify other factors that might interfere with the incidence of malignant or benign diseases. Other limitations in the study may relate to the choice of the study areas with precise population sizes. Indeed, the small number of départements (8) could limit the significance of the differences observed. Cantons may also be too small to contain sufficient numbers of patients.

Altogether, these limitations could explain the discrepancy in results obtained in some départements such as the Haute-Savoie, where the very high risk of benign disease (mainly goiter), is associated with a cancer incidence was lower than the regional average, both in men and women. Such limitations are intrinsic to a population study performed in real life situations and may also explain the lack of a comparable study in the literature.

In conclusion, In the Rhône-Alpes population with high rates of thyroid cancer incidence and of thyroid surgery, a number of correlations were found according to gender and tumor size. However, the general incidence of cancer was not directly related to surgical activity. Geographical variability may be related to heterogeneous medical and pathological practices.
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Legends of tables and figures

Table 1 Gender distribution of pathological diagnosis in the 3169 patients who had undergone thyroid surgery in the Rhône-Alpes région in the year 2002.

Table 2: Age-group distribution of the percentage of cancers discovered in goiters.

Table 3 Distribution among the départements, according to gender, of the thyroid intervention rate (TIR), thyroid intervention benign rate (TIBR) and thyroid intervention goiter rate (TIGR). The incidence rates of cancers, microcancers and supracentimetric cancers, and the prevalence of cancers in all interventions are also shown. (Age adjusted incidence rates).

Table 4: Incidence rates of benign diseases and cancers / 100 000 person-year according to urban/rural characteristics of the canton.

Figure 1: Distribution among each département of the thyroid intervention rate (TIR), thyroid intervention benign rate (TIBR), thyroid intervention goiter rate (TIGR) and the incidence rates of cancers (crude rates). Rhône-Alpes represents the mean values of the whole région.

Figure 2: Distribution of incidence rates of supra and infracentimetric cancers in men and women according to département

Figure 3: Correlations between TIBR and incidence of cancers, in men and women according to département (non-parametric Spearman correlation tests).

Figure 4: Correlations between TIBR (A), TIGR (B) and incidence of microcancers in women (non-parametric Spearman correlation tests).

Figure 5: Correlations between TIGR and prevalence of cancers in interventions for clinical goiter (A), between TIGR and incidence of supracentimetric cancers (B), and relative risks (RR) of cancer and goiter (C), in men (non-parametric Spearman correlation tests) according to département.

Figure 6: Distribution of relative rates of benign (A) and cancer (B) incidences in men according to canton. The covariate introduced in the model is the urban / rural characteristic of the canton.
Figure 1
Figure 2

Graph showing the distribution of cancer cases between men and women in different regions of France, categorized by cancer size.
Figure 3

Men

Incidence of cancer

TIBR

Women

Incidence of cancer

TIBR

$r = 0.40$

ns

$r = 0.04$

ns
Figure 4

Women

(A) Incidence of microcancer vs. TIBR. The correlation coefficient is $r = 0.71$, with a p-value of $0.05$.

(B) Incidence of microcancer vs. TIGR. The correlation coefficient is $r = 0.61$, with a p-value of $0.11$.
Figure 5
Figure 6
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<th>Men</th>
<th>Women</th>
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<td><strong>Cancers</strong></td>
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<td>522 (20.7)</td>
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<td><strong>Benign diseases</strong></td>
<td>486</td>
<td>1992</td>
<td>2478</td>
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<td>- Solitary adenomas</td>
<td>215 (44)</td>
<td>690 (34.6)</td>
<td>905 (36)</td>
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<tr>
<td>- Benign goiters</td>
<td>218 (44)</td>
<td>1000 (51)</td>
<td>1218 (49.2)</td>
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<td>- Hyperthyroidism</td>
<td>32 (6.5)</td>
<td>152 (7.6)</td>
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<td>- Others</td>
<td>21 (4.3)</td>
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Table 1
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Table 3
<table>
<thead>
<tr>
<th></th>
<th>Incidence rates in urban cantons</th>
<th>Incidence rates in rural and semi rural cantons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cancers</td>
<td>Benign</td>
</tr>
<tr>
<td>Men</td>
<td>6</td>
<td>19.8</td>
</tr>
<tr>
<td>Women</td>
<td>17</td>
<td>68.8</td>
</tr>
<tr>
<td>Total</td>
<td>11.8</td>
<td>45.5</td>
</tr>
</tbody>
</table>

Table 4