Regional Variation in Thyroid Cancer Incidence in Belgium Is Associated With Variation in Thyroid Imaging and Thyroid Disease Management

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Context: Increased thyroid cancer incidence is at least partially attributed to increased detection and shows considerable regional variation.

Objective: We investigated whether regional variation in cancer incidence was associated with variations in thyroid disease management.

Design: We conducted a retrospective population-based cohort study that involved linking data from the Belgian Health Insurance database and the Belgian Cancer Registry to compare thyroid-related procedures between regions with high and low cancer incidence.

Main Outcome Measures: Primary outcome measures were rates of TSH testing, imaging, fine-needle aspiration cytology (FNAC), and thyroid surgery. Secondary study outcomes were proportions of subjects with thyrotoxicosis and nodular disease treated with surgery, of subjects treated with surgery preceded by FNAC or with synchronous lymph node dissection, and of thyroid cancer diagnosis after surgery.

Results: The rate of TSH testing was similar, but the rate of imaging was lower in the low incidence region. The rate of FNAC was similar, whereas the rate of surgery was lower in the low incidence region (34 [95% CI 33; 35 ] vs 80 [95% CI 79; 81 ] per 100 000 person years in the high incidence region; \( P < .05 \)). In the low incidence region compared to the high incidence region, surgery represented a less chosen therapy for euthyroid nodular disease patients (47% [95% CI 46; 48] vs 69% [95% CI 68; 70]; \( P < .05 \)), proportionally more surgery was preceded by FNAC, more cancer was diagnosed after total thyroidectomy, and thyroid cancer patients had more preoperative FNAC and synchronous lymph node dissection.

Conclusion: Regional variation in thyroid cancer incidence, most marked for low-risk disease, is associated with different usage of thyroid imaging and surgery, supporting variable detection as a key determinant in geographic variation. (J Clin Endocrinol Metab 98: 4063–4071, 2013)
cancer incidence has been associated with enhanced use of ultrasound (US), fine-needle aspiration cytology (FNAC), and surgery (8, 9). Recently, this view has been challenged. A real increase may also be present because several studies reported an increase of large tumors and of more advanced disease stages (10–13). The etiology of a possible real increase may be due to higher exposure to ionizing radiation (mainly from multiple diagnostic procedures at a young age) and other environmental factors like iodine intake (14–16).

Geographical variation in thyroid cancer incidence and associations with various environmental factors have also received worldwide attention. Case control studies of dietary iodine intake in regions with a high thyroid cancer incidence gave inconsistent results (17, 18). Geographical variation was not associated with iodine sufficiency or deficiency in Sicily where an association with a volcanic environment has been described (19). Higher thyroid cancer incidences have been described near nuclear power reactors (20), but this finding has not been confirmed in France (21) or Belgium (22). On the contrary, a higher incidence in urban areas compared to rural areas is consistent across studies (19, 23). The geographic link of high thyroid cancer incidence with urbanization and small size tumors suggests variations in medical practice (24, 25).

According to the Belgian Cancer Registry (BCR), 1992 new cases of thyroid cancer were registered in Belgium during the period 2004–2006, corresponding to a global incidence rate of 5.8 per 100 000 person years. As shown in Figure 1, substantial variations in incidence were reported across the 2 largest territorial regions unrelated to urbanization, with a lower incidence in the northern part (Flanders; 6 million inhabitants; 4.1/100 000 person years) compared to the southern part of the country (Wallonia; 4 million inhabitants; 8.3/100 000 person years). Geographical variation was mainly reflecting differences in PTC and especially PTC T1 incidence, which was 3-fold higher in Wallonia (4.6 per 100 000 person years) than in Flanders (1.4 per 100 000 person years) (26). More recent data (available up to 2010) confirm this variation (www.kankerregister.org).

We analyzed the spectrum of medical activities associated with the diagnosis of thyroid cancer and possible differences between the northern low and southern high thyroid cancer incidence regions (subsequently designated as “low incidence region” and “high incidence region”).

**Patients and Methods**

**Analysis of BCR database: distinct thyroid cancer histotypes and size categories**

All thyroid cancer patients diagnosed between 01/01/2004 and 12/31/2006 were retrieved from the BCR database. This database contains all information from oncological care programs and from all pathology laboratories related to hospitals,
guaranteeing exhaustiveness and allowing for incidence calculation by subtype and by T category.

Identification of diagnostic tests: TSH and imaging tests

Data were retrieved from the 7 Belgian Health Insurance (BHI) organizations merged to monitor health care consumption and expenditure in Belgium. Because health insurance is obligatory, 99% of Belgian residents are represented in the BHI database. A “permanent sample” of these data constitutes a representative sample (1/40 for the population aged 0–64 y and 1/20 for the population aged ≥65 y). The permanent sample contains individual data (age, sex, and place of residence) and reimbursement codes by procedure, admission, drug delivery, etc, including date, provider, institution, and cost. For the analysis of testing rates at the regional level, the place of residence was considered. The random sample minimizes the risk of selection bias.

The following diagnostic tests were retrieved from the permanent sample for the period 2003–2008: serum TSH testing, neck US, carotid duplex, computed tomography (CT) scan, magnetic resonance imaging (MRI), and positron emission tomography (PET) scan. Whereas reimbursement codes for US are specific for the neck region, only 1 global code was available for CT and MRI (including neck, thoracic, and abdominal imaging). “High-tech” imaging (CT or MRI or PET) was considered as a whole. All diagnostic tests were considered in the global permanent sample as well as in the “restricted” permanent sample, the latter excluding subjects with a history of thyroid disease at the time of detection—ie, when the diagnostic test is performed. Individuals treated with thiamazole, levothyroxine, radioactive iodine, or thyroid surgery in the year preceding any of the above-mentioned diagnostic tests were defined as having a history of thyroid disease.

Identification of therapy-related strategies for thyrotoxicosis and thyroid nodular disease: thyrostatics, radioiodine, FNAC, and surgery

The following therapy-related data were retrieved from the integral/nonsampled BHI database (2003–2008 period): FNAC, thiamazole, radioactive iodine, thyroid surgery (total thyroidectomy and lobectomy) with or without lymph node dissection (LND).

An individual with thyrotoxicosis was identified according to 1 of the following treatments: thiamazole, radioiodine administered on an outpatient basis (≤15 mCi), or thyroid surgery preceded by thiamazole or radioiodine. An individual with (non-toxic) thyroid nodular disease was identified by a diagnostic and/or therapeutic procedure: FNAC or thyroid surgery (excluding subjects treated with thiamazole or radioiodine but having had no FNAC before surgery).

Identification of surgical patients and surgically treated thyroid cancer patients in the linked databases

By secured procedures based on the patients’ unique national social security numbers (NIS/INSZ), we identified patients diagnosed with a thyroid cancer between 01/01/2004 and 12/31/2006 in the integral BHI database. Patients with complete data in both databases (97.6% of the thyroid cancer patients) were used for further analyses. We calculated the proportion of surgical thyroid cancer patients (with incidence dates between 01/01/2004 and 12/31/2006) in the 2004–2006 surgical cohort.

Statistical analyses

Diagnostic tests

We calculated standardized rates by region, adjusting for age and sex (rates per 1000 person years and 95% confidence interval [CI]). The direct standardization method and the European Standard Population were used, allowing comparisons between regions having different initial characteristics distribution. A marginal generalized estimating equation model was used to evaluate the differences in testing rates between the regions, taking into account the longitudinal aspect of the data. We tested the “region effect” at the 5% significance level (see also Supplemental Data, published on The Endocrine Society’s Journals Online web site at http://jcem.endojournals.org).

Thyroid diseases and therapeutic interventions

Age-standardized proportions (FNAC, thyroid surgery, thyrotoxicosis, thyroid nodular disease) were calculated using the direct method of standardization and the European Standard Population. The 95% CI for each proportion was calculated using the Wilson score method (27). To allow comparison between regions, the ratios of proportions (named comparative incidence figure or CIF) and their 95% CI were computed using the following formula:

\[
95\% \, CI = \exp(\text{ASP}) \pm 1.96 \times \sqrt{\frac{\text{Var}(\text{ASP})}{\text{ASP}^2} + \frac{\text{Var}(\text{ASP}^2)}{\text{ASP}^4}}
\]

where ASP is the age-standardized proportion. Proportions were considered significantly different if the 95% CI did not include the value 1.0.

The lifetime risk of undergoing thyroid surgery based on age-specific and sex-specific incidence rates reported between 2003 and 2008 was calculated, according to the following equation:

\[
\text{Cum}. \text{rate} \,(0-74) = \sum_{i=1}^{15} a_i
\]

where \(a_i\) is the age-specific incidence rate in the \(i\)th age class, which is \(t\) years long.

\[
\text{Cum}. \text{risk} = 100 \times [1 - \exp(-\text{cum}. \text{rate}/100)]
\]

All analyses were performed using SAS version 9.2 (SAS Institute Inc.).

Results

Regional variation in rates of TSH testing and imaging in the global population

TSH testing rate [95% CI] was slightly lower in the low incidence region compared to the high incidence region (366 [365; 368] vs 400 [399; 402] per 1000 person years; \(P = .0003\)). However, in the restricted population (excluding patients with a history of thyroid disease), this
difference was no longer statistically significant (338 [337; 339] vs 350 [349; 352] per 1000 person years, respectively; \( P/H11005 \).26).

Rates of imaging procedures (neck US, carotid duplex, and combined CT/MRI/PET) were significantly lower in the low incidence region compared to the high incidence region, both in the global population and in the restricted population (Table 1). More than 2-fold more neck US were performed in the high incidence region as compared to the low incidence region (Figure 2A). The rates of neck US and carotid duplex remained stable in the time period studied. A gradual increase in both regions was observed for CT/MRI/PET imaging: from 41 [40; 42] per 1000 person years in 2003 to 62 [61; 63] per 1000 person years in 2008 in the low incidence region; and from 62 [60; 63] per 1000 person years in 2003 to 86 [85; 88] per 1000 person years in 2008 in the high incidence region.

Regional variation in rates of FNAC and thyroid surgery

As depicted in Table 2 and Figure 2, B and C, the rate of FNAC was similar in both regions, but the rate of thyroid surgery was more than 2-fold lower in the low incidence region. The difference was more marked for total thyroidectomy as compared to lobectomy. The rate of surgery preceded by FNAC was similar in both regions.

The cumulative rate of thyroid surgery before the age of 75 years was 2.7% in the low incidence region compared to 6.5% in the high incidence region (Table 2).

Regional variation in the management of thyrotoxicosis and thyroid nodular disease

For the 2003–2008 time period, 48 127 and 15 828 patients with thyrotoxicosis, 26 875 and 24 065 patients with (nontoxic) thyroid nodular disease, and 13 553 and 17 408 surgical patients were retrieved and analyzed for the low incidence region and the high incidence region, respectively.

The rate of (treated) thyrotoxicosis was higher in the low incidence region compared to the high incidence region (102 [101; 103] vs 63 [62; 64] per 100 000 person years; \( P/H110021 \).05), whereas the rate of (nontoxic) thyroid nodular disease was lower in the low incidence region compared to the high incidence region (66 [66; 67] vs 110 [109; 112] per 100 000 person years; \( P/H110021 \).05).

As shown in Table 3, no more than 10% of thyrotoxic patients underwent thyroid surgery in both regions, with proportionally more thyroid surgery in the high incidence region as compared to the low incidence region (\( P/H110021 \).05). The management of nontoxic thyroid nodular disease was also different between the regions. A surgical approach was chosen in 69% of the patients in the high incidence region and in 47% of the patients in the low incidence region.

Regional difference in surgical cohorts with regard to preoperative diagnosis (thyrotoxicosis or thyroid nodular disease)

In the high incidence region, a minor proportion of thyroid surgery was preceded by treatment for thyrotoxicosis, whereas in the low incidence region this proportion was more marked (Table 3). FNAC preceded thyroid surgery in 18% of the patients in the high incidence region, whereas this proportion was 2-fold higher in the low incidence region.

Regional differences in surgical cohorts with regard to postoperative cancer diagnosis and in thyroid cancer surgical cohorts with regard to preoperative FNAC and LND

The BCR contained 1992 tumor records for the period 2004–2006. Among them, 1960 patient records with

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### Table 1. Rates of Imaging in the Global Population and a Restricted Population (Excluding Subjects With a History of Thyroid Disease) of Belgium by Region (2003–2008)

<table>
<thead>
<tr>
<th>Standardized (Age and Sex) Rate (European Standard Population)</th>
<th>Longitudinal Data Analysis (GEE Model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Incidence Region</td>
<td>High Incidence Region</td>
</tr>
<tr>
<td>Neck US</td>
<td>6.8 [6.6; 7.0]</td>
</tr>
<tr>
<td>Carotid duplex</td>
<td>11.3 [11.1; 11.4]</td>
</tr>
<tr>
<td>CT/MRI/PET-CT</td>
<td>51.9 [51.5; 52.3]</td>
</tr>
<tr>
<td>Restricted population</td>
<td>5.1 [5.0; 5.3]</td>
</tr>
<tr>
<td>Carotid duplex</td>
<td>11.0 [10.8; 11.2]</td>
</tr>
<tr>
<td>CT/MRI/PET-CT</td>
<td>50.5 [50.1; 50.9]</td>
</tr>
</tbody>
</table>

Abbreviation: GEE, generalized estimating equation. Data are expressed as age-standardized rates per 1000 person years [95% CI], based on permanent sample.
identification of a national social security number and complete data were retained. In the health insurance database (BHI), we identified 6747 and 8665 surgical patients for the low incidence region and the high incidence region, respectively. By coupling both databases, 1913 of 1960 (97.6%) cancer patients who underwent a surgical intervention were included for further analysis.

Within the surgical cohort, equal proportions of patients were diagnosed with thyroid cancer. The histological diagnosis of cancer after any surgery (including lobectomy) for nontoxic thyroid nodular disease was lower in the high incidence region (Table 4). This difference was more pronounced in the subgroup of patients that underwent total thyroidectomy. Furthermore, within the subgroup of patients with total thyroid removal, the proportion of PTC was similar, but the proportion of PTC T1a was higher in the high incidence region.

Finally, in the subgroup of surgical patients with histological diagnosis of thyroid cancer, one-third had preoperative FNAC in the high incidence region as compared to two-thirds in the low incidence region (Table 4). The proportion of patients that underwent LND synchronously with the first thyroid surgery was 2-fold lower in the high incidence region as compared to the low incidence region. These significant differences persisted after exclusion of the PTC T1a subgroup from the thyroid cancer surgical patient group as well as from the subgroup of patients with PTC.

Discussion

We observed a significant difference in the incidence of thyroid cancer in the 2 major regions of Belgium (incidence rate of 4.1 per 100 000 person years in Flanders, the low incidence region; compared with 8.3 per 100 000 person years in Wallonia, the high incidence region). The difference mainly reflects a variation in the diagnosis of T1 cancers (especially PTC T1a). Therefore, we evaluated the factors contributing to these differences.

First, we studied a possible regional difference in frequency of TSH testing and imaging studies that could increase the probability of bringing a patient’s occult thyroid nodule to medical attention. Although the rate of TSH testing was slightly lower in the low incidence region, this difference disappeared after excluding subjects with a history of thyroid disease. Imaging rates, however, were markedly different, with less neck US, carotid duplex, and high-tech imaging (CT/MRI/PET) rates in the low incidence region; this difference was confirmed after excluding subjects with a history of thyroid disease. Due to the lack of information regarding the indication for the imaging studies, it was not possible to trace which proportion was performed for the investigation of a clinically evident thyroid nodule. Similarly, our study design cannot provide an answer to what extent the regional difference in imaging rates can be explained by a different threshold for imaging or by a difference in the prevalence of thyroid nodules or other comorbidities. The very large sample size, however, results in robust findings showing major differences for all imaging exams, and this probably translates...
into a higher probability of visualization of (occult) thyroid nodules in the high incidence region.

Second, regional differences in the use of thyroid-specific procedures linked to thyroid cancer diagnosis (FNAC and thyroid surgery) were investigated. Whereas rates of FNAC were similar in both regions, the rate of surgery was 2-fold higher in the high incidence region. This higher surgical rate was present for all types of surgery and was most pronounced for total thyroidectomy. To understand this major regional difference, thyroid surgery was further studied in patient groups for whom thyroid surgery was 1 of several treatment options, ie, thyrotoxicosis and thyroid nodular disease. As expected, thyroid surgery represented a therapeutic option in a minority of thyrotoxicosis patients in both regions. Whereas the incidence of treated thyrotoxicosis was higher in the low incidence region, the proportion of thyroid surgery in this patient group was slightly higher in the high incidence region. Possible contributing factors for a difference in incidence of thyrotoxicosis are: difference in iodine status (28, 29), in autoimmune thyroid disease, more intensive detection, and/or treatment of hyperthyroidism in the low incidence region. Finally, a variable approach for thyroid disease in general could influence the number of persons at risk for hyperthyroidism. In a population with a high surgical rate, the number at risk for toxic multinodular disease in the older age categories will decrease with time, in line with our finding of a doubling of the lifetime risk for thyroid surgery in the high vs the low incidence region (6.46 vs 2.71% in the low incidence region for the age category 0–74 y).

The rate of thyroid nodular disease as defined in this study (patients in whom a more invasive diagnostic/therapeutic strategy—FNAC or thyroid surgery—was performed) was 2-fold higher in the high incidence region. A different prevalence of thyroid nodular disease could relate to a slightly lower iodine status in the high incidence region as compared to the low incidence region. A different prevalence of thyroid nodular disease could relate to a slightly lower iodine status in the high incidence region as compared to the low incidence region. Also, different thresholds for FNAC and/or thyroid surgery are potential explanations. In the high incidence region, a conservative approach was chosen in one-third of the patients with thyroid nodular disease, suggesting a lower threshold

<table>
<thead>
<tr>
<th>Table 2. Rates of FNAC and Thyroid Surgery and Cumulative Risk for Thyroid Surgery by Region (2003–2008)</th>
</tr>
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<tbody>
<tr>
<td>Low Incidence Region</td>
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<tr>
<td>----------------------</td>
</tr>
<tr>
<td>FNAC</td>
</tr>
<tr>
<td>Thyroid surgery</td>
</tr>
<tr>
<td>Lobectomy</td>
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<tr>
<td>Total thyroidectomy</td>
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<tr>
<td>Thyroid surgery preceded by FNAC</td>
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</tbody>
</table>

Cumulative risk for thyroid surgery, %

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Low Incidence Region</th>
<th>High Incidence Region</th>
</tr>
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<tbody>
<tr>
<td>0–24 y</td>
<td>0.10</td>
<td>0.18</td>
</tr>
<tr>
<td>0–29 y</td>
<td>0.23</td>
<td>0.43</td>
</tr>
<tr>
<td>0–34 y</td>
<td>0.43</td>
<td>0.81</td>
</tr>
<tr>
<td>0–39 y</td>
<td>0.67</td>
<td>1.29</td>
</tr>
<tr>
<td>0–44 y</td>
<td>0.93</td>
<td>1.88</td>
</tr>
<tr>
<td>0–49 y</td>
<td>1.23</td>
<td>2.60</td>
</tr>
<tr>
<td>0–54 y</td>
<td>1.55</td>
<td>3.40</td>
</tr>
<tr>
<td>0–59 y</td>
<td>1.87</td>
<td>4.23</td>
</tr>
<tr>
<td>0–64 y</td>
<td>2.20</td>
<td>5.05</td>
</tr>
<tr>
<td>0–69 y</td>
<td>2.47</td>
<td>5.81</td>
</tr>
<tr>
<td>0–74 y</td>
<td>2.71</td>
<td>6.46</td>
</tr>
</tbody>
</table>

Table 3. Surgical Treatment of Thyrotoxicosis and Thyroid Nodular Disease, Surgical Cohort, and Preoperative Diagnosis by Region (2003–2008)

<table>
<thead>
<tr>
<th>Low Incidence Region</th>
<th>High Incidence Region</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyrotoxicosis, treated with thyroid surgery</td>
<td>6.7 [6.2; 7.2]</td>
<td>10.1 [9.2; 11.0]</td>
</tr>
<tr>
<td>Thyroid nodular disease, treated with thyroid surgery</td>
<td>47.1 [46.3; 48.0]</td>
<td>69.1 [68.2; 70.0]</td>
</tr>
<tr>
<td>Thyroid surgery</td>
<td>14.4 [13.6; 15.3]</td>
<td>6.7 [6.2; 7.3]</td>
</tr>
<tr>
<td>Preceded by thyrotoxicosis</td>
<td>41.3 [40.2; 42.5]</td>
<td>18.0 [17.1; 18.9]</td>
</tr>
</tbody>
</table>

Data are expressed as age-standardized proportions (% [95% CI]), based on BHI database.
for surgery. In the low incidence region, the conservative approach was chosen in half of the patients.

The proportion of patients with thyrotoxicosis before surgery (around 10%) was within expected ranges and higher in the low incidence region as compared to the high incidence region. On the contrary, the use of FNAC in the surgical cohort was less intensive than anticipated, but nevertheless 2-fold higher in the low incidence region. Because FNAC is considered the most valuable, cost-effective, and accurate method in the evaluation of the patient with thyroid nodules (30), the low overall rate and this variation were unexpected. As to the reasons of variable use of FNAC before surgery, one could hypothesize variable estimations of strengths and limitations of FNAC by physicians/medical schools and/or variable referral patterns of patients with thyroid nodules. The higher surgical rate but similar surgical rate preceded by FNAC (resulting in a lower proportion of surgical patients with preoperative FNAC) in the high incidence region is suggestive of less selective surgery. This is expected to result in a lower proportion of postoperative thyroid cancer diagnosis in surgical patients. This impact was not observed in the present study when considering the complete thyroid surgery cohort, due to heterogeneity of the cohort. Hence, our study showed more thyrotoxicosis in the low incidence region surgical cohort and confirmed a previous finding of a higher preponderance of total thyrotoxicity and thyroid cancer diagnosis was 14.6% in the low incidence region and 11.6% in the high incidence region, in accordance with expectations of more selective surgery in the low incidence region with more preoperative FNAC.

Within the thyroid cancer cohorts, surgery was more frequently preceded by FNAC in the low incidence region (59.5 vs 27.8% in the high incidence region), implying a larger proportion of thyroid cancer patients undergoing first extensive thyroid surgery including LND in the low incidence region (22.3 vs 12.0% in the high incidence region) is also in agreement with the higher proportion of preoperative FNAC, allowing for preoperative cancer diagnosis, and with lower proportions of low-risk disease (PTC T1a) in the low incidence region. Significant differences, however, persisted after exclusion of the PTC T1a subgroup. The proportion of LND in the PTC subgroup excluding PTC T1a is lower than observed in physician surveys on cancer management. Recently, in the United States, 47% of the physician-respondents recommended central LND (32), and in Belgium in 2006, more than 40% would have recommended at least central LND (33).

The major strength of the linked BCR-BHI database in the study of thyroid cancer is its large dataset covering all age groups in a population with equal access to medical care due to a quasi-universal health insurance coverage, thereby excluding major confounding by variations in socioeconomic status.

Our study has several limitations, linked to the retrospective and ecological study design, the use of administrative data, and the definition of thyroid disease on the basis of diagnostic or therapeutic procedures, precluding definitive conclusions about a causal association. Second,
confounding by other unmeasured factors such as urbanization cannot be excluded. However, lower rates of urbanization in the southern region are unlikely to account for its higher incidence rates. Probable confounding by a slightly lower iodine intake in the high incidence region as compared to the low incidence region should be considered with regard to variation of nodular disease. Nevertheless, these factors are unlikely to explain the major difference in thyroid cancer incidence because the overall incidence of thyroid cancer is generally considered independent from iodine intake in the population (34). Lastly, we could not control for possible variations in medical school influences or in pathological evaluation of surgical specimens. The higher proportion of thyroid cancer in patients with total thyroidectomy in the low incidence region diminishes the chance of differences in pathology criteria being a major determinant of geographic variation.

In conclusion, we observed a different rate of thyroid cancer diagnosis in the 2 major regions of Belgium mainly reflecting a difference in the incidence of low-risk disease. In the high thyroid cancer incidence region, we observed a higher usage of imaging and a more frequent surgical approach in patients with thyrotoxicosis or thyroid nodular disease. Similar rates of surgery preceded by FNAC in both regions did not point to a higher rate of clinically discovered thyroid cancer driving the higher surgical rate in the high incidence region. A less selective surgical approach increasing the number of specimens with incidental postoperative cancer detection is more likely to cause the higher rate of thyroid cancer in the high incidence region. Additional studies are needed to confirm the association of increased usage of imaging and surgical procedures with higher thyroid cancer incidence.

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