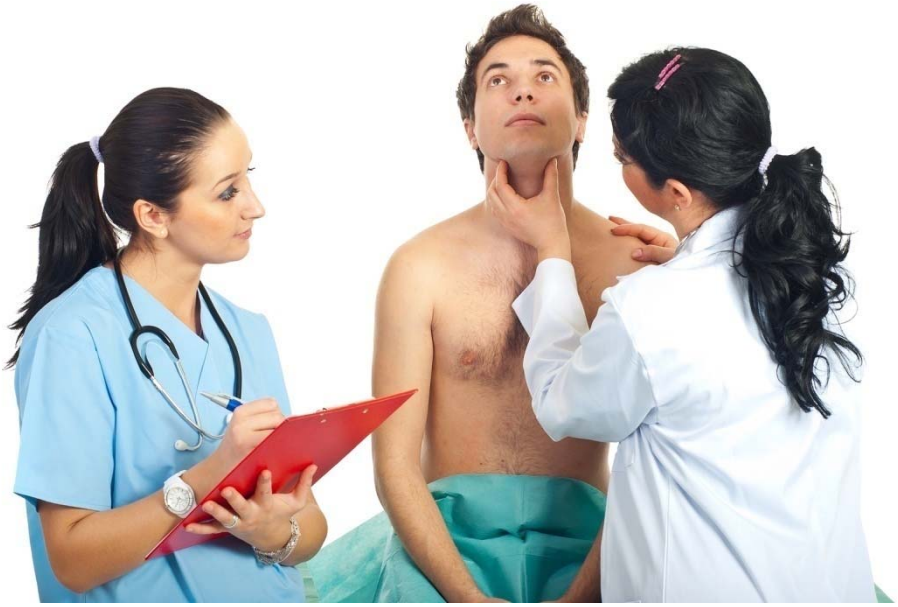
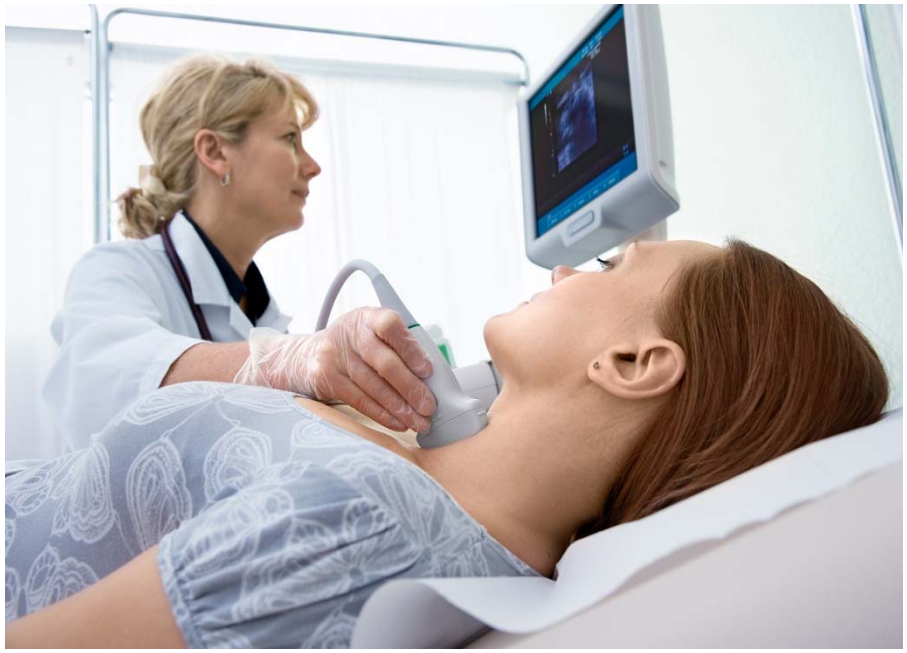
KCE REPORT 177C

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

REGIONAL DIFFERENCES IN THYROID CANCER INCIDENCE IN BELGIUM: ROLE OF DIAGNOSTIC AND THERAPEUTIC STRATEGIES FOR THYROID DISEASE





Belgian Health Care Knowledge Centre

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KCE REPORT 177C
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REGIONAL DIFFERENCES IN THYROID CANCER INCIDENCE IN BELGIUM: ROLE OF DIAGNOSTIC AND THERAPEUTIC STRATEGIES FOR THYROID DISEASE

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The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.

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Finally, this report has been approved by common assent by the Executive Board.

Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.

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FOREWORD

Whenever a cancer is increasing in frequency and when, in addition, this frequency exhibits considerable geographical differences, the public opinion inevitably will utter concern. It poses questions to the political authority and, in the best case, the latter turns to the scientists for advice. The problem of thyroid cancer is a good example. The Minister of Health has indeed commissioned the KCE and the Scientific Institute of Public Health (IPH) to shed a scientific light on the geographical variability in the frequency of thyroid cancer, as revealed in the statistics of Belgian Cancer Registry Foundation.

Such kind of geographical variation of a fairly rare phenomenon in a relatively small territory is one of the most challenging research issues in epidemiological science. Rarely one finds a single cause or explanation and this while public opinion and consequently the press are clamoring for action. However thorough research in such matters often disappoints. So, no, you cannot simply point an accusing finger to Chernobyl, diet or any other 'smoking gun'. Cancer is often multi-causal, and so is thyroid cancer.

The hypothesis of an environmental factor was examined by the IPH. In their final report, dated April 2012, they looked more specifically at the number of cases of thyroid cancer around Belgian nuclear installations. They noticed a slight increase around the sites of Fleurus and Mol / Dessel, but not around the nuclear power plants of Doel and Tihange. Such increases are certainly not exceptional and the IPH stated that there is no proven link with nuclear activity.

The KCE looked at the issue from a different angle. Could it be that in some parts of the country more thyroid cancers are found because of higher detection rates and that the differences in frequency thus have more to do with the use of diagnostic tests and surgical interventions than with the presence of more disease in the population?

In answering this intriguing question we began to look at the situation in other countries, particularly in border regions in the Netherlands and France. The analysis of Belgian data was done in partnership with the Cancer Registry and we thank them for this fruitful collaboration.

And although, likewise, present report provides no definitive evidence, it offers nevertheless much food for thought, which, as we dare hope, will stimulate endocrinologists and all other disciplines involved to have their ‘turn to serve’ in this debate.

Jean-Pierre CLOSON
Deputy General Director

Raf MERTENS
General Director

SUMMARY

INTRODUCTION

Thyroid cancer incidence rates have been rising since the early 1970s in several countries in Europe and elsewhere. This increase mainly concerns papillary thyroid cancer. The 5-year survival rate has improved to reach 91% (France, late 1990s), probably due to a larger proportion of tumours with good prognosis that are detected at the early stages of development and to more effective treatments.

According to the Belgian Cancer Registry (BCR), 1 992 new cases of thyroid cancer were registered in Belgium during the period 2004-2006, corresponding to an overall incidence rate of 5.8 per 100 000 person years (PY), which can be qualified as intermediate compared with other European countries (between <2 cases for Serbia to >10 cases per 100 000 PY in France).

Geographical variations have been reported in several countries, without clear explanations. In Belgium, the global incidence rate resulted from substantial variations between the 3 regions: the highest incidences are reported for the Brussels Capital Region and the Walloon Region (6.7 per 100 000 PY) compared with lower incidences in the Flemish Region (3.3 per 100 000 PY).

The Netherlands explain their low incidence (3.1 per 100 000 PY) by suitable iodine consumption, limited exposure to radiations, a more conservative diagnostic approach for asymptomatic thyroid nodules, the increased use of radioactive iodine for the treatment of goitres (toxic and non-toxic) and better preoperative selection of patients through increased use of FNAC (fine-needle aspiration cytology). In France, the rising thyroid cancer rates are correlated with the increasing use of total thyroidectomy for benign pathologies (goitre or nodular disease), thus exposing more larger volume surgical specimens to anatomical pathological exam.

The Dutch Province of Limburg, close to the Belgian border, reported similar thyroid cancer incidence rates as those reported in the Flemish Region for males (2.1 per 100 000 PY) but lower rates for females (3.6 per 100 000 PY *vs* 6.1 per 100 000 PY). At the Southern side, very similar incidence rates are reported by the French Departments of Marne-

Ardennes and the Walloon Region (4.7 *vs* 4.4 per 100 000 PY for men; 14.0 *vs* 12.2 per 100 000 PY for women).

In Belgium, the geographical differences in thyroid cancer remain as yet unexplained. Potential reasons are environmental factors (iodine deficiency, chemical pollutants, ionizing radiation sources, proximity of nuclear sites), differences in etiologic or predisposing factors inducing thyroid carcinoma, or detection bias. This last hypothesis suggests that the more or less intensive use of diagnostic and therapeutic procedures across the regions would lead to the serendipitous discovery of small tumours. In support of the hypothesis of detection bias, a difference in incidence of small, early-stage cancers, especially small papillary thyroid cancers has been demonstrated by the BCR in parallel with a higher frequency of thyroid surgery per capita in the Brussels Capital Region and in the Walloon Region, according to hospital discharge data[2]. A causal association was not established in this study that also only focused on surgical interventions.

OBJECTIVES OF THE STUDY

An in-depth analysis of thyroid cancer incidence and diagnostic and therapeutic procedures including imaging, fine-needle aspiration cytology (FNAC), functional tests, surgical procedures and use of thyroid medications and radioactive iodine (I^{131}) is necessary to link the use of these procedures for benign or malignant thyroid disease and thyroid cancer incidence.

The diagnostic and therapeutic strategies were thus each studied separately for the treatment of thyrotoxicosis, thyroid nodules and thyroid cancer. The analyses were performed for the country as a whole and by Region.

The KCE was commissioned to perform this study by the Minister of Public Health and Social Affairs and worked in close collaboration with the Belgian Cancer Registry. In parallel, the Minister also commissioned the Belgian Scientific Institute of Public Health (ISP/WIV) to assess the possible health risks for populations living near nuclear power plants or other facilities that can be at the origin of radioactive material leakage, by means of an epidemiological study at the national level. This separate report was published in April 2012.

METHODS

A retrospective study was conducted at the national level and by Region. When one of the three Regions is mentioned (Brussels Capital, Flemish or Walloon Regions), this refers to the Region in which the patient lives and not that in which he/she was treated.

The data on thyroid cancer (ICD-10 code C73) were retrieved from the Belgian Cancer Registry (date of incidence between 01/01/2004 and 31/12/2006). The incidences (number of cases per 100 000 person years) were standardised by age (direct standardisation, European Standardised Rates). The data used to identify the diagnostic and therapeutic strategies were obtained from the InterMutualistic Agency (2003-2008). These two databases were combined at an individual level.

In the absence of specific diagnoses for benign thyroid pathologies (thyrotoxicosis and thyroid nodules), they were only identified by the therapeutic strategies used: thyroid medications (thiamazole), low-dose radioactive iodine (I^{131}≤15mCi per treatment) and surgery (partial or total thyroidectomy) for thyrotoxicosis; FNAC and/or thyroidectomy for non-toxic thyroid nodules.

VARIABILITY OF SCREENING AND DIAGNOSTIC STRATEGIES

An incidental finding can be defined as the unsought information that was generated in the course of seeking the information one desired, related or not to the thyroid gland. Serum TSH(thyroid-stimulating hormone) is a very sensitive screening test for thyroid dysfunction and is frequently included in broader biochemical evaluations (400 tests per 1 000 PY between 2003 and 2008). Medical imaging exams (ultrasound of the neck or carotids, computed tomography (CT scan), positron emission tomography (PET scan) and magnetic resonance imaging (MRI)) are also highly sensitive exams that can by chance reveal the presence of a tumour on the thyroid gland.

TSH measurements in patients without history of thyroid disease are performed at the same frequency in the three Regions of the country. However, medical imaging exams (neck and carotid ultrasounds, CT scan, PET scan and MRI) are performed more often in the Walloon and Brussels Capital Regions (+30 to 40%) than in the Flemish Region. The differences observed have a potential clinical impact since these exams are particularly sensitive for the detection of thyroid nodules at a subclinical stage.

VARIABILITY OF TREATMENT FOR THYROTOXICOSIS

Thyrotoxicosis, which manifests as elevated T3 and/or T4 hormone levels, is a relatively common pathology. Because the consequences of this condition can be serious (including atrial fibrillation), it is always treated and thus could be identified in our database. Based on the available data, the age-standardised thyrotoxicosis rates are 87 cases per 100 000 PY, which corresponds to the expected rate for a country like Belgium that is known for its moderate iodine deficiency.

Taking into account the age of patients, most patients were treated with medications (around 69%) or radioactive iodine (around 22%) and the others underwent a surgical procedure.

Though the incidence of thyrotoxicosis seems to be higher in the Flemish Region (102 cases per 100 000 PY) than in the Brussels Capital Region (79 cases per 100 000 PY) and in the Walloon Region (63 cases per 100 000 PY), more surgical procedures were recorded proportionally in thyrotoxic patients in the Walloon and Brussels Capital Regions (10.1% and 8.3% *vs* 6.7%). And yet, surgical procedures are always accompanied by an anatomical pathological exam and the probability of detecting a malignant nodule is thus also higher.

The cumulative risk of undergoing thyroid surgery increases throughout the life. However, it is always higher in the Walloon and the Brussels Capital Regions. Before the age of 50 years, this risk is two times higher in the Walloon Region (2.6%) than in the Flemish Region (1.2%). Before the age of 75 years, the cumulative risk rises to 6.5% in the Walloon Region, 4.5% in the Brussels Capital Region and only to 2.7% in the Flemish Region.

VARIABILITY OF TREATMENT FOR THYROID NODULES

A nodular disease is defined by the presence of one or more nodules on the thyroid gland, as detected by clinical examination (palpation) or medical imaging (ultrasound, scintigraphy or other). Unlike thyrotoxicosis, if thyroid hormone levels are normal, if there is no discomfort due to increased volume and if there is no suspected cancer, no treatment is required. Patients who are not treated cannot be identified in our database, thus leading to underestimation of the incidence of this pathology as reported in Belgium for the period in question.

Based on FNAC and surgical procedures recorded, the incidence of nodular disease would be higher in the Walloon and Brussels Capital Regions (around 110 per 100 000 PY) than in the Flemish Region (around 66 per 100 000 PY).

Again here, there are many more surgeries in the Walloon Region than in the Flemish Region and the Brussels Capital Region (standardized proportions, 69% vs. 47-48%); however, taking into account all thyroid surgeries, only 18% of the patients underwent a preoperative FNAC in the Walloon Region versus 31% in the Brussels Capital Region and 41% in the Flemish Region.

In the three Regions, the low levels of use of fine-needle aspiration cytology (FNAC) prior to surgery were rather unexpected as this technique is recognised as the only precise, accurate and cost-effective method for the evaluation of patients with thyroid nodules or nodular goitres. reduces the rate of unnecessary thyroid surgeries for patients with benign asymptomatic nodules and allows appropriate surgery in patients (pre-surgically) diagnosed with thyroid cancer

The more frequent choice to perform surgery to treat nodular diseases in the Walloon Region could increase the probabilities of discovering thyroid tumours by chance.

POTENTIAL CONFOUNDING FACTORS AND BIASES

Significant confounding factors were not included in this study. Environmental factors and exposure to radiation for diagnostic or therapeutic reasons (dental X-rays, nuclear medicine, radiotherapy, PET scan, ...) in particular could not be evaluated.

The results of the study conducted by the Belgian Scientific Institute of Public Health on the health risks associated with the fact of residing near nuclear sites and power plants (within a 20-km radius) were mixed. No increased incidence of thyroid cancer was observed around the sites of Doel and Tihange. No scientific conclusion could be drawn for the French site in Chooz. Lastly, a slight increase in thyroid cancer incidence was reported around the sites of Mol-Dessel and Fleurus. Nevertheless, comparable or even higher rates were also reported in other geographical areas without nuclear sites.

Regional data analyses still remain rather artificial from an epidemiological standpoint. Aggregations of events based on other geographical definitions ((e.g. comparison of eastern and western districts, comparison of urban and rural areas, or comparison of coastal and in-land areas) may have revealed other types of associations. This bias, which is recognised in ecological analyses, cannot be ruled out in this study.

CONCLUSION

A converging array of findings points to a strong association between the more intensive use of specific diagnostic and surgical strategies in the Walloon Region and the higher incidence of thyroid cancers such as papillary microcarcinomas (T1a) in that Region. The probability of chance detection (by imaging or anatomical pathological exam) and consequently the probability of overdiagnosis and overtreatment of these small tumours is higher than their detection based on clinical symptoms.

However, several methodological limitations the use of retrospective data and the inference of thyroid disease on the basis of therapeutic procedures (in the absence of true diagnoses), preclude us from drawing definitive conclusions about a causal link between the more or less intensive use of the diagnostic and therapeutic procedures and the incidence of thyroid cancer. Furthermore, the study did not allow us to evaluate the pertinence of choices made by clinicians when making diagnoses or proposing treatments. However, it did reveal significant variability in the management of the thyroid disease.

This study suggests in particular that compliance with international guidelines recommending a more frequent use of FNAC in preoperative assessments could be improved. The training and experience of pathologists in practising and interpreting cytological exams also required a special attention.

Compliance with good practice recommendations for the management of thyrotoxicosis and thyroid nodules could be reinforced, which would also help to reduce variability in the diagnostic and therapeutic strategies used in Belgium.

Finally, a more detailed prospective analysis should be performed in order to test the hypothesis of a link between the increased incidence of small cancers on the one hand and diagnostic activities using highly sensitive methods and surgical treatment on the other hand.

RECOMMENDATIONS[a]

For the National Council for Quality promotion and/or scientific societies

- **In order to reduce the variability in diagnostic and therapeutic medical practice and provide a high level of quality of the management of patients with thyroid disease, it is recommended to disseminate good clinical practices:**
  - **for the use of thyroid tests when complaints and symptoms are absent;**
  - **for the management of patients with thyrotoxicosis and/or nodular disease;**
  - **for preoperative assessments before any surgery performed on the thyroid gland; in particular, fine-needle aspiration cytology should be used more frequently and cytological exam should require a special attention.**

For the Minister after the consultation with relevant bodies (Technical Medical Council, National Council for Hospital Facilities)

- **To monitor the implementation of good clinical practices in thyroid disease management and to take measures if unjustified variability in medical practices is observed.**

For persons in charge of the Health Research System[b]

- **In order to test the hypothesis of a causal link between the incidence of thyroid cancer and the intensity of diagnostic and therapeutic practices, it is recommended to conduct a deep analysis at the individual level, on the trends over time of the cancer incidence, controlled for tumour size and the evolution of medical practice. The study design should include confounding factors related to practitioners and hospital centres and to document diagnoses made during the diagnostic strategy, before and after surgery.**

a The KCE alone is responsible for the recommendations made to public authorities

b As described by the Cour des Comptes in its audit on January 2010 : « Scientific support for the Federal Health Policy »

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
BCR	Belgian Cancer Registry
CI	Confidence Interval
CIF	Comparative Incidence Figure
CT	Computed Tomography
EPS	Echantillon Permanent / Permanente Steekproef
ESR	European Standardized Rate
^{18} FDG-PET	18-fluorodeoxyglucose Positron Emission Tomography
FNAC	Fine-Needle Aspiration Cytology
GEE	Generalized Estimating Equation
IARC	International Agency for Research on Cancer
IMA / AIM	InterMutualistic Agency (Agence InterMutualiste/InterMutualistisch Agentschap)
IRR	Incidence Rate Ratio
MRI	Magnetic Resonance Imaging
NIS	Alphanumerical code for geographical situation (Province/Provincie, Arrondissement, Commune/Gemeente)
PY	PY
RR	Relative Risk
SEER	Surveillance, Epidemiology and End Results
SIR	Standardized Incidence Ratio
TNM	Classification of cancers including Tumour, Nodes, Metastases
WHO	World Health Organization
WSR	World Standardized Rate

SYNTHESIS

1. INTRODUCTION

Thyroid cancer is a relatively rare neoplasm. However, worldwide, it represents more than 95% of all cancers of the endocrine system[1]. According to the Belgian Cancer Registry (BCR)[2], 1 992 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 (PY), which is an intermediate rate compared to other European countries (<2 for Serbia to >10 per 100 000 PY in France).

Worldwide, increase in thyroid cancer rates were reported between the 1970s and the 2000s, mainly due to papillary cancer[3-6]. In Belgium, no trustworthy data were available before 1999, when the first data became available for the Flemish Region. Increasing rates were reported between 1999 and 2008 in the Flemish Region (from 1.4 to 2.0 for males; from 2.7 to 5.2 for females)[2]. As data were only available over 5 years for the Walloon and the Brussels-Capital Region, time trends were difficult to interpret.

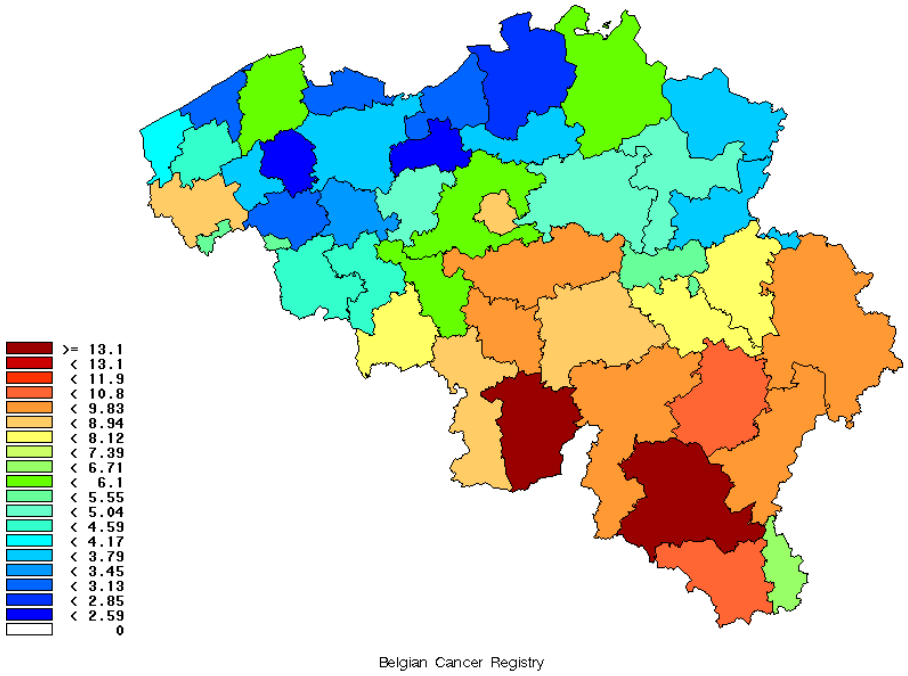
Mortality rates reported in Belgium between 2004 and 2008 (between 0.1 and 0.8 per 100 000 PY in women and between 0.1 and 0.4 per 100 000 PY in men)[2] are in the same ranges than those reported internationally[7]. Overall 5-year survival is improving over time to reach 91% in France at the end of the 1990s[3]. A possible reason for the improved survival is the rise of incidence of histological types (papillary and follicular) with good prognosis combined with the increased diagnosis of very small cancers (≤1cm and ≤2 cm) that have little risk of progression and more effective treatment delivered without delay[1].

In a lot of countries, geographical variations in thyroid cancer incidence were reported, without a real explanation. However, we noticed that in Belgium, the global incidence rate resulted from substantial variations between the 3 regions; higher incidence rates were reported in the Brussels Capital Region and the Walloon Region (6.7 per 100 000 PY) compared to lower incidence rates in the Flemish Region (3.3 per 100 000 PY). In all three regions, the most frequent histological diagnosis was papillary carcinoma but with a significantly higher incidence in the Brussels-Capital Region and the Walloon Region (6.8 per 100 000 PY) than in the Flemish Region (2.7 per 100 000 PY). In the Brussels-Capital

and the Walloon Regions, the incidence of T1 (≤ 2 cm diameter) cancers was more than 3-fold higher than in the Flemish Region, and even more than four times higher in the case of the very small T1a (≤ 1cm) tumours. This proportional difference was observed both for T1 papillary and medullar carcinoma.

A large variation in incidence was also observed between districts, with a 17-fold difference between the lowest and the highest incidence rates (Figure 1).

Figure 1. Map of the incidence of thyroid cancer by district, males & females, 2004-2006



The Dutch Province of Limburg, close to the Belgian border, reported similar thyroid cancer incidence rates as those reported in the Flemish Region for males (2.1 per 100 000 PY) but lower rates for females (3.6 per 100 000 PY vs. 6.1 per 100 000 PY). At the Southern side, very similar incidence rates are reported by the French Departments of Marne-Ardennes and the Walloon Region (4.7 vs. 4.4 per 100 000 PY for men ; 14.0 vs. 12.2 per 100 000 PY for women).

In the Netherlands, low incidence rates reported for the whole country since 1990's (3.1 per 100 000 PY in 2010) are explained by an appropriate iodine intake and a reduced radiation exposure. In addition, the Netherlands would have a more conservative diagnostic approach towards asymptomatic thyroid nodules, an increased application of radioactive iodine in the treatment of (toxic and nontoxic) goitre as well as by a better preoperative patient selection after the increasing use of fine-needle aspiration cytology[4]. In France, the sharp increase of thyroid cancer incidence in a 30-years period[8] was correlated with the increasing use of total thyroidectomy exposing the pathologist to a larger amount of thyroid tissue to be examined, thereby increasing the probability of incidental small cancer detection[8].

In Belgium, the geographical differences in thyroid cancer remain as yet unexplained. Potential reasons are environmental factors (iodine deficiency, chemical pollutants, ionizing radiation sources, proximity of nuclear sites), differences in etiologic or predisposing factors inducing thyroid carcinoma, or detection bias. This last hypothesis suggests that the more or less intensive use of diagnostic and therapeutic procedures across the regions would lead to the serendipitous discovery of small tumours. In support of the hypothesis of detection bias, a difference in incidence of small, early-stage cancers, especially small papillary thyroid cancers has been demonstrated by the BCR in parallel with a higher frequency of thyroid surgery per capita in the Brussels-Capital Region and in the Walloon Region, according to hospital discharge data[9]. A causal association was not established in this study that also only focused on surgical interventions.

An in-depth analysis of thyroid cancer incidence and diagnostic and therapeutic procedures including imaging, fine-needle aspiration cytology (FNAC), functional tests, surgical procedures and use of thyroid medications and radioactive iodine (^{131}I) is necessary to link the use of these procedures for benign or malignant thyroid disease and thyroid cancer incidence.

2. OBJECTIVES OF THE STUDY

The current study was commissioned by the Minister of Public Health and Social Affairs to analyze whether geographical differences in thyroid cancer epidemiology can be attributed to differences in diagnostic/therapeutic approaches. In parallel, the Minister also commissioned the Belgian Scientific Institute of Public Health (ISP/WIV) to assess the possible health risks for populations living near nuclear power plants or other facilities that can be at the origin of radioactive material leakage, by means of an epidemiological study at the national level. This separate report was published in April 2012[10].

The aim of the present study is to assess to what extent differences in thyroid cancer incidence mainly observed between the Flemish and the Walloon Regions and between districts can be explained by differences in diagnostic and therapeutic strategies. In order to reach this objective, the following research questions were studied:

1. What is the incidence of thyroid cancer in Belgium during the period 2004-2006 and the geographical distribution across regions and districts?
2. Is there an association between the incidence of thyroid diseases (including cancer) and the intensity of use of screening and diagnostic strategies across regions and districts?
3. Is there an association between the incidence of thyroid cancer and the intensity of use of thyroid surgery as treatment strategy for *a priori* benign thyrotoxicosis across regions?
4. Is there an association between the incidence of thyroid cancer and the intensity of use of thyroid surgery as treatment strategy for structural (nodular) disease across regions? Is a more intensive use of surgery for nodular disease associated by a more or less frequent use of FNAC of thyroid nodules?
5. Is a similar variability in thyroid cancer incidence and explanatory assumptions found in the international literature?

3. METHODS

To assess the association between diagnostic and therapeutic approaches of thyroid diseases and the variable thyroid cancer incidence across regions, a retrospective study was conducted at a national level. Data were individual-based. The analysis was stratified by region and district whenever possible.

On the one hand, all thyroid cancer data from the BCR were used. All patients with a diagnosis of thyroid cancer (ICD-10 code C73) and an incidence date between 01/01/2004 and 31/12/2006 were included. Patient characteristics (patient identification code, gender, Zip code of their home address and date of birth) and tumour characteristics (incidence date, topography, laterality, size, histology, differentiation grade, cTNM, pTNM) were retrieved from the BCR database. Based on these data, age-specific and age- and sex-standardized incidence rates were calculated (direct standardization, making use of a European standard population). In this report, the European standard rate (ESR), expressed as the number of new cases per 100 000 persons per year, was reported. On the other hand, diagnostic and therapeutic procedures for all patients with a history of non-cancerous thyroid disease or with a thyroid cancer were retrieved from the IMA databases (InterMutualistic Agency), using the respective nomenclature codes. To cover the majority of diagnostic and therapeutic interventions received by patients with a cancer incidence date included in the period 2004-2006, health insurance data were collected for the period 2003-2008.

More specific methods used to answer the different research questions will be reported in the corresponding sections.

4. VARIABILITY OF SCREENING AND DIAGNOSTIC STRATEGIES

4.1. Introduction and methods

The hypothesis is that a more intensive use of screening/diagnostic procedures could potentially lead to more incidental thyroid disease detection, resulting in additional diagnostic or therapeutic activities, potentially revealing the presence of thyroid tumour(s).

An *incidental finding* can be defined as the unsought information that was generated in the course of seeking the information one desired. In this part of the study, the following tests were considered to potentially lead to incidental findings: serum thyroid-stimulating hormone (TSH) dosage, neck ultrasound (US), duplex carotid ultrasound (US), CT scan, Positron Emission Tomography (PET scan) and Magnetic Resonance Imaging (MRI).

Serum TSH is a very sensitive screening test for thyroid dysfunction and is frequently included in broader biochemical evaluations. Neck US is often considered for patients with clinical abnormalities at the level of the thyroid, but it is also frequently performed for reasons unrelated to the thyroid. Consequently, neck US might lead to incidental detection of thyroid disease due to the proximity of other anatomical structures under investigation. In the same way, the thyroid gland is well imaged during duplex carotid US, and thyroid masses or abnormalities may be incidentally discovered. Finally, high-tech imaging techniques such as PET scan or MRI substantially increase diagnostic possibilities and often offer images of an extensive anatomical region. However, their widespread use also has deleterious effects, in particular the increased incidental discovery of cancers that would otherwise remain silent (overdiagnosis). Other specific screening activities, i.e. examinations or tests performed in asymptomatic persons, such as palpation of the neck, combined with a TSH dosage in the context of a general periodic physical examination, can lead to incidental cancer detection.

The permanent sample (EPS) of administrative data was used to calculate the rates of tests. Analyses were performed both on the global Belgian population and on a “Restricted” Population (excluding the patients with a history of thyroid disease). To identify the latter category of patients, previous targeted treatments were identified (thiamazole [Strumazol®] or elthyroxine [LT4] or radioactive iodine [^{131}I] or thyroidectomy) during the year preceding any of the tests considered.

A marginal generalized estimating equation (GEE) model was used to evaluate the differences in testing rates between the regions, taking into account the longitudinal aspect of the data, adjusting for age and sex and allowing for between-district variability. Whatever the geographical level considered (region or district), it corresponded to the place of residence of the patient and not the place where (s)he was diagnosed or treated. All results obtained on a district level are available in the full report.

4.2. Association between screening/diagnostic procedures and incidental or case detection

Table 1 shows the rates for all tests considered for the period 2003-2008. Three rates are reported: a crude rate for the global population, and a ESR per region both for the global Belgian population and the population without a history of thyroid disease (restricted population). For each comparison between two regions, an incidence rate ratio (IRR) was computed as the exponent of the coefficient resulting from the GEE model with its 95% confidence interval (95%CI).

Table 1. Rates of all considered diagnostic tests performed in the period 2003-2008; comparisons between Belgian Regions

	Rates (per 1 000 PY) per Region (period 2003-2008) European Standard Population				IRR : Incidence Rate Ratio (exponent of regression coefficients) GEE model			
Parameter	**Belgium**	**Brussels Capital Region (Bxl)**	**Flemish Region (Fl)**	**Walloon Region (W)**	**Fl vs W IRR [95%CI] (p-value)**	**Bxl vs W IRR [95%CI] (p-value)**	**Fl vs Bxl IRR [95%CI] (p-value)**	**Overall p-value for region effect**
TSH dosage								
Crude rate – Global Population	**434.2 [432.0 - 436.4]**	382.7 [375. - 389.8]	428.8 [426.0 - 431.5]	459.1 [455.2 - 463.1]				
Std. rate – Global Population	**377.0 [376.1 - 377.9]**	359.7 [356.8 - 362.7]	366.3 [365.2 - 367.5]	400.7 [399.0 - 402.3]	0.93 [0.90 - 0.96] (p<.0001)	0.89 [0.79 - 1.01] (p= 0.07)	1.04 [0.92 -1.18] (p=0.49)	p=0.0003
Std. rate – Restricted Population	**340.6 [339.8 - 341.5]**	320.6 [317.7 - 323.4]	338.3 [337.2 - 339.4]	350.1 [348.6 - 351.7]	0.98 [0.95 - 1.02] (p=0.30)	0.91 [0.80 - 1.03] (p= 0.13)	1.08 [0.95 -1.23] (p=0.22)	p=0.2564
Neck US								
Crude rate – Global Population	**12.4 [12.1 - 12.7]**	15.8 [14.4 - 17.1]	7.3 [7.0 - 7.6]	20.6 [19.9 - 21.4]				
Std. rate – Global Population	**11.6 [11.5 - 11.8]**	15.8 [15.1 - 16.4]	6.8 [6.6 - 7.0]	19.3 [19.0 - 19.7]	0.39 [0.36 - 0.42] (p<.0001)	0.82 [0.71 - 0.96] (p=0.0125)	0.47 [0.40 - 0.54] (p<.0001)	p<.0001
Std. rate – Restricted Population	**7.9 [7.8 - 8.1]**	10.5 [10.0 - 11.1]	5.1 [5.0 - 5.3]	12.5 [12.2 - 12.8]	0.44 [0.40 - 0.47] (p<.0001)	0.84 [0.73 - 0.96] (p=0.0086)	0.52 [0.46 - 0.59] (p<.0001)	p<.0001
Neck US combined with a TSH within a 4-month period								
Crude rate – Global Population	**9.5 [9.2 - 9.8]**	12.1 [10.9 - 13.3]	5.3 [5.0 - 5.6]	16.3 [15.6 - 16.9]				
Std. rate – Global Population	**8.8 [8.6 - 8.9]**	12.0 [11.5 - 12.6]	4.8 [4.7 - 4.9]	15.1 [14.7 - 15.4]	0.36 [0.32 - 0.39] (p<.0001)	0.79 [0.67 - 0.94] (p=0.0075)	0.45 [0.38 - 0.53] (p<.0001)	p<.0001
Std. rate – Restricted Population	**5.5 [5.4 - 5.6]**	7.6 [7.2 - 8.1]	3.3 [3.2 - 3.4]	9.1 [8.8 - 9.3]	0.39 [0.36 - 0.43] (p<.0001)	0.80 [0.68 - 0.94] (p=0.0076)	0.49 [0.42 - 0.57] (p<.0001)	p<.0001

Rates (per 1 000 PY) per Region (period 2003-2008) European Standard Population					IRR : Incidence Rate Ratio (exponent of regression coefficients) GEE model			
Parameter	**Belgium**	**Brussels Capital Region (BxI)**	**Flemish Region (Fl)**	**Walloon Region (W)**	**Fl vs W IRR [95%CI] (p-value)**	**BxI vs W IRR [95%CI] (p-value)**	**Fl vs BxI IRR [95%CI] (p-value)**	**Overall p-value for region effect**
Duplex carotid ultrasonography								
Crude rate – Global Population	**17.7 [17.2 - 18.2]**	19.3 [17.5 - 21.2]	16.1 [15.5 - 16.7]	20.1 [19.2 - 21.1]				
Std. rate – Global Population	**12.9 [12.8 - 13.1]**	16.6 [16.0 - 17.2]	11.3 [11.1 - 11.4]	15.0 [14.7 - 15.3]	0.74 [0.71 - 0.78] (p<.0001)	1.17 [1.02 - 1.35] (p=0.0247)	0.63 [0.55 - 0.73] (p<.0001)	p<.0001
Std. rate – Restricted Population	**12.5 [12.3 - 12.6]**	16.0 [15.4 - 16.6]	11.0 [10.8 - 11.2]	14.4 [14.1 - 14.6]	0.76 [0.72 -0.79] (p<.0001)	1.16 [1.03 - 1.32] (p=0.0189)	0.65 [0.57 - 0.74] (p<.0001)	p<.0001
High-tech imaging tests								
Crude rate – Global Population	**73.2 [72.3 - 74.1]**	80.6 [77.1 - 84.1]	63.5 [62.4 - 64.6]	88.5 [86.7 - 90.3]				
Std. rate – Global Population	**61.2 [60.9 - 61.5]**	75.9 [74.6 - 77.3]	51.9 [51.5 - 52.3]	74.9 [74.2 - 75.6]	0.69 [0.63 - 0.76] (p<.0001)	0.99 [0.88 - 1.11] (p=0.8535)	0.70 [0.62 - 0.79] (p<.0001)	p=0.0002
Std. rate – Restricted Population	**58.8 [58.5 - 59.2]**	73.2 [71.9 - 74.5]	50.5 [50.1 - 50.9]	71.4 [70.7 - 72.1]	0.71 [0.64 - 0.78] (p<.0001)	1.00 [0.88 - 1.13] (p=0.9422)	0.71 [0.63 - 0.80] (p<.0001)	p=0.0002
High-tech imaging tests combined with a TSH within a 4-month period								
Crude rate – Global Population	**45.5 [44.7 - 46.2]**	50.6 [47.8 - 53.5]	39.4 [38.5 - 40.3]	55.0 [53.5 - 56.5]				
Std. rate – Global Population	**36.6 [36.3 - 36.8]**	46.2 [45.2 - 47.2]	30.8 [30.5 - 31.1]	44.9 [44.4 - 45.4]	0.68 [0.60 - 0.78] (p<.0001)	0.98 [0.84 - 1.14] (p=0.75)	0.70 [0.61 - 0.81] (p<.0001)	p=0.0008
Std. rate – Restricted Population	**34.1 [33.9 - 34.4]**	43.2 [42.2 - 44.2]	29.3 [29.0 - 29.6]	41.3 [40.8 - 41.8]	0.71 [0.62 - 0.82] (p<.0001)	0.98 [0.84 - 1.15] (p=0.7959)	0.73 [0.63 - 0.84] (p<.0001)	p=0.0018

Overall, the standardized rates of diagnostic tests potentially leading to incidental cancer detection are consistently higher in the Walloon Region and/or the Brussels-Capital Region compared to the Flemish Region. Apart from serum TSH testing, all the standardized rates in the Brussels-Capital Region were close to the rates reported for the Walloon Region.

As expected, measurement of serum TSH is very frequently used for screening thyroid dysfunction in the general population: the rates in Belgium are around 400 tests per 1 000 PY. However, in patients without a history of thyroid disease, the TSH testing rates were similar between regions. We hypothesize that TSH testing would be more intensive either for the follow-up of patients with a history of thyroid disease or the monitoring of their treatment.

As compared TSH, neck US was much less frequently performed (around 12 per 1 000 PY) and mainly in combination with a TSH dosage within a 4-month time frame (9.5 per 1 000 PY). Neck US was less frequent in the Flemish Region than in the other two regions, both in the global population and in the population without a history of thyroid disease (restricted population). Since the indication for the neck US is not traceable in this type of study, no explanation can be formulated with certainty.

For duplex carotid US, findings were quite similar as for neck US; differences between regions were smaller but still statistically significant (11.3 in the Flemish Region *versus* 15 in the Walloon Region).

For the high-tech imaging tests (CT scan, PET scan or MRI), standardized rates were moderately high (crude rate around 70 per 1 000 PY in Belgium). Higher standardized rates were observed in the Walloon Region as compared to the Flemish Region (74.9 vs. 51.9 per 1 000 PY). According to the American Thyroid Association (ATA) guidelines (2009)[11], approximately 1–2% of persons undergoing ^{18}Fluoro-Deoxy-Glucose-PET imaging for other reasons have thyroid nodules discovered incidentally. Moreover, ^{18}FDG-positive nodules bear an increased risk of malignancy and the cancers may be more aggressive. Consequently, these lesions require prompt evaluation with subsequent diagnostic and therapeutic procedures (diagnostic thyroid US, FNAC, biopsy,…).

In conclusion, in Belgium and for the period studied (2003-2008), there is substantial geographical variation in the use of a panel of diagnostic tests potentially leading to the incidental detection of thyroid cancer, or to further investigations and treatments, that can eventually also lead to the detection of more cases. However, as in this study no clinical information was available on the indications for these diagnostic tests, nothing can be said on the appropriateness of their use.

5. VARIABILITY OF TREATMENT STRATEGIES FOR THYROTOXICOSIS

5.1. Introduction and methods

The next question was to see in how far the regional variability in incidence of thyroid cancer could be linked to the intensity of use of thyroid surgery as a treatment strategy for *a priori* benign thyrotoxicosis. Three main treatment options are available for thyrotoxicosis: 1) antithyroid drugs, 2) radioactive iodine (^{131}I) at low doses, and 3) surgery (total or partial thyroidectomy). As the surgical specimen is systematically examined by a pathologist, the probability to discover an indolent thyroid tumour is higher after surgical resection than with the other two therapeutic options. The underlying hypothesis is that a more intensive use of surgical resection in one region could lead to a higher incidental detection of thyroid cancer, thereby raising the incidence in this region.

The choice of a specific treatment is in principle determined by the aetiology of thyrotoxicosis, the thyroid volume and/or coexisting medical conditions. Surgical resection is more frequently performed in case of a large goitre, pregnancy or child wish and pronounced ophthalmopathy[12]. Total thyroidectomy is the preferred surgical approach in view of the relapse rate after partial thyroidectomy (30% in one study)[13] and because the rate of complications is similar between both procedures in experienced hands[12].

As no diagnostic information was available, patients were considered thyrotoxic whenever they received at least once Strumazol or ^{131}I or a combination of both. All patients defined as thyrotoxic between 2003 and 2008 were included in the analysis of the association between thyrotoxicosis and thyroid surgery. The analysis of the association between thyrotoxicosis management and the incidence of thyroid cancer only involved patients with thyroid cancer diagnosed between 2004 and 2006. Analyses per region were based on the residence of the patient and not on the location where they were treated.

5.2. Association between thyrotoxicosis management and thyroid cancer incidence

In Belgium, the age-standardized incidence of thyrotoxicosis as defined in this study was around 87 per 100 000 PY. However, rates were significantly higher in the Flemish Region (around 102 per 100 000 PY) than in the Brussels-Capital Region (around 79 per 100 000 PY) and the Walloon Region (around 63 per 100 000 PY).

Table 2. Crude and age-standardized proportions of thyrotoxic patients treated with surgery, medication only or ^{131}I, by region

	Total	Brussels-Capital Region	Flemish Region	Walloon Region
Proportions (% and 95%CI) of :				
Thyrotoxicosis treated with surgery	4.6 [4.4 - 4.7]	5.5 [4.9 - 6.1]	3.8 [3.7 - 4.0]	6.5 [6.1 - 6.9]
Thyrotoxicosis treated with medication only	64.5 [64.1 - 64.8]	68.0 [66.8 - 69.2]	67.0 [66.6 - 67.5]	55.5 [54.7 - 56.2]
Thyrotoxicosis treated with ^{131}I	30.4 [30.1 - 30.8]	25.4 [24.3 - 26.6]	28.8 [28.4 - 29.2]	37.1 [36.3 - 37.8]
Surgical patients with thyrotoxicosis	9.2 [8.9 - 9.5]	8.7 [7.7 - 9.6]	13.6 [13.0 - 14.2]	5.9 [5.6 - 6.3]
Age-Standardized Proportion (% and 95%CI) of :				
Thyrotoxicosis treated with surgery	7.7 [7.3 - 8.1]	8.3 [7.2 - 9.4]	6.7 [6.2 - 7.2]	10.1 [9.2 - 11.0]
Thyrotoxicosis treated with medication only	69.1 [68.5 - 69.7]	73.1 [71.5 - 74.6]	71.1 [70.5 - 71.8]	61.6 [60.4 - 62.9]
Thyrotoxicosis treated with ^{131}I	22.4 [22.0 - 22.9]	17.2 [16.1 - 18.3]	21.8 [21.2 -22.3]	26.8 [25.8 -27.8]
Surgical patients with thyrotoxicosis	10.3 [9.8 - 10.8]	10.4 [9.0 - 11.7]	14.4 [13.6 - 15.3]	6.7 [6.2 - 7.3]

The age-standardized rate of thyrotoxicosis found in this study (87.4 per 100 000 PY) is within expectations for a mild iodine-deficient country as Belgium[14, 15]. However, the 61.5% higher rate of thyrotoxicosis in the Flemish as compared to the Walloon Region represents is unexpected. Regional variability in the incidence of hyperthyroidism has been described with higher incidences in moderate iodine-deficient regions compared to mild iodine-deficient regions, due to more toxic nodular disease in moderate iodine deficiency[15]. However, mild iodine deficiency is present in all regions in Belgium[16]. Therefore the difference in thyrotoxicosis rate in the different regions in Belgium can most probably not be explained by variability in iodine status.

Hypothetical contributing factors include auto-immune thyroid disease or more intensive detection and/or treatment of thyrotoxicosis. Finally, a variable approach for thyroid disease in general can influence the number of persons at risk for hyperthyroidism, i.e. in a population with a high surgical rate the number at risk for toxic multinodular disease in the older age categories will decrease (as they might already have undergone thyroid surgery).

The cumulative risk of undergoing thyroid surgery in Belgium and by region based on age and gender-specific incidence rates reported between 2003 and 2008 increases throughout the life. However, whatever the age category, this cumulative risk is always higher in the Walloon Region compared with the other two Regions. Before the age of 50 years, the risk to undergo such thyroid surgery is two times higher in the Walloon Region (2.6%) than in the Flemish Region (1.2%). Before the age of 75 years, the cumulative risk rises to 6.5% in the Walloon Region, 4.5% in the Brussels Capital Region and only to 2.7% in the Flemish Region.

As expected, surgery was performed in a minority of thyrotoxic patients (7.7% for Belgium). The majority of thyrotoxic patients were treated with antithyroid medication only (69%) or radioiodine only (22%). However, there was a relatively higher rate of antithyroid treatment in the Brussels-Capital Region and in the Flemish Region. On the other hand, surgery and radioiodine were more often chosen as treatment for thyrotoxicosis in the Walloon Region. While the incidence of thyrotoxicosis was higher in the Flemish Region (102 vs. 63 in the Walloon Region per 100 000 PY), the proportion of thyroid surgeries in thyrotoxic patients was higher in the Walloon Region (10.1% vs. 6.7% in the Flemish Region) (Table 2).

When focusing on patients with thyroid cancer, the proportion of patients with evidence of thyrotoxicosis in the year preceding their first surgery is low (4.6% in Belgium) but significant differences were reported between the Flemish (6.2%) and the Walloon Region (3.0%).

In conclusion, an interplay of geographical variations in incidence of thyrotoxicosis and its treatment approach makes that the number of patients in whom thyroid surgery is performed and in whom incidental thyroid cancers can potentially be detected are slightly higher in the Walloon Region than in the Flemish Region. Given the inability to control for potential confounding factors in this study, these results should be interpreted with caution.

6. VARIABILITY OF TREATMENT STRATEGIES FOR NODULAR DISEASE

6.1. Introduction and methods

This chapter aimed to evaluate the association between the incidence of thyroid cancer and the intensity of use of thyroid surgery as treatment strategy for structural (nodular) disease across regions. Three main treatment options are available for nodular disease: 1) a conservative approach combined with a regular follow-up if thyroid functions tests show no abnormalities and if there is no volume problem or suspicion of cancer; 2) a total or partial thyroidectomy in case of a volume problem and/or suspicion of cancer, and 3) radioiodine (^{131}I) at low doses, which is most often performed in case of concomitant thyrotoxicosis without major volume problem or suspicion of cancer.

A more intensive use of surgery for nodular disease could be explained by a less frequent use of FNAC to exclude thyroid cancer pre-operatively. As for thyrotoxicosis management, the probability to discover an indolent thyroid tumour is higher after a surgical resection than with other therapeutic options.

As no diagnostic information was available, patients were considered to have (non-toxic) nodular disease whenever they underwent at least once FNAC (or biopsy) or thyroid surgery or a combination of both, between 2003 and 2008. This definition does not include patients with thyroid nodules diagnosed clinically or after imaging (ultrasound, scintigraphy or other) in whom further diagnostic or therapeutic procedures were considered unnecessary (e.g. absence of suspicious features of the nodule(s) at ultrasound, small diameter of the nodule, absence of symptoms related to the thyroid volume). Despite an underestimation of the total population with nodular thyroid disease, this definition offers the most accurate estimate of patients with thyroid nodules requiring a more invasive diagnostic or therapeutic strategy. Another limitation is that no data are available on the thyroid weight after surgery, nor on the presence or not of symptoms related to the thyroid volume and potentially leading to the decision of thyroid surgery instead of a conservative approach.

The association between nodular disease management and the incidence of thyroid cancer relied only on patients with thyroid cancer diagnosed between 2004 and 2006.

6.2. Association between nodular disease management and thyroid cancer incidence

In Belgium, the age-standardized rate of nodular disease as defined in this study was around 85 per 100 000 PY. However, rates were significantly lower in the Flemish Region (around 66 per 100 000 PY) and higher in the Brussels-Capital Region (around 113 per 100 000 PY) and in the Walloon Region (around 110 per 100 000 PY). Globally, more than half of patients with nodular disease were treated with surgery, whereas a conservative approach was preferred in 44.1% of the patients. The latter strategy was more common in patients of 70 years and older (56.0%).

Whereas two thirds of patients were surgically treated in the Walloon Region, the conservative approach was chosen in 1 out of 2 patients in the Flemish and the Brussels-Capital Region. Consequently, age-standardized proportions of surgery for nodular disease were higher in the Walloon Region (69%) than in the Flemish Region (47%) and the Brussels-Capital Region (48%).

The Brussels-Capital Region reported the highest rates of FNAC, followed or not by surgery (around 79 per 100 000 PY) compared with the Flemish Region (around 50 per 100 000 PY) and the Walloon Region (around 48 per 100 000 PY).

Thyroid surgery was preceded by FNAC in only 18% of all patients with surgery and evidence of nodular disease. This approach is indicative of intermediate or high pre-surgical probability of thyroid cancer. The age-standardized proportion for this sequential procedure was higher in the Flemish Region (around 23%) than in the Brussels-Capital Region (around 17%) and in the Walloon Region (13%). Among the group of all thyroid surgery patients (disregarding the reason for surgery) these proportions were 41%, 31% and 18% respectively.

The proportion of thyroid cancer patients among all surgical patients was quite similar in the three regions (between 10.3% and 11.5%).

Among thyroid cancer patients, surgery was preceded by FNAC in 60% of the cases in the Flemish Region versus 43% in the Brussels-Capital Region and 28% in the Walloon Region. A first extensive surgery including lymph node resection, which indicated a very high pre-surgical probability of thyroid cancer, was performed in only 17% of thyroid cancer patients. This rate was also particularly lower in the Walloon Region (12%) compared to the two other regions, reaching 20-22%.

Low utilization of FNAC

The use of FNAC in surgical patients was less frequent than anticipated. Indeed FNAC is considered as the single most valuable, cost-effective, and accurate method in the evaluation of the patient with thyroid nodules or a nodular goitre[11, 17-19]. As such, FNAC reduces the rate of unnecessary thyroid surgeries for patients with benign asymptomatic nodules[20] and allows appropriate surgery in patients (pre-surgically) diagnosed with thyroid cancer. On the other hand, not every nodule that is clinically or radiologically diagnosed deserves an examination by FNAC[4].

Given the lower than anticipated proportion of pre-operative FNAC, an additional analysis investigating the proportion of patients with a pre-operative combination of FNAC and neck US or scintigraphy was performed. This showed age-standardized proportions of 65% in Belgium in all thyroid surgery patients and 78.2% in thyroid cancer surgery patients. The Flemish Region reported the highest rates both for all surgical patients (70.0%) and for cancer patients (84.2%) whereas the Walloon Region reported the lowest rates both for all surgical patients (60.6%) and for cancer patients (73.3%).

Table 3. Crude and age-standardized proportions of patients with nodular disease treated with surgery (preceded or not by a FNAC) or with a conservative approach, by region

	Total	Brussels-Capital Region	Flemish Region	Walloon Region
Outcome measure on all cases: Proportions % [95%CI]				
A. Nodular disease treated with surgery	54.7 [54.3 - 55.1]	45.8 [44.6 - 47.0]	44.8 [44.2 - 45.4]	68.3 [67.7 - 68.9]
B. Nodular disease with conservative approach	45.3 [45.1 - 46.0]	54.5 [53.3 - 55.7]	55.4 [54.8 - 56.0]	31.9 [31.3 - 32.5]
C. Nodular disease treated with surgery preceded by FNAC	15.9 [15.6 - 16.2]	15.3 [14.5 - 16.2]	20.0 [19.5 - 20.5]	11.5 [11.1 - 12.0]
D. Surgical patients with preoperative cytological diagnosis	26.8 [26.3 - 27.2]	30.9 [29.3 - 32.4]	39.6 [38.8 - 40.4]	16.0 [15.4 - 16.5]
Outcome measures on all cases: Age-Standardized proportions [95%CI]				
A. Nodular disease treated with surgery	56.1 [55.5 - 56.7]	48.0 46.4 - 49.6]	47.1 [46.3 - 48.0]	69.1 [68.2 - 70.0]
B. Nodular disease with conservative approach	44.1 [43.5 - 44.7]	52.3 [50.7 - 53.8]	53.1 [52.2 - 53.9]	31.2 [30.3 - 32.1]
C. Nodular disease treated with surgery preceded by FNAC	18.0 [17.6 - 18.5]	16.6 [15.4 - 17.8]	22.5 [21.7 - 23.2]	13.4 [12.7 - 14.1]
D. All surgical patients with preoperative cytological diagnosis	28.9 [28.2 - 29.6]	31.0 [29.0 - 32.9]	41.3 [40.2 - 42.5]	18.0 [17.1 - 18.9]

Table 4. Crude and age-standardized proportions of cancer patients surgically treated according to their presurgical probability of thyroid cancer, by region (2004-2006)

	Total	Brussels-Capital Region	Flemish Region	Walloon Region
Outcome measure on cancer cases: Proportions % [95%CI]				
E. Surgical patients with final diagnosis of thyroid cancer	9.9 [9.5 - 10.4]	12.4 [10.9 - 14.1]	10.1 [9.4 - 10.8]	9.3 [8.7 - 10.0]
F. Surgical patients with only postoperative diagnosis of thyroid cancer	5.9 [5.5 - 6.2]	6.8 [5.7 - 8.1]	4.2 [3.7 - 4.7]	7.0 [6.5 - 7.5]
G. Cancer patients with intermediate/high preoperative probability of cancer	40.9 [38.6 - 43.3]	45.1 [38.5 - 52.0]	58.5 [54.7 - 62.1]	25.1 [22.3 - 28.2]
H. Cancer patients with a very high probability of thyroid cancer	15.1 [13.4 - 16.8]	16.0 [11.6 - 21.6]	20.5 [17.6 - 23.7]	10.3 [8.4 - 12.6]
Outcome measures on cancer cases: Age-Standardized proportions [95%CI]				
E. Surgical patients with final diagnosis of thyroid cancer	10.6 [9.9 - 11.3]	11.5 [9.6 - 13.4]	10.8 [9.7 - 11.9]	10.3 [9.3 - 11.3]
F. Surgical patients with only postoperative diagnosis of thyroid cancer	6.1 [5.5 - 6.6]	6.5 [5.0 - 8.0]	4.4 [3.7 - 5.1]	7.4 [6.5 - 8.2]
G. Cancer patients with intermediate/high preoperative probability of cancer	42.6 [39.3 - 45.9]	43.4 [33.9 - 52.9]	59.5 [54.5 - 64.4]	27.8 [23.4- 32.3]
H. Cancer patients with a very high probability of thyroid cancer	17.2 [14.5 - 19.8]	20.2 [11.9 - 28.5]	22.3 [17.9 - 26.6]	12.0 [8.6 - 15.3]

In conclusion, the rate of nodular disease, estimated through the performance of an invasive procedure (FNAC or surgery) was substantially higher in the Walloon Region (around 110 per 100 000 PY) than in the Flemish Region (around 66 per 100 000 PY). Higher procedural rates for surgery were recorded in the Walloon Region compared to the Flemish Region, with same rates of all FNAC but lower proportions of surgical interventions *preceded* by FNAC.

A different prevalence of thyroid nodular disease / thyroid cancer as well as different thresholds for FNAC and/or surgery are potential explanations. The present study of an ecological type does not allow to conclude on their precise/relative contribution, due to potential confounders and abovementioned limitations. The pathological evaluation of surgical specimens can also contribute to a variable detection of thyroid tumour, according to thresholds used to label a small abnormality as “cancer” or degree of scrutiny in examining thyroid gland (more or less slices per thyroid gland and more or less thick sections)[21, 22].

However it points to room for improvement regarding optimal use of US and FNAC in selecting patients for appropriate surgery. Additional studies evaluating possible reasons of underuse of (US guided) FNAC as a pre-surgical strategy could be of benefit.

7. CONCLUSION

In comparison with other European countries, Belgium has an intermediate thyroid cancer incidence. During the period 2004-2006, the European standardized incidence rate was 5.8 per 100 000 person years. The Walloon Region is characterized by a higher thyroid cancer incidence, which is mainly explained by T1 (mostly infracentrimetric, T1a) thyroid papillary carcinoma.

The aim of this study was to assess to what extent differences in thyroid cancer incidence between the Belgian Regions could be explained by differences in diagnostic and therapeutic strategies, with special reference to thyrotoxicosis and nodular disease. The following diagnostic procedures were analyzed: TSH testing, neck US, duplex carotid US, CT scan, MRI, PET scan and FNAC. Therapeutic strategies included surgery, antithyroid drugs and radioiodine.

Globally, in the Walloon Region, higher rates were reported for the use of diagnostic imaging methods potentially leading to the incidental discovery of a thyroid nodule. Moreover, surgical interventions were more frequently performed in the Walloon Region for the management of nodular disease but also for thyrotoxicosis. This combination of a higher use of sensitive imaging modalities and a higher use of surgery could lead to substantially more incidental discoveries of very small thyroid nodules, thereby revealing the existing disease reservoir of thyroid cancer[22], whether dormant or not. In fact, the incidence of T1 papillary carcinoma was 3-fold higher in the Walloon Region (4.6 per 100 000 PY) compared to the Flemish Region (1.4 per 100 000 PY). Moreover, this incidence difference was especially pronounced in T1a tumours (≤1 cm).

A converging array of findings points to a strong association between the use of specific diagnostic and therapeutic strategies and cancer incidence.

Unfortunately, numerous methodological limits, linked to the ecological study design, the use of retrospective data and the inference of thyroid disease on the basis of diagnostic or therapeutic procedures, preclude us from drawing definitive conclusions about a causal link between the diagnostic and therapeutic procedures studied and thyroid cancer incidence, on whatever geographical level. Aggregation of events at one geographical level, i.e. the region or the district, could lead to observe associations between different variables that would not be observed at the individual level or at other aggregation scales (e.g. comparison of eastern and western districts, comparison of urban and rural areas, or comparison of coastal and in-land areas). This type of study can be subject to bias, in particular the ecological fallacy (the failure of group level data to properly reflect individual level associations)[23, 24].

The variability in diagnostic and therapeutic procedures could possibly also be related to the medical specialty (endocrinologist, surgeon, specialist in nuclear medicine, …) of the physicians who examined and treated these patients, and to the actual hospital where they were admitted. In Belgium, endocrine care is almost exclusively hospital-based but not restricted to large referral centres. But it has not been possible to include practitioner and hospital characteristics in this study.

Finally, this study suggests areas of improvement in the preoperative use of FNAC, both in the North and in the South of the country. Using FNAC as proposed by international consensus and guidelines could help the clinician to delineate benign nodules from malignant ones that would require further treatment. The dissemination of recent international guidelines for patients with thyroid nodules and differentiated thyroid cancer[11] and for patients with thyrotoxicosis[25] could certainly also contribute to the reduction of the variability in diagnostic and therapeutic strategies in Belgium.

Further studies at an individual (patient) level with a stronger design (e.g. a nested case-control where more information on patient history is collected among cases and a sample of controls, a prospective study including patients followed for a thyroid disease,…) are therefore needed, to evaluate the association between diagnostic/therapeutic practices and thyroid cancer diagnosis and tumour size, and to draw more firm conclusions on the impact of the geographical variability of such practices and cancer incidence figures.[26]

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SCIENTIFIC SUMMARY

1. INTRODUCTION

According to the Belgian Cancer Registry (BCR)[2], 1 992 new cases of thyroid cancer were registered in Belgium during the period 2004-2006, for a global incidence rate of 5.8 per 100 000 person years (PY). Substantial variations in incidence were reported across the different regions: 3.3 per 100 000 PY in the Flemish Region versus 6.7 in the Brussels Capital Region and the Walloon Region (European Standardized Rate, ESR). Moreover, substantial variations in thyroid cancer incidence were also observed across the different districts (arrondissements).

At this point, it is unclear whether the observed geographical difference in thyroid cancer in Belgium during this period is to be attributed to environmental factors (iodine deficiency, chemical pollutants, ionizing radiation sources, proximity of nuclear sites), to potential non-environmental differences in etiologic or predisposing factors inducing thyroid carcinoma, or to a detection bias, i.e. differences in use of sensitive diagnostic/therapeutic procedures. Supporting the hypothesis of detection bias, a difference in incidence of small, early-stage cancers, especially small papillary thyroid cancers has been demonstrated by the BCR in parallel with a higher number of thyroid surgeries per capita in the Brussels Capital Region and in the Walloon Region, according to hospital discharge data[9].

An in-depth analysis of thyroid cancer incidence and diagnostic and therapeutic procedures including imaging, fine-needle aspiration cytology (FNAC), functional tests, surgical procedures and use of thyroid medications and radioactive iodine (^{131}I) is necessary.

Therefore, the current study was commissioned by the Minister of Public Health and Social Affairs, to analyze whether geographical differences in thyroid cancer epidemiology are to be attributed to differences in diagnostic/therapeutic strategies. In parallel, the Minister also commissioned the Belgian Scientific Institute of Public Health (ISP/WIV) to assess the possible health risks for populations living in the proximity of nuclear power plants or other facilities that can be at the origin of radioactive material leakage, by means of an epidemiological study at the national level. This separate report was published in April 2012[10].

2. RESEARCH QUESTIONS

The aim of the present study is to assess to what extent differences in thyroid cancer incidence mainly observed between the Flemish and the Walloon Regions and between districts can be explained by differences in diagnostic and therapeutic strategies. In order to reach this objective, the following research questions were studied:

1. What is the incidence of thyroid cancer in Belgium during the period 2004-2006 and the geographical distribution across regions and districts?
2. Is there an association between the incidence of thyroid diseases (including cancer) and the intensity of use of screening and diagnostic strategies across regions and districts?
3. Is there an association between the incidence of thyroid cancer and the intensity of use of thyroid surgery as treatment strategy for *a priori* benign thyrotoxicosis across regions?
4. Is there an association between the incidence of thyroid cancer and the intensity of use of thyroid surgery as treatment strategy for structural (nodular) disease across regions? Is a more intensive use of surgery for nodular disease associated by a more or less frequent use of FNAC of thyroid nodules?
5. Is the variability in thyroid cancer incidence and explanatory assumptions found in the international literature?

3. GEOGRAPHICAL DISTRIBUTION OF THYROID CANCER INCIDENCE IN BELGIUM (2004-2006)

3.1. Introduction

The aim of this chapter is to describe the thyroid cancer incidence in Belgium, for the whole country, the three regions and at the level of the districts. There are 43 administrative districts (arrondissement) representing an administrative level between the municipalities (*gemeenten/communes*) and the provinces. Brussels-Capital forms a single district. The Flemish Region includes 22 districts and the Walloon Region the remaining 20 districts.

Thyroid cancer incidence was also reported by sex and age, by histological type and by tumour size.

3.2. Methodology

3.2.1. Data selection

All invasive thyroid cancer records were selected from the Belgian Cancer Registry (BCR) database, based on the following criteria:

- ICD-10: C73
- Incidence date between 01/01/2004 and 31/12/2006

This selection resulted in 2 003 records. After quality control of these data, 11 records were excluded. Therefore, there were 1 992 new diagnoses of thyroid cancer in 2004, 2005 and 2006 in Belgium.

3.2.2. Data collection of BCR database

3.2.2.1. Notification and submission to the registry

The data flow relied on all information (notifications) coming from the oncological care programs (clinical network) and from all pathological anatomy laboratories related to hospitals (pathology network).

- **Clinical network**

Hospitals have to register all new cancer diagnoses, irrespective of the fact the diagnosis is discussed during a multidisciplinary oncological consultation. Each tumour has to be recorded by means of a standard form including a confined set of variables (see 3.2.3).

- **Pathology network**

The pathological anatomy laboratories encode the received specimens following classification rules approved by the Consilium Pathologicum Belgicum. In the Flemish Region most of the laboratories follow the Codap-2007 classification. Various coding systems are used in the Walloon Region and Brussels Capital Region. Every (pre-)malignant diagnosis is encoded and yearly transferred to the Belgian Cancer Registry, accompanied by the protocols as foreseen by law. After quality control, the specimen classification is converted to a tumour registration in ICD-O-3 at the BCR.

3.2.2.2. Quality control and data linkage

Every tumour record is subjected to an automated quality control in which the format and the contents of each field are checked. In addition, the contents of the fields are checked for inconsistencies against the other fields. Associations are checked between topography and gender, topography and histology and age and tumour characteristics. These checking procedures were based on the IARC guidelines[27]. Also a number of manual interventions is carried out.

Subsequently, the individual tumour records from clinical sources and pathological anatomy laboratories are linked by means of the unique patient identifier[a]. If these tumour records contain data on the same tumour, the data from the various sources are combined to form one definitive tumour record (merging process). At this stage it is determined whether or not this concerns a second (third, etc.) primary tumour. The linkage of the data is largely an automated process, but in less than 20% of the data links, manual intervention is necessary. In the more complex cases, the data source is consulted to provide additional information.

3.2.3. Dataset

Patient data

- Unique patient identification code: National Social Security Number (INSZ/NISS)
- Gender
- Zip code of home address
- Date of birth

The knowledge of the residence of patient allows to map the cancer incidence at different geographical levels: regions, districts, and municipalities.

Tumour data

- Incidence date
- Basis for the diagnosis
- Topography
- Laterality
- Histology
- Differentiation grade
- Clinical stage (cTNM)
- Pathological stage (pTNM)
- Treatment
- WHO score at the time of diagnosis (performance grade)

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[a] Since 2006, the Belgian Cancer Registry has the authorisation to use the national social number as unique patient identifier. To protect the privacy of the patients, strict rules are applied.

To code tumour characteristics, this data set uses The International Classification of Disease for Oncology (third edition: ICD-O-3 for the reported years 2004-2006). The staging of the tumour has to be defined according to the TNM Classification of Malignant Tumours (sixth edition[28] for the reported years 2004-2006).

Follow-up data

- Date of death
- Date of last contact

The vital status (dead, alive) of each patient is collected based on the National Social Security Number (INSZ/NISS) at the Kruispuntbank van de Sociale Zekerheid/Banque Carrefour de la Sécurité Sociale. An update is regularly done.

Additional variables for specific studies can be added to the standard database. For this study, each protocol was reviewed to complete the information concerning the pathological stage (TNM) and to add the size of the tumour.

3.2.4. Calculation of incidence rates

The incidence data presented in this study concern the years 2004 to 2006. Population data were obtained from the Directorate-general Statistics Belgium[b].

Incidence is the number of new cases occurring in a given time period in a specified population. It provides a direct estimate of the probability or risk of illness, and is expressed in different ways in this report:

- The ***age-specific incidence rate*** is the number of newly diagnosed cases in a particular 5-year age group over a specified time period and expressed per 100 000 persons per year.
- The ***age-standardized incidence rate*** is a weighted average of the individual age-specific rates using an external standard population. It is the incidence that would be observed if the population had the age structure of the standard population (European or World Standard Population). Since age has a powerful influence on the risk of cancer, this standardization is necessary when comparing several populations that differ with respect to their age structure. In this report, European Standardized incidence Rates (ESR) were reported. These are expressed as the number of new cases per 100 000 persons per year.

3.3. Incidence of thyroid cancer in Belgium

3.3.1. General

In Belgium, the European standardized incidence rate of thyroid cancer for 2004-2006 was 5.8 per 100 000 PY. As shown in Table 5, the total number of new thyroid cancer cases was 1 992 in the period 2004-2006. On average, 664 new cases were diagnosed annually. A slightly increasing number of cases was detected between 2004 and 2006. However, the period under consideration is too short to perform a reliable time trends analysis.

[b] Directorate-general Statistics Belgium and Economic Information, Federal Public Service Economy, SMEs, Self-employed and Energy (http://www.statbel.fgov.be/).

Table 5. Incidence of thyroid cancer by sex, Belgium 2004-2006

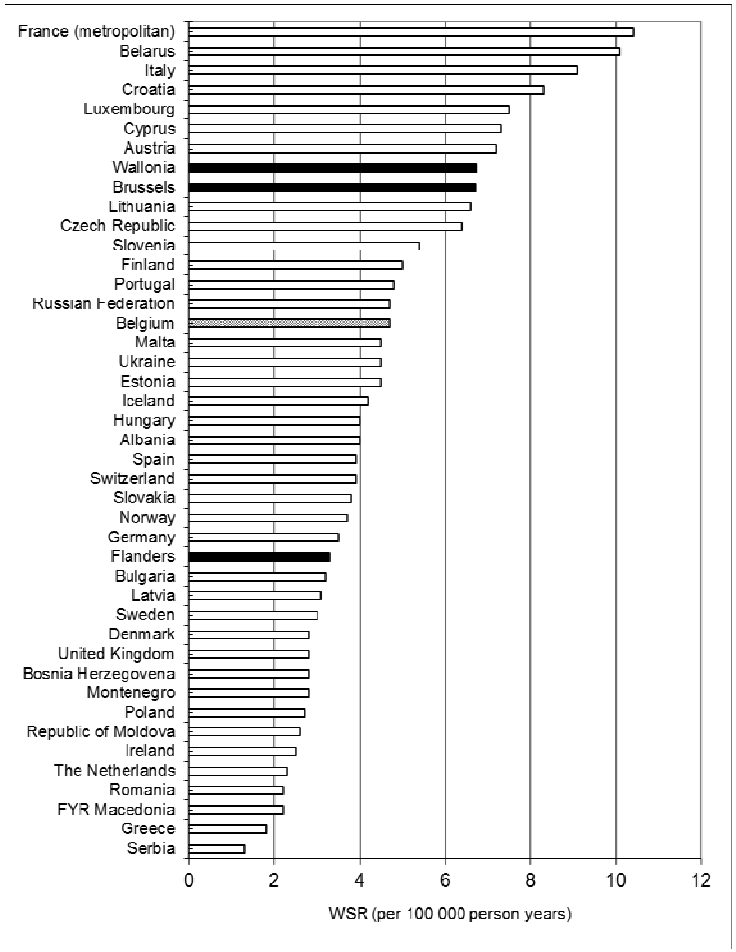
	2004			2005			2006			2004-2006		
	N	ESR	95%CI	N	ESR	95%CI	N	ESR	95%CI	N	ESR	95%CI
Males	154	2,72	[2,28 ; 3,15]	173	3,13	[2,66 ; 3,60]	174	3,09	[2,63 ; 3,55]	501	2,98	[2,72 ; 3,24]
Females	476	8,35	[7,58 ; 9,11]	506	8,61	[7,84 ; 9,38]	509	8,90	[8,12 ; 9,69]	1491	8,63	[8,18 ; 9,08]
Total	630	5,54	[5,10 ; 5,98]	679	5,90	[5,45 ; 6,35]	683	6,01	[5,55 ; 6,46]	1992	5,82	[5,56 ; 6,08]

Source: Belgian Cancer Registry, 2008

3.3.2. Comparison with other European countries

The world standardized rate (WSR) incidence of thyroid cancer in European countries (Figure 2) ranges from 1.3 per 100 000 PY for Serbia to 10.4 per 100 000 PY for France. Compared to other European countries, Belgium has an intermediate thyroid cancer incidence. With an incidence of 6.7 per 100 000 PY the Brussels-Capital Region and the Walloon Region are situated above the median European value of 4 per 100 000 PY, while the Flemish Region has an incidence of 3.3 per 100 000 PY.

Figure 2. European comparison of thyroid cancer incidence (WSR)



Note. For Belgium and its three regions, the incidence rate for 2004-2006 is reported for the other European countries, the incidence rate for 2008 as reported in GLOBOCAN 2008 is presented, http://globocan.iarc.fr/.

3.3.3. Incidence by sex

Thyroid cancer incidence is much higher in females. In males the incidence for 2004-2006 was 3.0 per 100 000 PY and in females 8.6 per 100 000 PY (Table 5). Consequently, the male/female ratio was 1:3. Geographical distribution of incidence rates also indicates some differences according to sex, even if the global repartition is somewhat similar (see Figure 3 and Figure 4).

Figure 3. Incidence of thyroid cancer in females, Belgium, 2004-2006

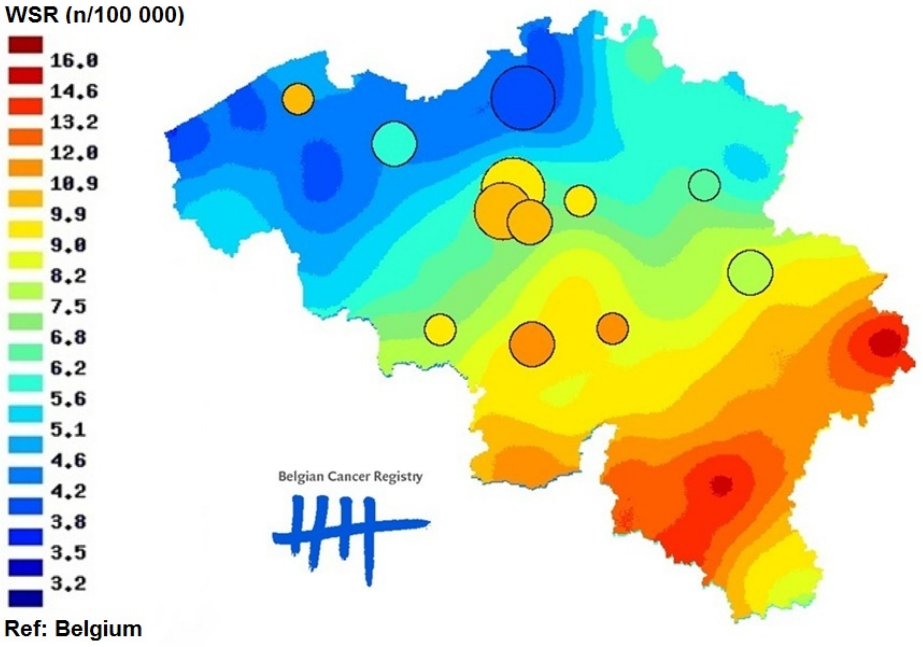
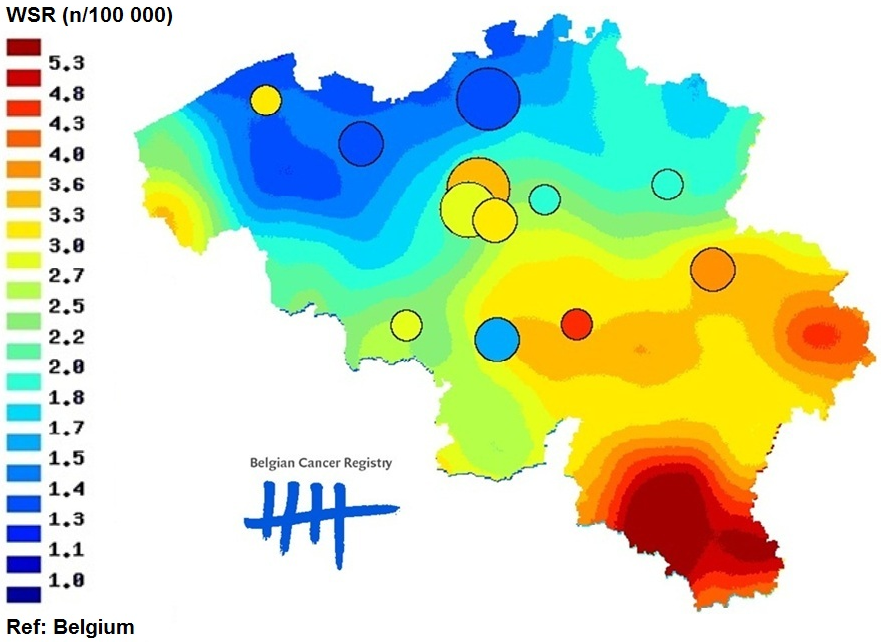


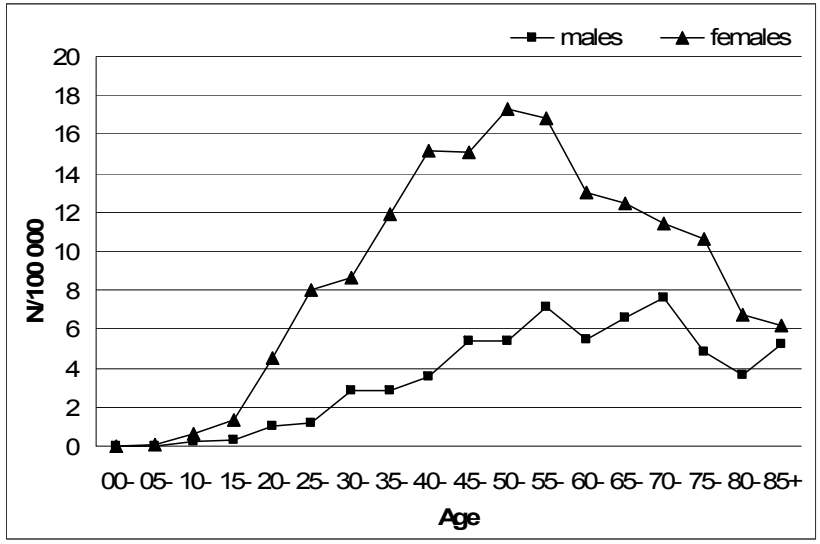
Figure 4. Incidence of thyroid cancer in males, Belgium, 2004-2006



3.3.4. Incidence by age

The age-specific incidence showed an increase starting from the age of 15 years in both sexes. In women, this increase was very steep and peaked at 50-55 years old with a decrease afterwards, while in men the increase was more gradual. The incidence decreased after the age of 70 (Figure 5).

Figure 5. Age-specific incidence by sex, Belgium 2004-2006

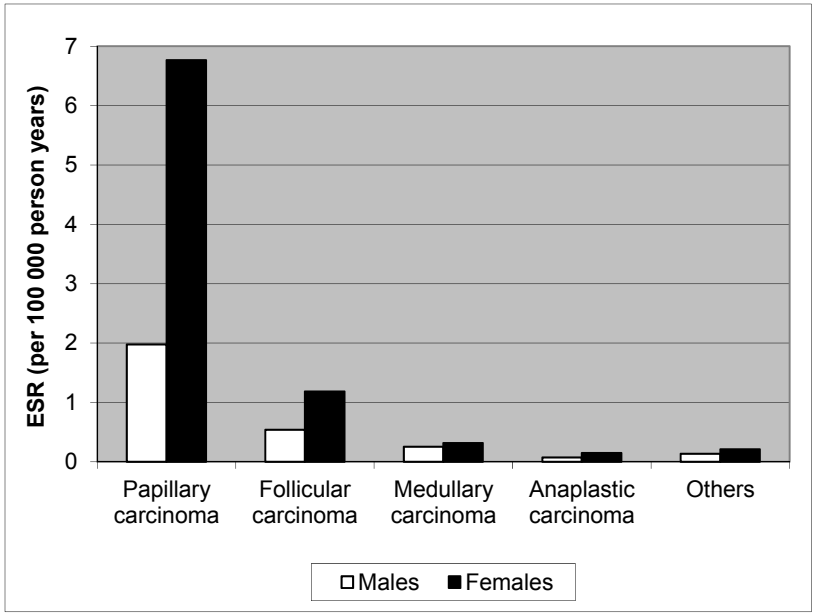


Source: Belgian Cancer Registry, 2008

3.3.5. Incidence by histological type

Papillary carcinoma was the most frequent histological type (73%), followed by follicular carcinoma (15%), medullary carcinoma (5%), anaplastic carcinoma (3%) and other types (3%). The male/female ratio for papillary carcinomas was 1:3 whereas this ratio was lower for the other histological types (Figure 6 and Appendix 1).

Figure 6. Incidence of thyroid cancer by histological type and sex, Belgium 2004-2006

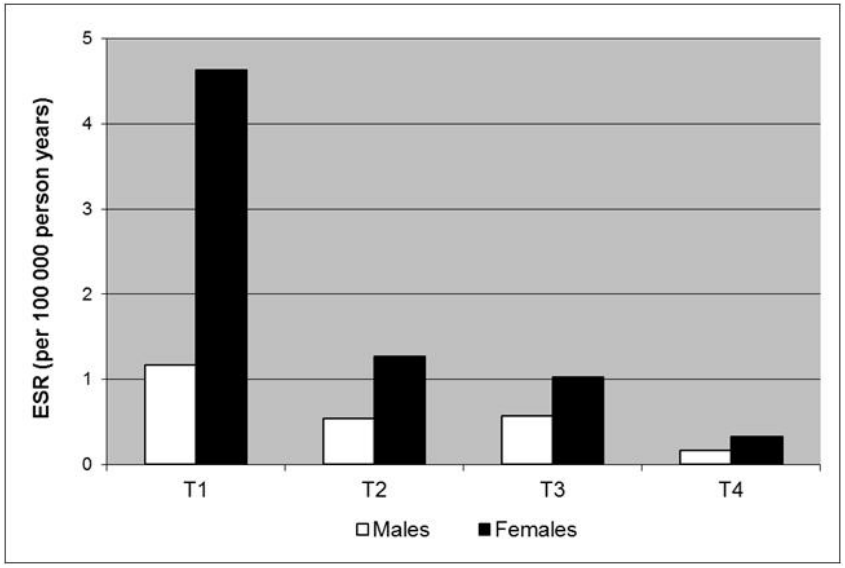


Source: Belgian Cancer Registry, 2008

3.3.6. Incidence by T category (and size)

For 83% of the registered cancer cases (1 651/1 992 thyroid cancers), T-category was known (using the sixth edition of TNM classification of malignant tumours, UICC)[28]. More than half of these tumours (58.6%, n=967) were T1 tumours (size≤2cm) of which 61.3% (n=593) were T1a tumours (≤1cm), 22.3% (n=216) were T1b (1cm<size≤2cm), and for 16.3% (n=158) the size was unknown. The proportions of T2, T3 and T4 tumours were 18.3, 16.8 and 6.3% respectively. The proportion of T1 tumours was higher in females than in males (62.3 versus 47.2%). As a consequence, the male/female ratio for T1 tumours was 1:4 whereas it was about 1:2 for the other T categories (Figure 7 and Appendix 2).

Figure 7. Incidence of thyroid cancer by T category and sex, Belgium 2004-2006



Source: Belgian Cancer Registry, 2008

Key points

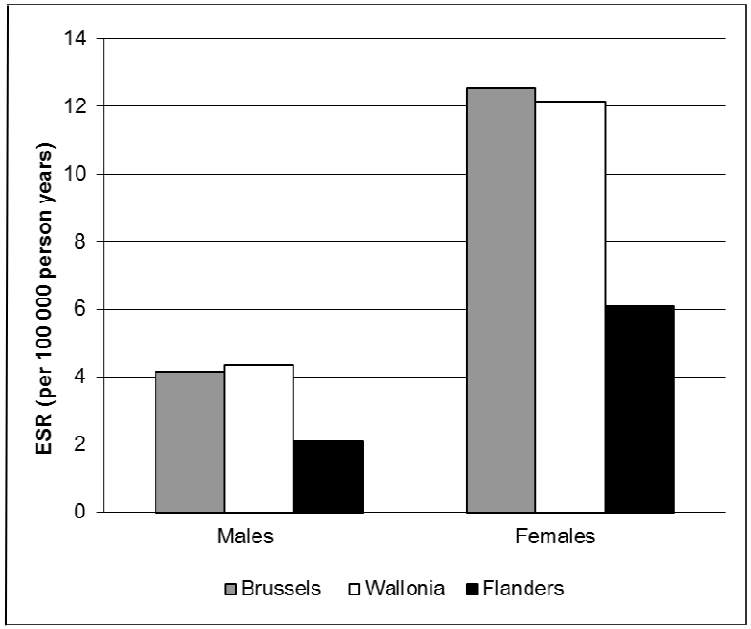
- **The European standardized incidence rate of thyroid cancer in Belgium was 5.8 per 100 000 PY, with a male/female ratio of 1:3.**
- **The age-specific incidence was the highest:**
  - **for the age category of 50-55 years in females,**
  - **for the age category of 55-70 years in males.**
- **The most frequently reported histological type was papillary carcinoma (73%) with a male/female ratio of 1:3.**
- **More than half (58.6%) of cases with known T size were < 2cm (T1), with a male/female ratio of 1:4.**

3.4. Incidence of thyroid cancer by region

3.4.1. General

In comparison with the Flemish Region, thyroid cancer incidence for 2004-2006 was twice as high in the Brussels-Capital Region and the Walloon Region (Figure 8 and Appendix 3). The incidence for 2004-2006 was respectively 4.1, 4.4 and 2.1 per 100 000 PY in the Brussels-Capital, the Walloon and the Flemish Regions in males and 12.5, 12.2 and 6.1 per 100 000 PY in females.

Figure 8. Incidence of thyroid cancer by region, 2004-2006



Source: Belgian Cancer Registry, 2008

3.4.2. Incidence by histological type

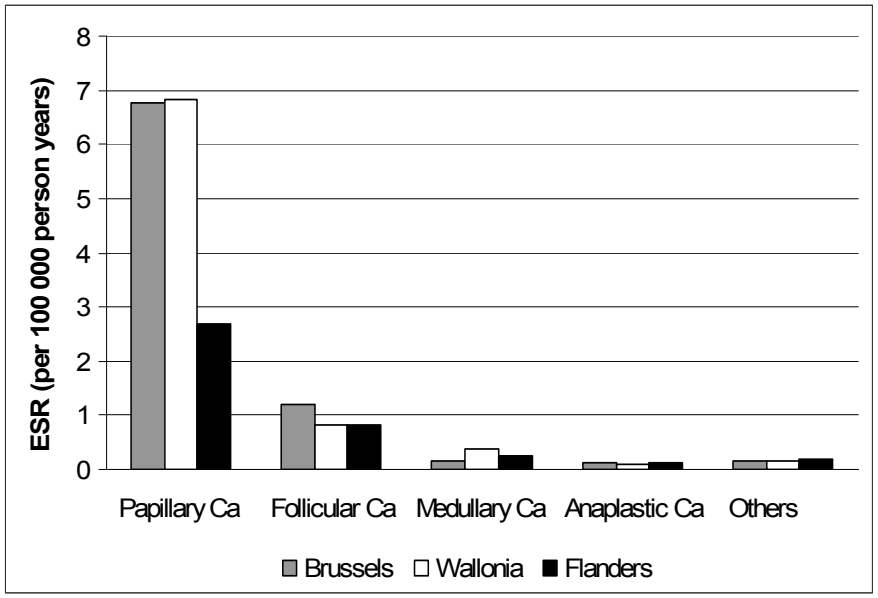
The frequency and the incidence of different histological types are reported in detail in Appendix 4, by sex and region.

In the three regions, the most frequent histological diagnosis was papillary carcinoma with a lower proportion in the Flemish Region than in the other regions (80.1, 81.0 and 62.9% in the Brussels-Capital Region, the Walloon Region and the Flemish Region respectively). In the Flemish Region, the other histological types were relatively more frequent than in the Brussels-Capital Region and the Walloon Region, and this was particularly the case for the anaplastic carcinoma (4.8% in the Flemish Region versus 1.6 and 1.3% in the Brussels-Capital Region and the Walloon Region, respectively).

The incidence of papillary carcinoma was higher in the Brussels-Capital Region and in the Walloon Region (6.8 per 100 000 PY) than in the Flemish Region (2.7 per 100 000 PY). The incidence of other histological types did not show a difference between the three regions (Figure 9 and Appendix 4).

As for the whole country, the frequency of the papillary subtype was higher in females than in males, without clear differences for the sex ratio between the different regions.

Figure 9. Incidence of thyroid cancer by histological type, males & females, 2004-2006



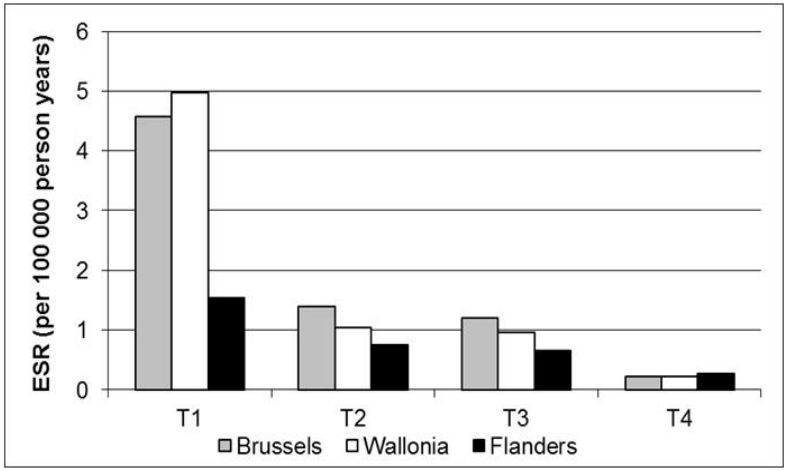
Source: Belgian Cancer Registry, 2008

3.4.3. Incidence by T category and size

Appendix 5 reports the thyroid cancer incidence for 2004-2006 by T-category for males, females and both sexes together for the three Belgian regions.

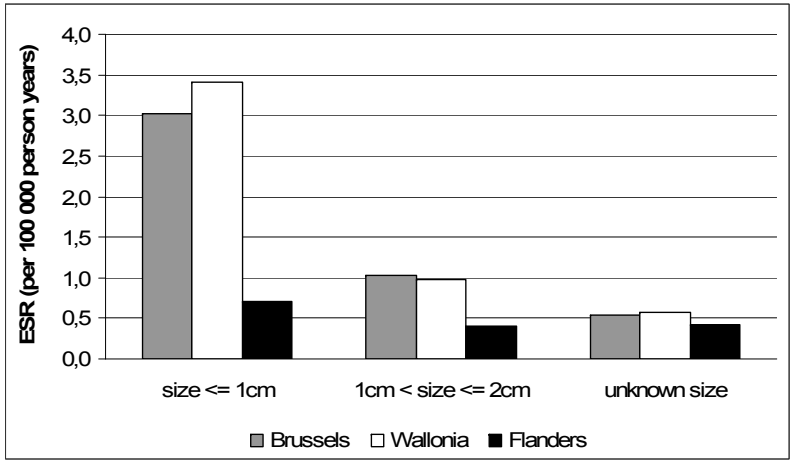
In the Brussels-Capital and the Walloon Regions, the incidence of T1 (≤ 2 cm diameter) cancers was more than 3-fold higher than in the Flemish Region, and even more than four times higher in the case of the very small T1a (≤ 1cm) tumours (Figure 10, Figure 11). Although less pronounced and not significant, the incidence of T2 (2cm<size≤4cm) and T3 cancers was also higher in the Brussels-Capital Region and the Walloon Region than in the Flemish Region. The incidence rates of T4 showed no difference between the three regions.

Figure 10. Incidence of thyroid cancer by T category, males & females, 2004-2006



Source: Belgian Cancer Registry, 2008

Figure 11. Incidence of T1 thyroid cancer by size, males & females, 2004-2006



Source: Belgian Cancer Registry, 2008

3.4.4. Incidence by T category and histological type

3.4.4.1. T1 tumours

Papillary thyroid carcinomas

More than 80% of T1 tumours were papillary carcinoma in the three regions (89.1, 93.0, and 87.2% in the Brussels-Capital Region, the Walloon Region and the Flemish Region respectively). The incidence of T1 papillary carcinoma was higher in the Brussels-Capital Region and in the Walloon Region than in the Flemish Region (4.1, 4.6, and 1.4 per 100 000 PY respectively). Again, this different incidence was especially pronounced in T1a tumours (Figure 12).

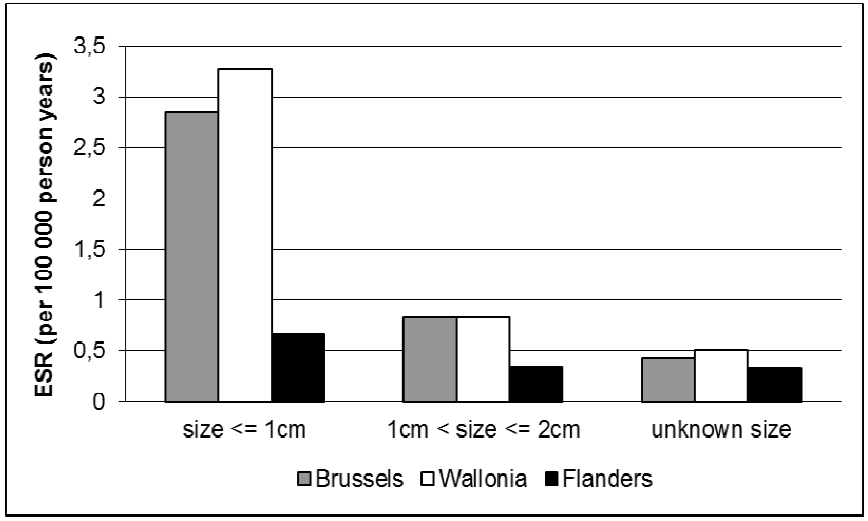
Non-papillary thyroid carcinomas

In the Walloon Region, the incidence of T1 medullary carcinoma was also higher than in the Flemish Region and in the Brussels-Capital Region (0.14, 0.05 and 0.04 per 100 000 PY in the Walloon Region, the Brussels-Capital and the Flemish Regions respectively). In the Brussels-Capital Region, the incidence of follicular cancer was higher than in the Flemish Region and the Walloon Region (0.40, 0.16 and 0.14 per 100 000 PY in the Brussels-Capital Region, the Walloon Region and the Flemish Region respectively).

3.4.4.2. T2, T3 and T4 tumours

Papillary carcinoma remained the most frequent histological type in the T2 and T3 categories for all three regions. Although the differences were less pronounced, the incidences of T2 and T3 papillary carcinomas were again higher in the Brussels-Capital Region and the Walloon Region as compared to the Flemish Region, where 30.9% of T3 tumours were follicular carcinoma. For T4 tumours, the most frequent histological type was the anaplastic carcinoma in the three regions (57.1% in the Brussels-Capital Region and the Flemish Region, 41.4% in The Walloon Region). In the Walloon Region, 34.5% of T4 tumours were papillary carcinoma and the incidence was higher than in other regions (0.09 per 100 000 PY in the Walloon Region versus 0.04 in the Brussels-Capital Region and the Flemish Region) (Appendix 6).

Figure 12. Incidence of T1 papillary carcinomas by size, males & females, 2004-2006



Source: Belgian Cancer Registry, 2008

Key points

- **The incidence of thyroid cancer was 2 times higher in the Brussels-Capital Region and the Walloon Region than in the Flemish Region.**
- **The male/female ratio was 1:3 for all regions.**
- **The most frequent histological type was papillary carcinoma, whatever the tumour size (T1, T2 and T3) in the three regions, with an incidence in the Brussels-Capital Region and the Walloon Region of 6.8 and in the Flemish Region of 2.7 per 100 000 PY.**
- **In the Flemish Region, the other histological types, such as anaplastic carcinoma, were relatively more frequent than in the Brussels-Capital Region and the Walloon Region.**

- **In the Brussels-Capital and the Walloon Regions, the incidence of T1 (≤ 2 cm diameter) cancers was more than 3-fold higher than in the Flemish Region, and even more than four times higher in the case of the very small T1a (≤ 1cm) tumours.**

3.5. Incidence by district

3.5.1. General

Table 6 shows the descriptive analysis of the thyroid cancer incidence for all districts, and Appendix 7 reports statistics on incidence by district and sex.

The thyroid cancer incidence for 2004-2006 by district ranged from 18.4 (Neufchâteau) to 1.1 (Tielt) per 100 000 PY, which represents a 17-fold difference between the districts with the highest and the lowest incidence. In the Brussels-Capital Region, the incidence was 8.4 per 100 000 PY, for the Walloon districts the incidence ranged from 18.4 (Neufchâteau) to 4.2 (Tournai) per 100 000 PY, and for the Flemish districts from 8.7 (Ieper) to 1.1 (Tielt) per 100 000 PY. Globally, 75% (15/20) of the Walloon districts had an incidence higher than 5.9 per 100 000 PY. On the contrary, 21 Flemish districts (95.5%) had an incidence lower than this incidence value. So, most of the districts with the highest incidences belonged to the Brussels-Capital Region and the Walloon Region, as can be seen from Figure 13. The Belgian map in Figure 13 represents the geographical distribution of the thyroid cancer incidence by district.

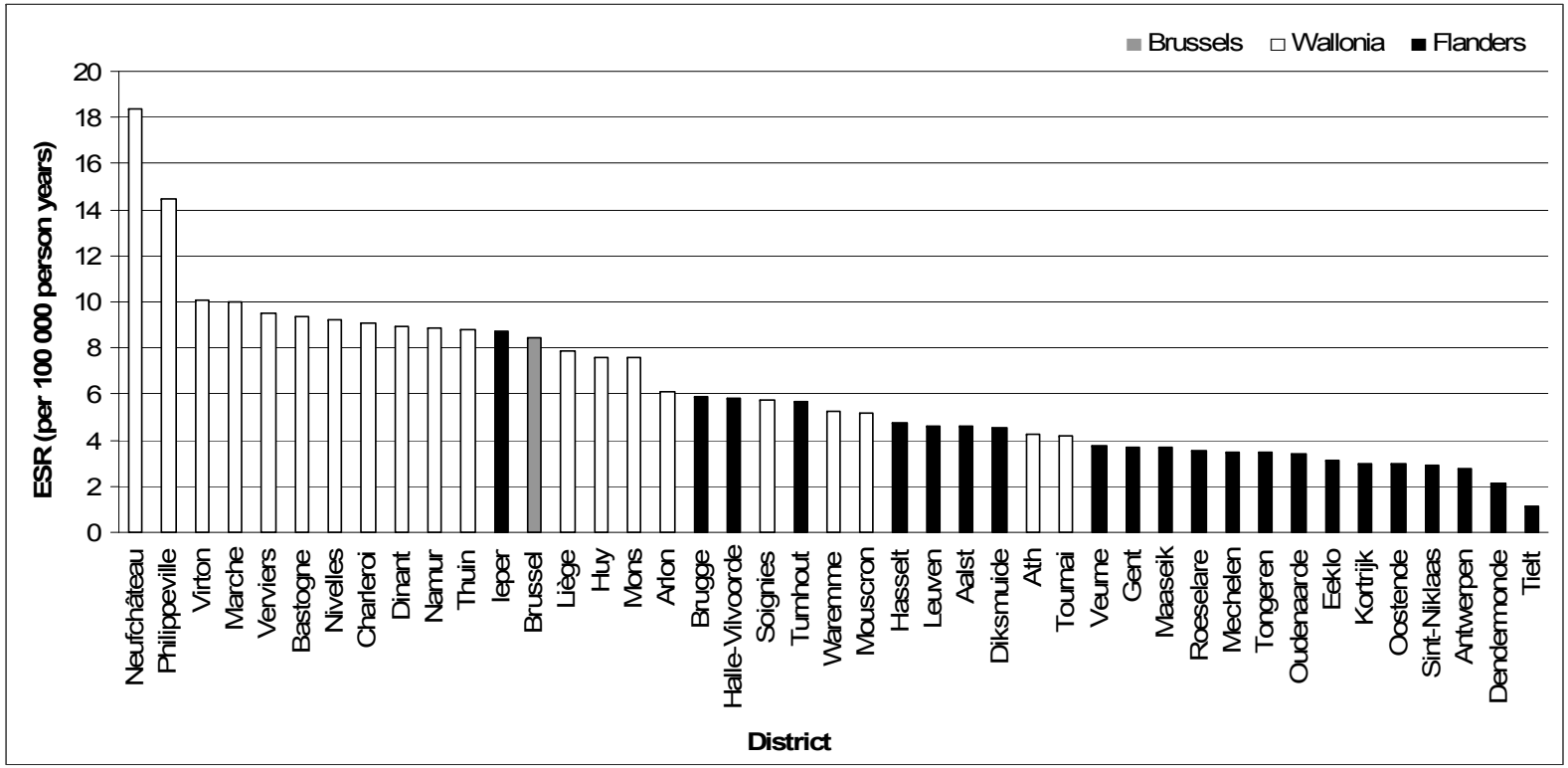
Table 6. Range and percentile of thyroid cancer incidence at district level, males & females, 2004-2006

	Min	Max	P25	P50	P75
Belgium (n=43*)					
Males	0,00	11,65	1,66	2,85	4,14
Females	2,19	25,07	5,66	7,11	12,32
Total	1,12	18,40	3,54	5,28	8,81
Wallonia (n=20*)					
Males	0,00	11,65	3,32	3,91	5,07
Females	4,39	25,07	8,18	12,14	14,68
Total	4,19	18,40	5,93	8,85	9,45
Flanders (n=22*)					
Males	0,00	7,59	1,07	1,79	2,62
Females	2,19	10,24	4,50	5,68	6,97
Total	1,12	8,73	3,01	3,61	4,64

* number of districts

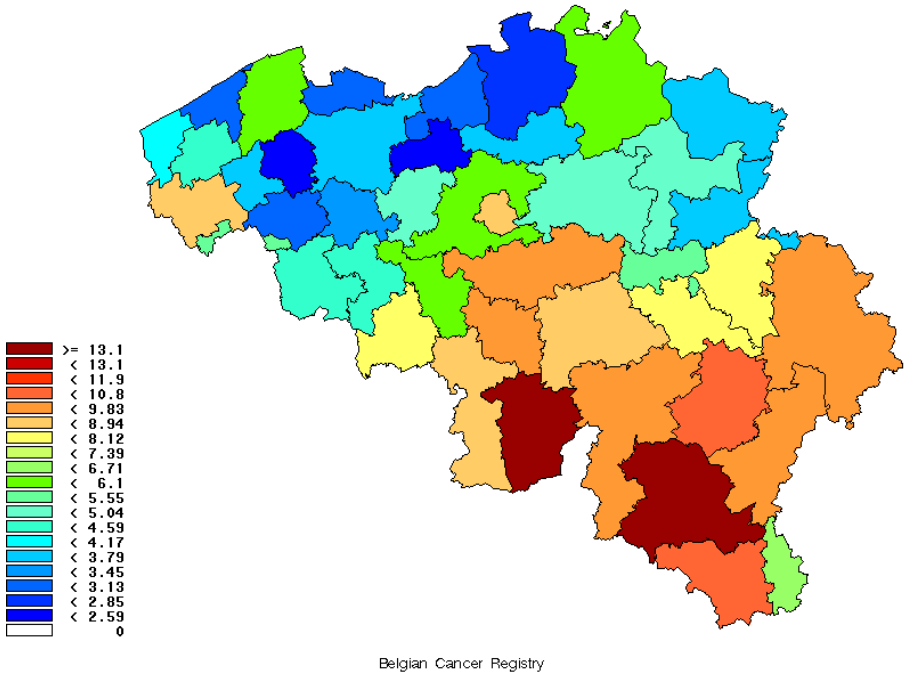
Source: Belgian Cancer Registry, 2008
Note. Statistics for Brussels were not reported in this table because this region includes only one district with the incidence of 4.14, 12.52, and 8.42 per 100 000 PY in males, females, and both sexes together respectively.

Figure 13. Incidence of thyroid cancer by district, males & females, 2004-2006



Source: Belgian Cancer Registry, 2008

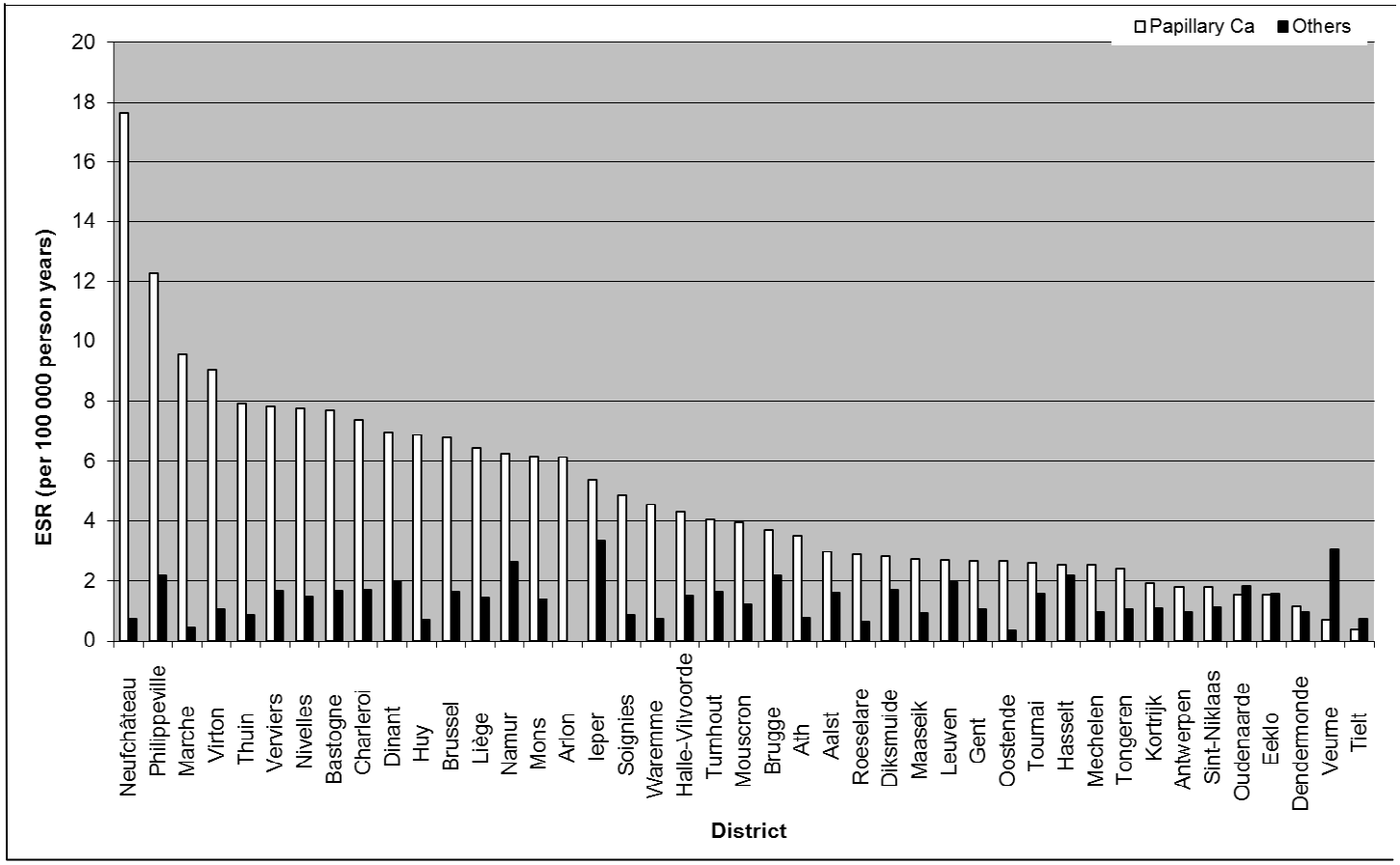
Figure 14. Map of the incidence of thyroid cancer by district, males & females, 2004-2006



3.5.2. Incidence by histological type

The incidence of papillary carcinoma was predominant in most of the districts except for Veurne and Tielt, where the incidence of all other histological types taken together was higher (Figure 15).

Figure 15. Incidence of papillary carcinoma and others, by district, males & females, 2004-2006



Source: Belgian Cancer Registry, 2008

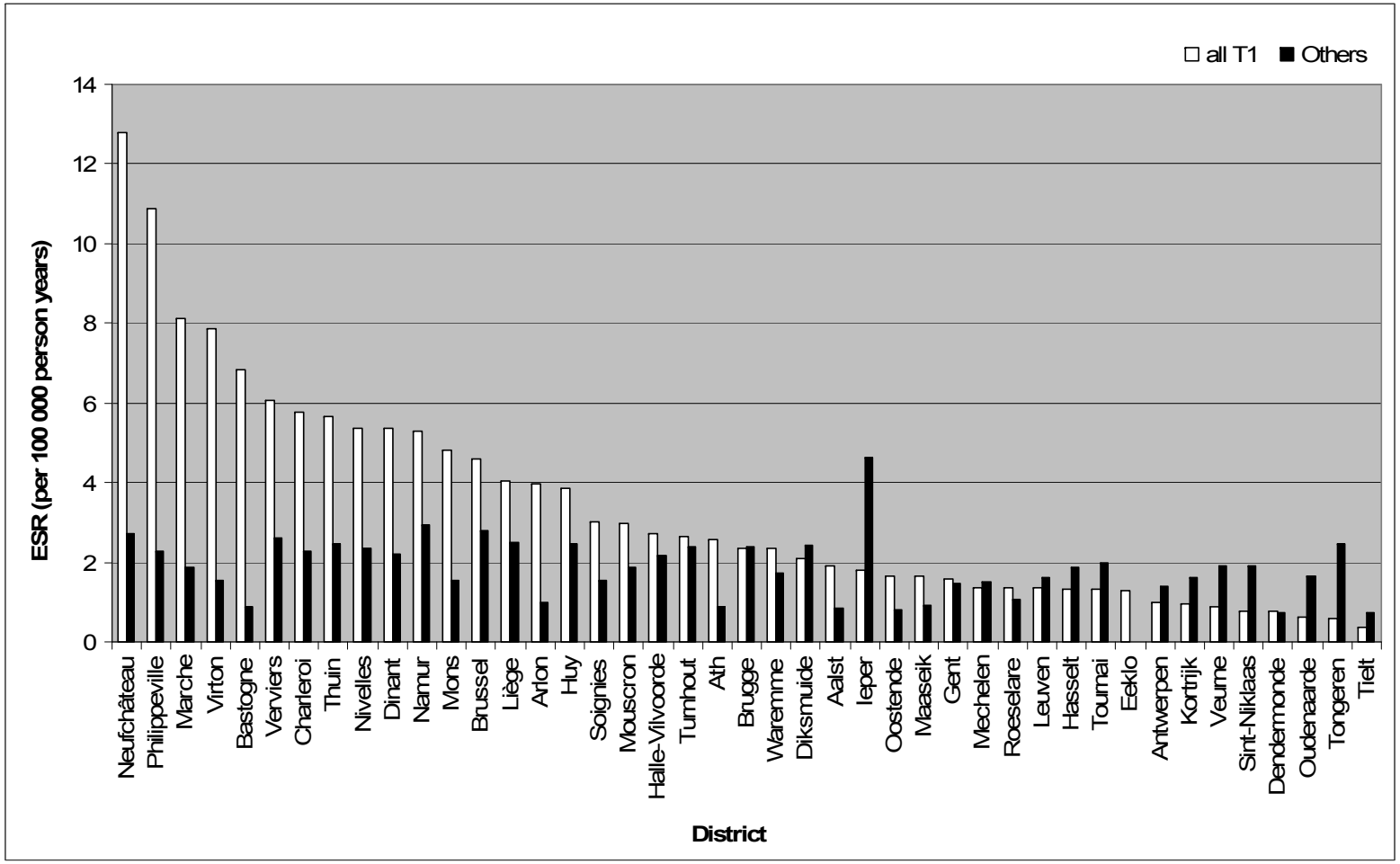
3.5.3. *Incidence by T category*

An analysis of the incidence of thyroid cancer according to tumour size showed that for almost all districts in the Walloon Region and the Brussels-Capital Region the incidence of T1 tumours was higher than the incidence of all other T categories combined (T2, T3, T4). In most of the Flemish districts, the incidence of T1 tumours was higher than or equal to the incidence of all other T categories combined (T2, T3, T4). However, the incidence ratio between the T2, T3, and T4 tumours combined and the T1 tumours was greater than 1.5 for 8 districts (7 districts in the Flemish Region - Tongeren, Oudenaarde, Ieper, Sint-Niklaas, Veurne, Tielt, Kortrijk - and 1 district in the Walloon Region – Tournai) (Figure 16).

Key points

- **Large variation of the incidence was observed between districts, with a 17-fold difference between the lowest and the highest incidence rates.**
- **Except in 2 Flemish districts, the incidence of papillary carcinoma was higher than the incidence of the other histological types in all districts.**
- **Except in 8 districts (7 in the Flemish Region, 1 in the Walloon Region), the incidence of T1 tumours was higher than the incidence of all other T categories combined.**

Figure 16. Incidence of thyroid cancer by district, by T category, males & females, 2004-2006



3.6. Incidence by municipality

The variability in overall incidence was very large with a 100-fold difference between the lowest incidence (excluding municipalities without any cancer case) and the highest incidence. An analysis by sex revealed the same 100-fold ratio for females, but a lower one for males (60-fold difference). The small number of cases by municipality does not allow drawing any firm conclusion.

Key point

- **Large variation in the incidence was observed between municipalities, with a 100-fold difference between the lowest and the highest incidence rates.**

4. VARIABILITY OF SCREENING AND DIAGNOSTIC STRATEGIES

4.1. Introduction and definitions

This chapter aimed to evaluate the association between the incidence of thyroid cancer and the intensity of use of screening and diagnostic strategies across regions. A more intensive use of screening/diagnostic procedures can potentially lead to more incidental thyroid disease findings, resulting in additional diagnostic or therapeutic activities potentially revealing the presence of thyroid tumour(s).

In a clinical context, an *incidental finding* can be defined as the unsought information that was generated in the course of seeking the information one desired. Thyroid *incidentaloma* is defined as an unsuspected, asymptomatic thyroid lesion that is discovered through an imaging study or during an operation unrelated to the thyroid gland[29]. The technologies used in medicine to generate images, scans, and data can now generate so much information that there is a significant potential for incidental findings. Thyroid nodules are commonly detected as incidental findings on all kind of imaging techniques including computed tomography (CT), sonography, magnetic resonance imaging (MRI), duplex carotid US and 2-[^{18}F] fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) performed for unrelated indications[30-32]. Also routine testing of serum Thyroid Stimulating Hormone (TSH) is widely performed in the absence of suggestive clinical features (symptoms or signs) or positive family history for thyroid disease. An abnormal TSH finding can evoke the ordering of thyroid imaging.

Some specific activities performed in a context of cancer screening can also lead to detect cancers in people who have no symptoms of the disease[22]. Screening can be defined as the application of a test to detect a potential disease or condition in a person who has no known signs or symptoms of that condition at the time the test is done[33]. Studies of screening can be classified according to the setting in which the decision to screen takes place. In case finding, testing for thyroid dysfunction is performed among patients who come to their physicians for unrelated reasons For example, components of general periodic physical

examination, such as seeking masses by palpating the neck combined with a TSH testing can lead to *case findings*[33].

The following tests were considered for incidental or case findings, respectively.

Tests potentially leading to incidental findings of thyroid disease = incidence of at least one of the following tests is considered as leading to an incidental finding:

- (Serum) TSH (Thyroid Stimulating Hormone) testing
- Neck US (Ultrasound)
- Duplex carotid US
- CT scan (Computerized axial Tomography)
- PET scan (Positron Emission Tomography)
- MRI (Magnetic Resonance Imaging)

Tests potentially leading to case findings of thyroid disease = Neck US with a TSH within a 4-month period

Age categories: The age categories considered in this research question are the following:

- < 35 years
- 35-44 years
- 45-54 years
- 55-64 years
- 65-74 years
- 75-84 years
- ≥ 85 years

Strata: Strata were defined as the combination of sex and age category (e.g.: Stratum 1 = Male < 35 years; Stratum 2 = Female < 35 years; Stratum 3 = Male 35 – 44 years. etc.)

4.2. Data Source

The analyses were based on the permanent sample (EPS) – Pharmanet datasets – available from 2002 to 2008. The permanent sample (EPS) is an instrument designed by IMA-AIM (Intermutualistic Agency, an agency set up by the seven Belgian Health Insurance Organizations (see www.nic-ima.be) and governmental partners (in particular the National Institute for Health and Disability Insurance, NIHDI) to study and monitor health care consumption and expenditure in Belgium. The sample is in effect drawn from the population of all persons who are a member of one of the seven Health Insurance Organizations. This implies that the very limited number of Belgian residents without public health insurance cover are excluded. The sampling fractions are 1/40 for the population aged 0-64, and 1/20 for the population of 65 and over. The EPS contains data on the specific reimbursement codes by procedure, service, admission, drug delivery, etc., including date, provider, institution and cost. In addition, it has data on age, sex and place of residence.

Data of 2002 were requested in order to identify the patients with history of thyroid disease (see later) but results were presented over the period 2003 to 2008. Selection of the data was performed based on the nomenclature codes attributed to the procedure mentioned here above for the incidental and case findings (See appendix for the complete list of codes).

4.3. Methodology

All the analyses were based on the assumption that the EPS was representative for the different tests at the level of the district (43 districts in Belgium) and the region (3 regions). Pre-assessment of the representativeness of the EPS data was performed for all parameters studied based on the 2008 data. The comparison of the total number of tests included in the EPS database (extrapolated to the entire population) *versus* the total number of tests contained in the overall NIHDI database by district was performed for all tests under investigation. Representativeness of the EPS for a test is assumed at the district level for all tests, unless otherwise specified. Whatever the geographical level considered (region or district), it corresponded to the place of residence of the patient and not the place where s/he was diagnosed or treated.

The number of tests performed per 1 000 PY were computed by district and region and by strata (combination of the age and sex categories) and test (or combination of tests). The different tests or combination of tests which are reported in the present project are:

Incidental findings:

- TSH,
- Neck US,
- Duplex carotid US,
- CT and/or PET scan and/or MRI,
- (CT and/or PET scan and/or MRI) with a TSH performed within a period of 4-month before or after one of these tests BUT excluding the following combination: (CT scan or PET scan or MRI) preceded by a US of neck within the 4-month before the imaging test. This last combination seems to correspond to a specific medical strategy to confirm or to infirm the presence of a pathology detected by ultrasound.

Case findings:

- Neck US with a TSH within a 4-month period before or after the US.

Standardization of the rates

For facilitating the comparison of the results between the regions and in order to adjust for age and sex, standardized rates were presented by region (see details in appendices). Direct standardization was the primary method used and indirect standardization methods were used as sensitivity analyses. The direct method allowed a comparison between regions. The direct standardized rate in each region is the expected rate if the age/sex distribution in each region was the same as in the standard population (European Standard Population[c]). The indirect method did not allow direct comparison between regions but a comparison with the standard population. This method averaged the specific rate of testing in the standard population (Belgian population 2008) weighted by the age/sex distribution of the region. The reported value was the standardized test (expressed in %). This is the ratio between the number of tests observed in the region and the number of expected tests (i.e. if the testing rate was the same as the testing rate in the Belgian population 2008 but with the age/sex distribution of the region).

Populations

Chapter 3 reported differences between regions in terms of thyroid cancer incidence rates with, higher rates being reported in the Brussels-Capital Region and in the Walloon Region. For thyroid cancer patients as for patients having any thyroid disease, the sub mentioned diagnostic tests are tests commonly performed in Belgium as in many other countries[22,30,31].

Therefore, in order to consider separately diagnostic tests performed in patients with and without history of thyroid disease, we have performed the analyses on 2 populations:

- The EPS population,
- The restricted EPS population (EPS excluding the patients with history of thyroid disease from the time of detection – i.e. when the diagnostic test is performed). Patient with history of thyroid disease = patient taking Strumazol (ATC code: H03BB02) or LT4 (Levothyroxine – ATC code: H03AA01) or dose ^{131}I (radioactive iodine) or surgery (thyroidectomy) during the year preceding any of the tests considered.

The percentage of individuals having at least once the test recorded in the administrative database was computed and indirect standardization was used taking the Belgian population in 2008 as standard population. This was done in order to have an idea of the proportion of the population undergoing the different tests and difference between regions, if any.

Statistical methodology

Several considerations were to be taken into account before the formal statistical analyses could be performed.

- *Representativeness of the EPS for each test*

  The representativeness of the EPS for the test, at district or region level, was tested against the number of tests performed among the total population. For this purpose, the data of 2008 were used. In case of lack of representativeness of the EPS data, no further analyses could be performed.

c http://www.wmpho.org.uk/localprofiles/metadata.aspx?id=META_EUROSTD

- *Weighted analyses*

  Due to the oversampling of people over 65 years in the EPS, weighted analyses were used.

- *Model Fitting*

  It was originally planned to use a Poisson regression model in order to test for possible differences in testing rates between regions. Investigations of the model showed that there was a larger variance than expected from the Poisson assumption (overdispersion). In order to avoid the underestimation of the standard errors, an alternative model, the negative binomial regression, was therefore preferred.

- *Longitudinal data analyses*

  A marginal generalized estimating equation (GEE) model was used to evaluate the differences in testing rates between the regions taking into account the longitudinal aspect of the data and allowing for between-district variability.

- *Working correlation*

  The working correlation represents the possible correlation between measurements at different time points. Several working correlations were considered (AR – auto-regression correlation (correlation between measurements is proportional to the temporal distance of the measurements, and EXCH – exchangeable (all correlations are the same for all times)). The working correlation structure that leads to smaller discrepancies between empirical and model based standard error will be kept.

- *Multiple testing issue*

  The overall region effect will be tested at the 5% significance level (*Is there differences between regions*?). If this test leads to a statistically significant result, individual comparisons will be tested. As there are 3 Belgian regions (Brussels-Capital, Flemish and Walloon Region), multiple testing issues should be considered when presenting the results. As the interest of the research question consisted in pairwise comparisons, we should take this multiple testing into account. The Sidak method[34] was used in the present research question.

- *Interpretation of the results*

  Statistical significance does not mean clinical relevance and therefore statistical results should be interpreted within the correct context.

All analyses were performed using SAS® enterprise guide and SAS® version 9.2 and full results are presented in the appendices.

4.4. Results

4.4.1. TSH testing

The EPS was representative at the district level for the TSH testing and the statistical analyses were therefore performed taking into account the variability of the district.

Figure 17. TSH rates per 1 000 PY per age category by region and sex – based on the EPS population (period 2003-2008)

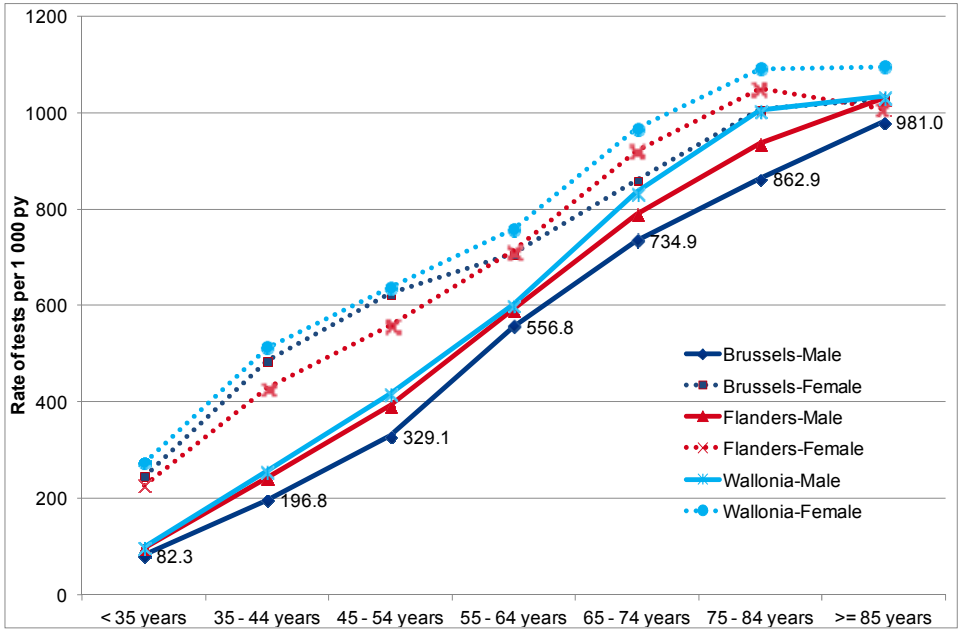
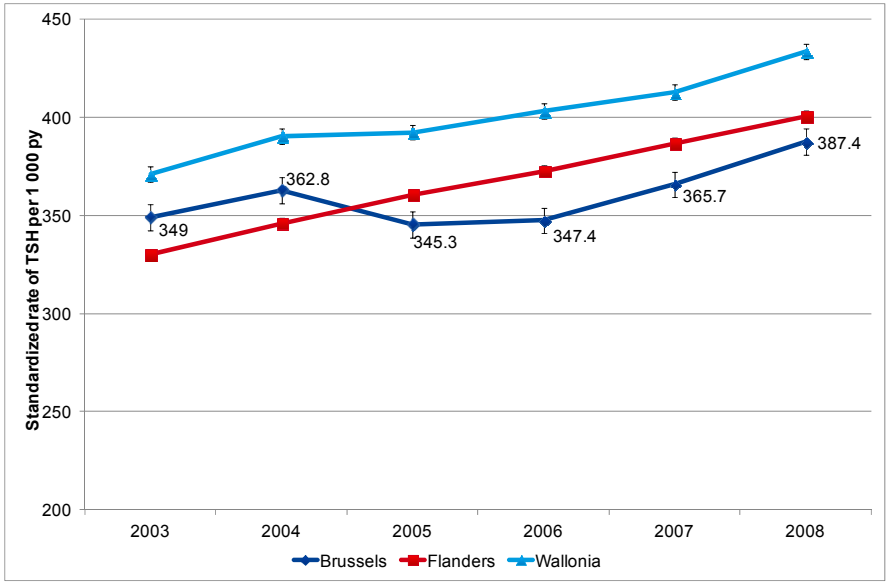


Figure 17 reported TSH rates per 1 000 PY per age category by region and sex during the period 2003-2008. Following observations can be made:

- rates increased over the age categories in all regions and for both sexes,
- rates were slightly higher in females than in males for almost all age categories with a less marked difference between sexes within higher age categories (≥ 65 years old).

Figure 18. European Standardized TSH rates per 1 000 PY by Region over time – based on EPS population



Evolution over time of the standardized rates (Figure 18) showed a moderate increase quite linear except for the Brussels-Capital Region. Globally, in 2008, a 11%, 21% and 17% increase was observed for the Brussels-Capital Region, the Flemish Region and the Walloon Region respectively, compared with 2003.

As shown in Table 7 over the period 2003-2008, the crude rate of TSH testing was quite high (from around 380 to 460 per 1 000 PY). Adjusting for age and sex, the standardized rates reflected some differences between regions with lower rates in the Brussels-Capital Region and the Flemish Region compared to the Walloon Region.

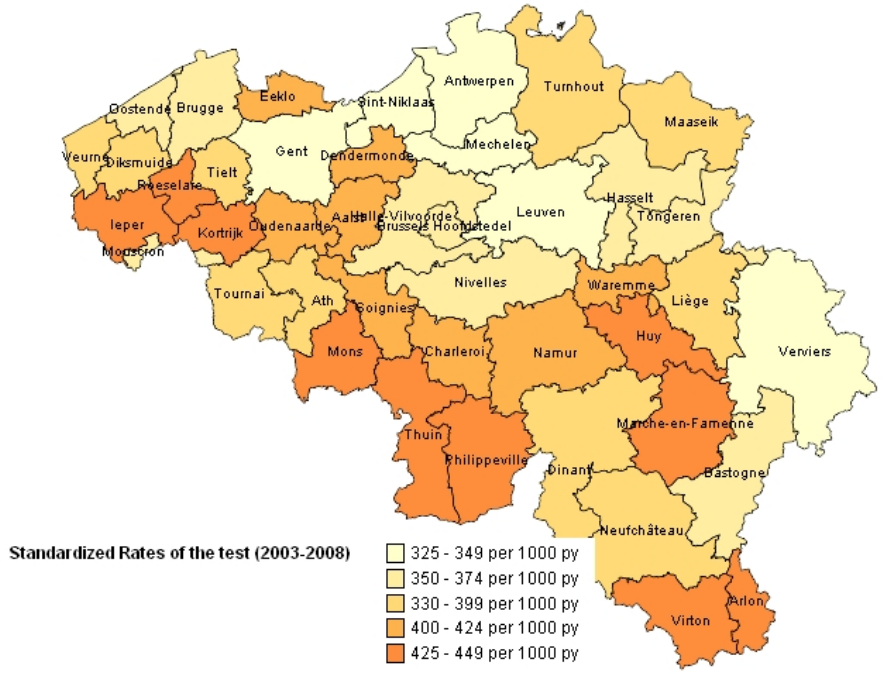
Additionally to the rates of TSH testing, the standardized percentage of individuals with at least one dosage performed on the year was computed and did not show differences between regions in any of the year under consideration (for 2008: 27.0% [95%CI: 20.8; 33.2] in the Brussels-Capital Region, 28.4% [95%CI: 25.9; 30.9] in the Flemish Region and 29.3% [95%CI: 25.9; 32.7] in the Walloon Region). So the observed difference in standardized rates might be suggestive of a difference in the intensity of testing between the regions rather than a difference in the proportion of people tested.

Table 7. Summary Table for TSH testing results

Parameter	Belgium	Brussels Capital Region (Bxl)	Flemish Region (Fl)	Walloon Region (W)	Fl vs W IRR [95%CI] (p-value)	Bxl vs W IRR [95%CI] (p-value)	Fl vs Bxl IRR [95%CI] (p-value)	Overall p-value for region effect
Crude rate – Global Population	**434.2 [432.0 ; 436.4]**	382.7 [375. ; 389.8]	428.8 [426.0 ; 431.5]	459.1 [455.2 ; 463.1]				
Std. rate – Global Population	**377.0 [376.1 ; 377.9]**	359.7 [356.8 ; 362.7]	366.3 [365.2 ; 367.5]	400.7 [399.0 ; 402.3]	0.93 [0.90 ; 0.96] (p<.0001)	0.89 [0.79 ; 1.01] (p= 0.07)	1.04 [0.92 ; 1.18] (p=0.49)	p=0.0003
Std. rate – Restricted Population	**340.6 [339.8 ; 341.5]**	320.6 [317.7 ; 323.4]	338.3 [337.2 ; 339.4]	350.1 [348.6 ; 351.7]	0.98 [0.95 ; 1.02] (p=0.30)	0.91 [0.80 ; 1.03] (p= 0.13)	1.08 [0.95 ; 1.23] (p=0.22)	p=0.2564
Rates (per 1 000 PY) per Region (period 2003-2008) European Standard Population					**Statistical analyses results (GEE model) IRR : Incidence Rate Ratio**			

Note. Std. Rate: standardized rate; Restricted population: population without history of thyroid disease

Figure 19. European Standardized Rates of TSH testing per 1 000 PY by District – based on EPS population (period 2003-2008)



As presented in Figure 19, the standardized rates of TSH testing (period 2003-2008) were higher in the South of Belgium than in the North, with districts in the Walloon Region reporting the highest rate being Mons, Thuin, Philippeville, Huy, Marche-en-Famenne, Virton and Arlon. Remarkable, in some districts in the Flemish Region (Ieper, Roeselaere and Kortrijk) high TSH testing rates were also reported. Visually, 4 groups of districts can be observed with high TSH testing rates. Furthermore, districts being located near the border with France have a high chance of high TSH testing rates.

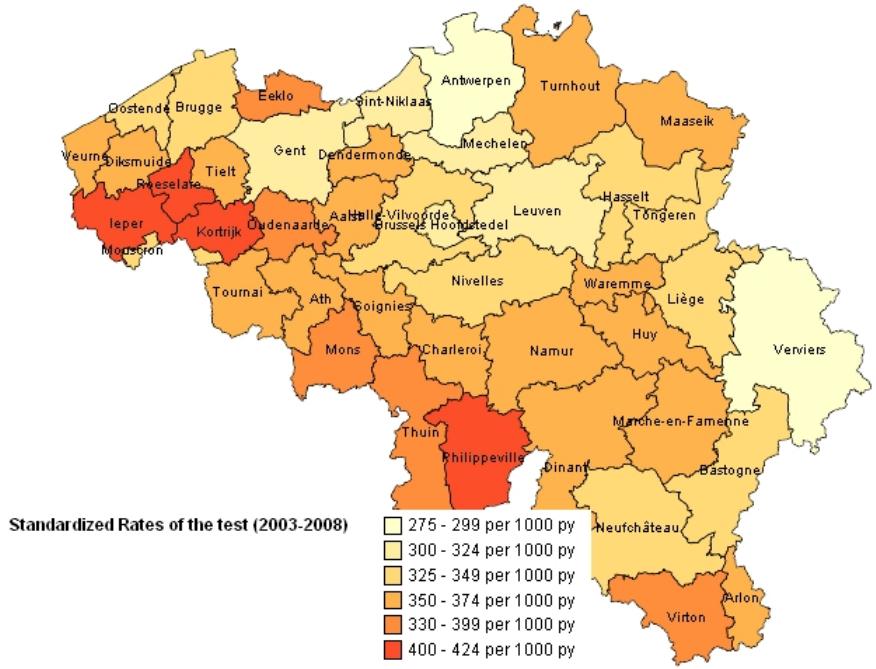
Statistical tests (using marginal GEE model), adjusting for age and sex, showed a significant difference for TSH testing rate between the Flemish Region and the Walloon Region (with a correlation structure = AR(1): RR=0.93 (95%CI [0.90;0.96]); p-value <0.001). No statistical difference was observed between the Flemish Region and the Brussels-Capital Region, or between the Brussels-Capital Region and the Walloon Region (see results in Table 7).

Analysis of the EPS-restricted population, i.e. excluding patients with history of thyroid disease when TSH testing was performed, resulted in similar conclusions in terms of differences between sexes (with more females undergoing TSH testing as compared to males) and increasing rates with age. However, the differences between regions were no longer statistically significant for any of the pairwise comparisons (overall p-value = 0.256).

Looking at the EPS-restricted population at district level, as shown in Figure 20, the differences in terms of rates of TSH testing between the north and the south of Belgium were no longer observed.

The percentage of patients with at least one TSH testing performed was similar regardless the population considered (global or restricted population).

Figure 20. European Standardized Rates of TSH testing per 1 000 PY by district – based on EPS-restricted population (2003-2008)



Differences between the results on the global population and restricted population might therefore be influenced by the variable incidence of thyroid disease between regions and districts. It was observed that the restriction from the global population to the population without history of thyroid disease (as defined in this project) was higher in the Walloon Region than in the Flemish Region (difference of 5% and 3%, respectively). Where the incidence of thyroid disease is higher, TSH testing is expected to be performed for the follow-up of patients and the monitoring of their treatment. However, this hypothesis was not formally tested and has to be taken with caution.

In order to investigate the multiplicity of the TSH testing in patients, additional analyses were performed on patients with at least one TSH testing recorded in the database on the period 2003-2008. The percentage of patients with more than 5 TSH tests (intensive TSH testing) recorded on the period 2003-2008 was calculated and standardized rates using the direct method were reported. From Table 8, it can be concluded that standardized rates of intensive TSH testing were statistically different across regions for the global population but quite similar between the Walloon and the Flemish Regions for the restricted population. The decrease in rates between the global population and the restricted population might suggest that TSH testing is more intensive in patients with history of disease and supports the previous hypothesis.

Table 8. Percentage of patients with more than 5 TSH tests within patients with at least one TSH testing

Parameter	Belgium	Brussels Capital Region (Bxl)	Flemish Region (Fl)	Walloon Region (W)
Crude rate – Global Population	**15.1% [15.0;15.2]**	12.7% [12.4;13.0]	14.8% [14.7;15.0]	16.2% [16.0;16.4]
Std. rate – Global Population	**10.3% [10.2;10.5]**	9.0% [8.6;9.3]	9.8% [9.7;10.0]	11.6% [11.3;11.8]
Std. rate – Restricted Population	**8.0% [7.9;8.1]**	6.4% [5.9;7.0]	8.1% [8.0;8.3]	8.2% [8.0;8.4]

Key points

- **Serum TSH is a very frequently used screening test for thyroid dysfunction in the general population (crude rate around 400 tests per 1 000 PY).**
- **TSH testing rates increased over the age categories in all regions and for both sexes, but remained slightly higher in females than in males.**
- **A moderate increase in TSH testing was observed over time in all regions (11%, 21% and 17% for the Brussels-Capital Region, the Flemish Region and the Walloon Region respectively).**
- **In the global population, standardized rates for TSH testing and TSH intensity were higher in the Walloon Region than in the Flemish Region.**
- **In the subpopulation without a history of thyroid disease, TSH testing is not higher in the Walloon Region than in the Flemish Region.**
- **In the subpopulation with a history of thyroid disease, TSH testing is likely to be more intensive in all regions.**

4.4.2. Neck Ultrasound

Neck ultrasound is often considered an extension of the physical examination for patients with clinical abnormalities at the level of the thyroid but it can also be performed for other reasons such as the investigation of lymph nodes, soft tissue masses and inflammatory conditions in the neck. It is also used to localize parathyroid adenoma(s) in primary hyperparathyroidism or for guidance during the placement of central venous catheters. As such, because of its location, the thyroid gland is often visualized during evaluations for issues unrelated to the thyroid gland[32]. Consequently, neck US might lead to incidental detection of thyroid disease due to the proximity of other anatomical structures under investigation. From Figure 21, it is clear that the neck US is a procedure more often used in women than in men in all regions. However, the rates by age category did not follow the same pattern in the Flemish Region compared to the Walloon Region or the Brussels-Capital Region.

For the Walloon Region and the Brussels-Capital Region peak rates were observed for women between 45 and 64 years (rates > 40 per 1 000 PY). Such peak rates were not observed for men in both regions.

Figure 21. Rates of neck US per 1 000 PY per age category by region and sex – based on EPS population (period 2003-2008)

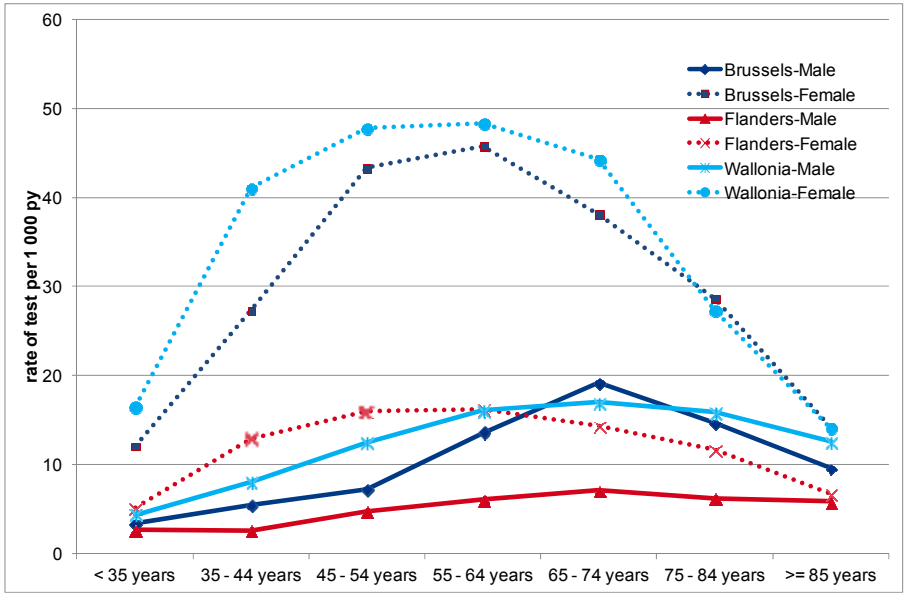


Figure 22 shows that the evolution over time remained quite stable for each region. Rate of neck US was lower in the Flemish Region compared to the Brussels-Capital Region and the Walloon Region.

Figure 22. European Standardized Rates of neck US by region per 1 000 PY – based on EPS population (2003-2008)

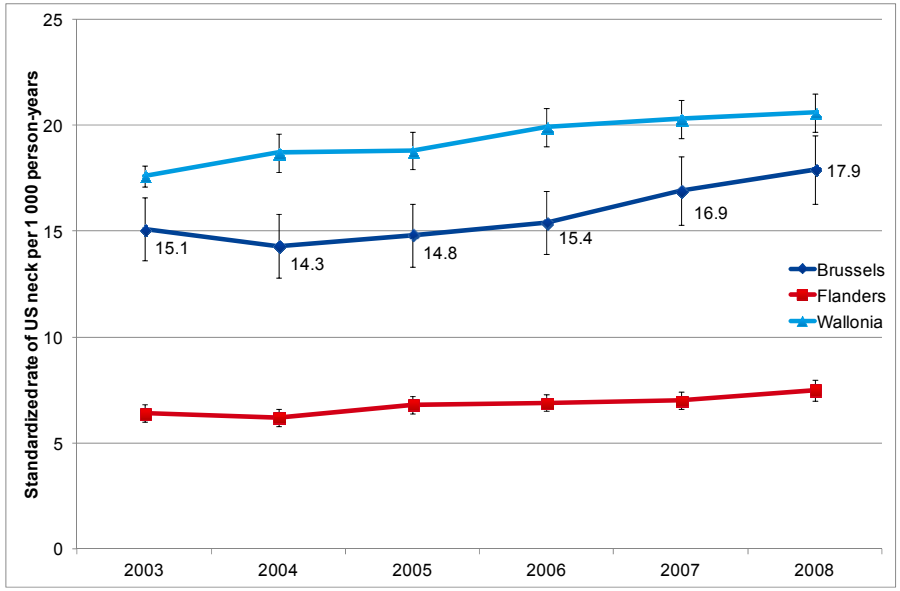
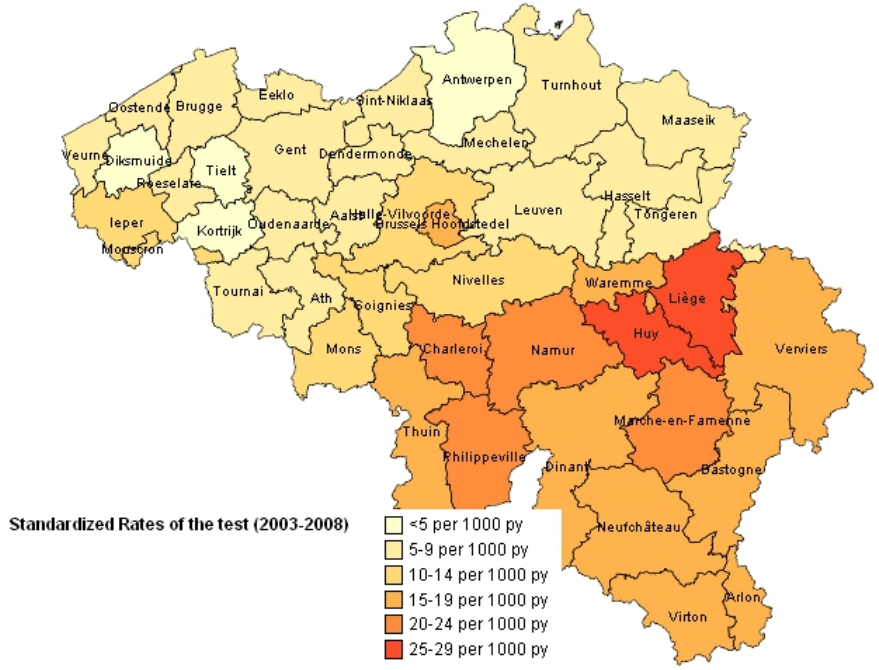


Table 9. Summary Table for Standardized rates of neck US (combined or not with a TSH testing within a 4-month period)

Parameter	Belgium	Brussels Capital Region (Bxl)	Flemish Region (Fl)	Walloon Region (W)	Fl vs W IRR [95%CI] (p-value)	Bxl vs W IRR [95%CI] (p-value)	Fl vs Bxl IRR [95%CI] (p-value)	Overall p-value for region effect
Neck US								
Crude rate – Global Population	12.4 [12.1 ; 12.7]	15.8 [14.4 ; 17.1]	7.3 [7.0 ; 7.6]	20.6 [19.9 ; 21.4]				
Std. rate – Global Population	11.6 [11.5 ; 11.8]	15.8 [15.1 ; 16.4]	6.8 [6.6 ; 7.0]	19.3 [19.0 ; 19.7]	0.39 [0.36 ; 0.42] (p<.0001)	0.82 [0.71 ; 0.96] (p=0.0125)	0.47 [0.40 ; 0.54] (p<.0001)	p<.0001
Std. rate – Restricted Population	7.9 [7.8 ; 8.1]	10.5 [10.0 ; 11.1]	5.1 [5.0 ; 5.3]	12.5 [12.2 ; 12.8]	0.44 [0.40 ; 0.47] (p<.0001)	0.84 [0.73 ; 0.96] (p=0.0086)	0.52 [0.46 ; 0.59] (p<.0001)	p<.0001
Neck US combined with a TSH within a 4-month period – Case findings								
Crude rate – Global Population	9.5 [9.2 ; 9.8]	12.1 [10.9 ; 13.3]	5.3 [5.0 ; 5.6]	16.3 [15.6 ; 16.9]				
Std. rate – Global Population	8.8 [8.6 ; 8.9]	12.0 [11.5 ; 12.6]	4.8 [4.7 ; 4.9]	15.1 [14.7 ; 15.4]	0.36 [0.32 ; 0.39] (p<.0001)	0.79 [0.67 ; 0.94] (p=0.0075)	0.45 [0.38 ; 0.53] (p<.0001)	p<.0001
Std. rate – Restricted Population	5.5 [5.4 ; 5.6]	7.6 [7.2 ; 8.1]	3.3 [3.2 ; 3.4]	9.1 [8.8 ; 9.3]	0.39 [0.36 ; 0.43] (p<.0001)	0.80 [0.68 ; 0.94] (p=0.0076)	0.49 [0.42 ; 0.57] (p<.0001)	p<.0001
Rates (per 1 000 PY) per Region (period 2003-2008) European Standard Population					**Statistical analyses results (GEE model) IRR : Incidence Rate Ratio**			

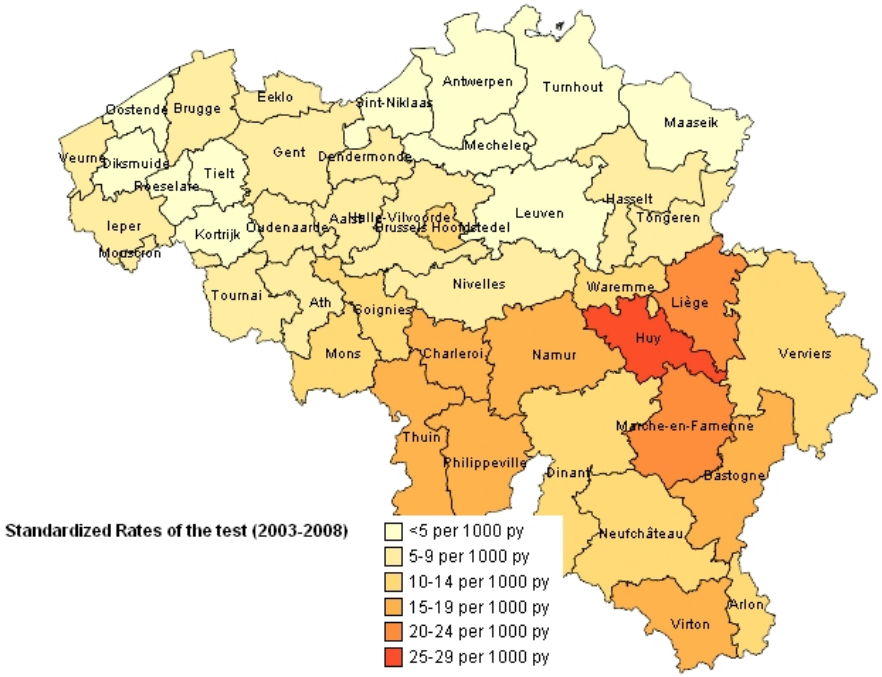
Statistical analysis shows that differences in rates between regions, adjusting for age and sex, were highly statistically significant ($p<0.001$) (see Appendices). Differences in rates for neck US were highly significant both in the EPS and in the EPS-restricted population which implies variable frequency of neck US in patients with or without thyroid disease. At district level (Figure 23), the standardized rates of neck US were higher in the Southern districts of Belgium than in the Northern ones with highest standardized rates in Huy and Liège (between 25 to 29 per 1 000 PY). No Northern district reported the highest rates categories for this imaging test.

Figure 23. European Standardized Rate of neck US per 1 000 PY by district – based on the EPS population (2003-2008)



Amongst all neck US investigations, we were also interested to the situations where US was followed or preceded, within a 4-month period, by a TSH testing (defined as *case findings*). As shown in Figure 23 and Figure 24, differences between the rates of neck US and the rates of neck US combined with a TSH testing within a 4-month period were slightly low (results were reported in Table 9). This might suggest that neck US is usually combined with a TSH testing within a 4-month period.

Figure 24. European Standardized Rates of Neck US with a TSH testing performed in a 4-month period per 1 000 PY by district – based on EPS population (2003-2008)



Key points

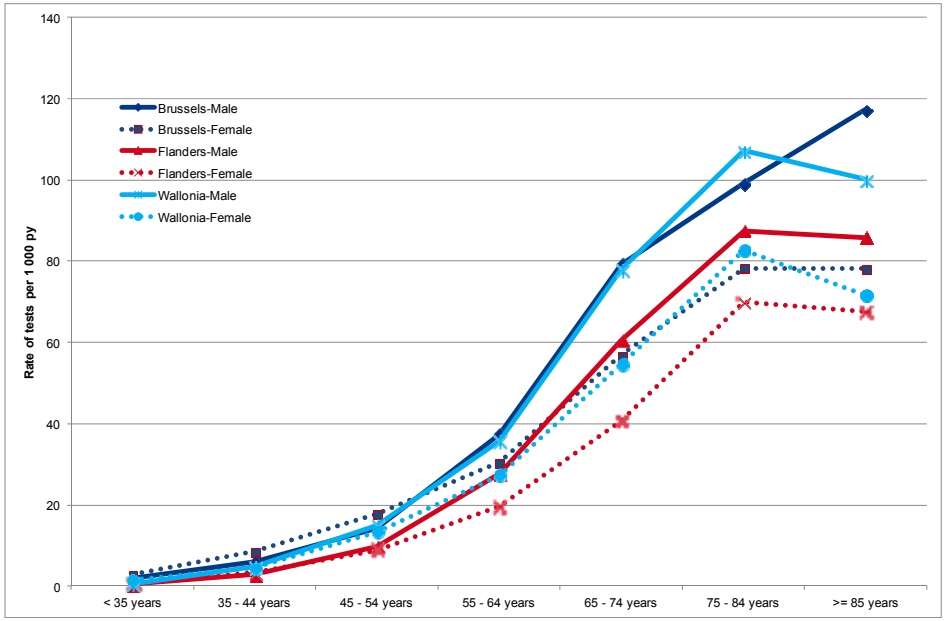
- **Neck US was less frequently performed than TSH testing (crude rate around 12 tests per 1 000 PY for Belgium) and mainly combined with a TSH testing within a 4-month timeframe. Such combination can potentially lead to case finding of thyroid nodule.**
- **The use of neck US remained quite stable over time for each region.**
- **In the Walloon Region the standardized rates of neck US are higher than in the Flemish Region (10 tests per 1 000 PY in the global population and 6 tests per 1 000 PY in patients without history of thyroid disease).**
- **The indication for the ordering of neck US is not traceable in the present study and only hypotheses can be formulated to explain the observed differences.**

4.4.3. Duplex Carotid US

Due to its anatomic proximity, the thyroid gland is well imaged during duplex carotid US, and thyroid masses or abnormalities may be incidentally discovered[35].

From Figure 25, it can be observed that the use of this exam increases with age. There is no clear difference between sexes before the age of 55 years. For the persons older than 55 years old, the duplex carotid US appears more frequently requested in males than in females in each region, which is in line with the expectation of more cardiovascular disease in males. Statistically significant differences in the rate of duplex carotid US exams were observed between the Flemish Region and both other regions (p-value <0.001). The difference in rates between the Brussels-Capital Region and the Walloon Region was statistically significant (with a correlation structure = exchangeable: RR=1.17 (95%CI [1.02;1.35]; p=0.0247). Nevertheless all those differences between regions remain very small and should be interpreted with caution.

Figure 25. Duplex carotid US rates per 1 000 PY per age category by region and sex – based on EPS population (2003-2008)



Evolution over time of the standardized rate was quite stable for all regions (see Figure 26).

Figure 26. European Standardized Rates of duplex carotid US per 1 000 PY over time – based on EPS population (2003-2008)

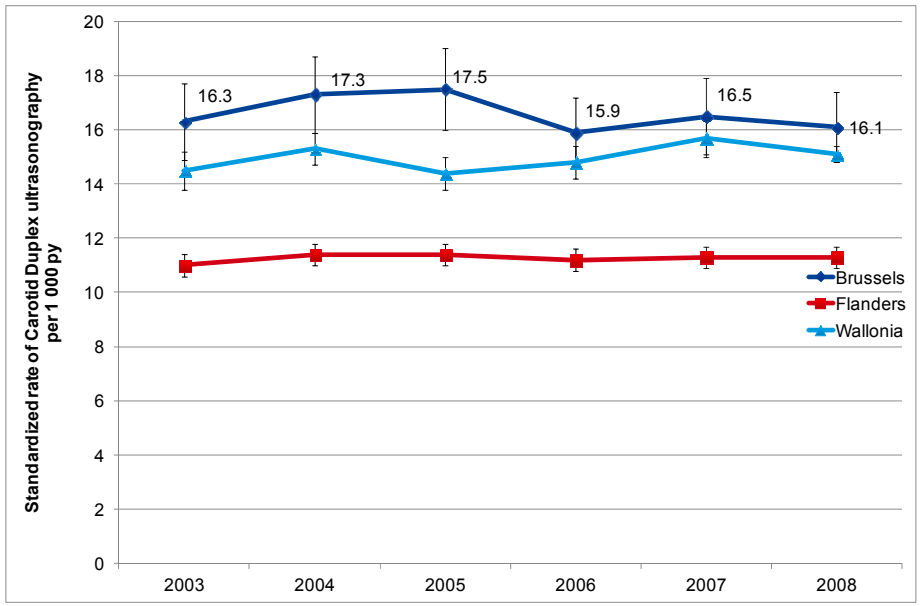
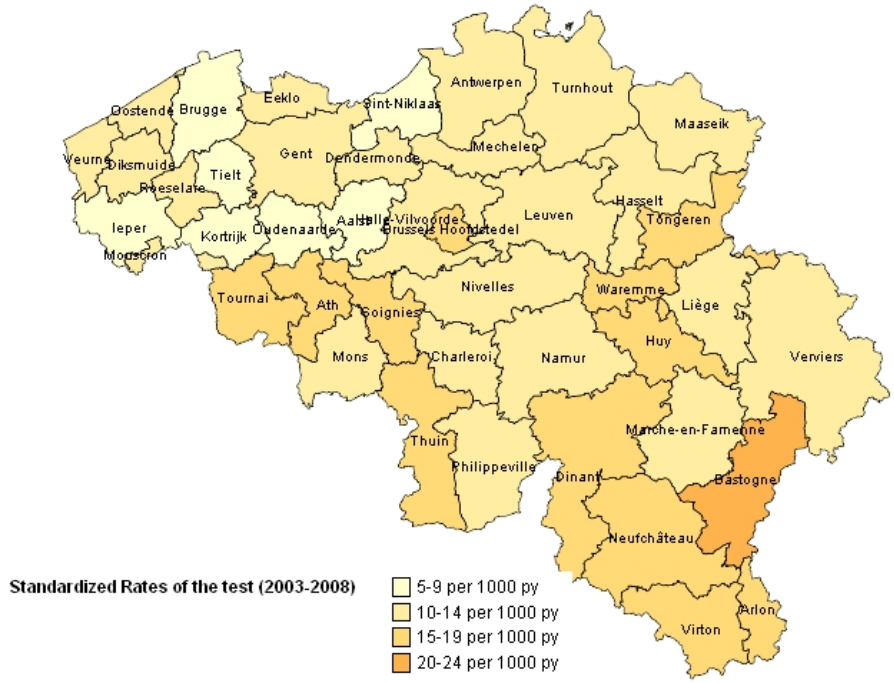


Table 10. Summary Table for Standardized rates of Duplex Carotid US

Parameter	Belgium	Brussels Capital Region (BxI)	Flemish Region (FI)	Walloon Region (W)	FI vs W IRR [95%CI] (p-value)	BxI vs W IRR [95%CI] (p-value)	FI vs BxI IRR [95%CI] (p-value)	Overall p-value for region effect
Crude rate – Global Population	**17.7 [17.2 ; 18.2]**	19.3 [17.5 ; 21.2]	16.1 [15.5 ; 16.7]	20.1 [19.2 ; 21.1]				
Std. rate – Global Population	**12.9 [12.8 ; 13.1]**	16.6 [16.0 ; 17.2]	11.3 [11.1 ; 11.4]	15.0 [14.7 ; 15.3]	0.74 [0.71 ; 0.78] (p<.0001)	1.17 [1.02 ; 1.35] (p=0.0247)	0.63 [0.55 ; 0.73] (p<.0001)	<.0001
Std. rate – Restricted Population	**12.5 [12.3 ; 12.6]**	16.0 [15.4 ; 16.6]	11.0 [10.8 ; 11.2]	14.4 [14.1 ; 14.6]	0.76 [0.72 ; 0.79] (p<.0001)	1.16 [1.03 ; 1.32] (p=0.0189)	0.65 [0.57 ; 0.74] (p<.0001)	<.0001
Rates (per 1 000 PY) per Region (period 2003-2008) European Standard Population					**Statistical analyses results (GEE model) IRR : Incidence Rate Ratio**			

Figure 27. European Standardized Rates of duplex carotid US per 1 000 PY by district – based on EPS population (2003-2008)



The rate of duplex carotid US was similar regardless the population considered (global population or restricted population). This is not surprising since this exam is not usually required for the follow-up of patients with thyroid disease and is therefore not expected to be more frequent in this sub-population.

Key points

- **Duplex carotid US was less frequently performed than TSH testing (crude rate around 18 tests per 1 000 PY for Belgium).**
- **This exam is not specific to detect thyroid abnormalities but might unmask an occult thyroid nodule (incidental finding).**
- **The use of this exam clearly increased with age, higher rates being observed in the population > 75 years old. Also, in the older population, the duplex carotid exams rates were higher in males than in females in all regions, in line with the expectation of more cardiovascular disease in males.**
- **Evolution of duplex carotid US use remained quite stable over time for each region.**
- **In the Walloon Region the standardized rates of duplex carotid US tests were slightly higher than in the Flemish Region (4 tests per 1 000 PY in the global population and 3 tests per 1 000 PY in the population without history of thyroid disease).**
- **The indication for the ordering of carotid duplex US is not traceable in the present study hampering us to explain the observed differences.**

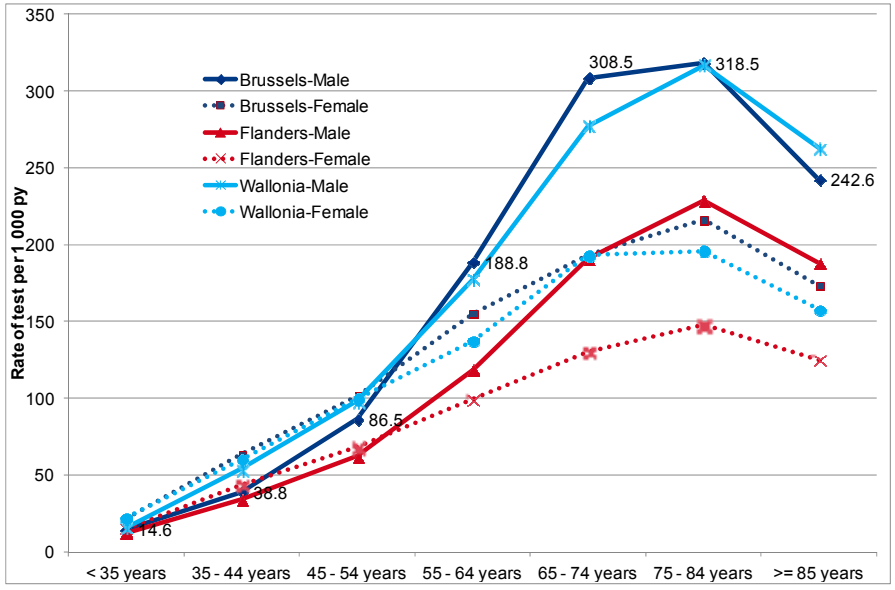
4.4.4. High-tech imaging test (CT scan, PET scan and MRI)

Contemporary high-tech imaging techniques substantially increase diagnostic possibilities and often offer whole-body images. Unfortunately, widespread application of high-resolution imaging modalities also has deleterious effects, particularly the increased discovery of incidentalomas. For example, the serendipitous discovery of clinically silent adrenal masses related to an increased use of abdominal CT scans performed for unrelated diseases has already been documented[36, 37]. Similarly, thyroid incidentalomas are commonly detected on all kind of imaging techniques including computed tomography (CT), sonography, magnetic resonance imaging (MRI) and 2-[^{18}F] fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) performed for unrelated indications[30-32].

From Figure 28 it can be observed that below the age of 55 years rates of high-tech imaging tests were quite similar between sexes. From the age of 55 years and above there was not only an increase in imaging testing but this increase was also more marked in males compared to females. For all three high-tech imaging tests together higher rates were reported in the Walloon Region and the Brussels-Capital Region compared to the Flemish Region. The analyses conducted at the level of regions showed statistical differences between the Flemish Region and the other regions (adjusted Sidak p-value <0.001) but not between the Walloon Region and the Brussels-Capital Region.

At the level of the district, the number of high-tech imaging tests (defined as CT scan, PET scan and MRI) in the EPS was found to be not representative of the number of the same exams performed in the overall Belgian population for the Year 2008. Therefore no statistical analyses at the district level were performed.

Figure 28. High-tech imaging test rates per 1 000 PY per age category by region and sex – based on EPS population (2003-2008)



A small increase in the standardized rates of imaging tests was also observed over the years for all regions (from around 60 per 1 000 PY in 2003 to 90 per 1 000 PY in 2008) (see Figure 29).

Figure 29. European Standardized Rates of high-tech imaging tests per 1 000 PY over time – based on EPS population (2003-2008)

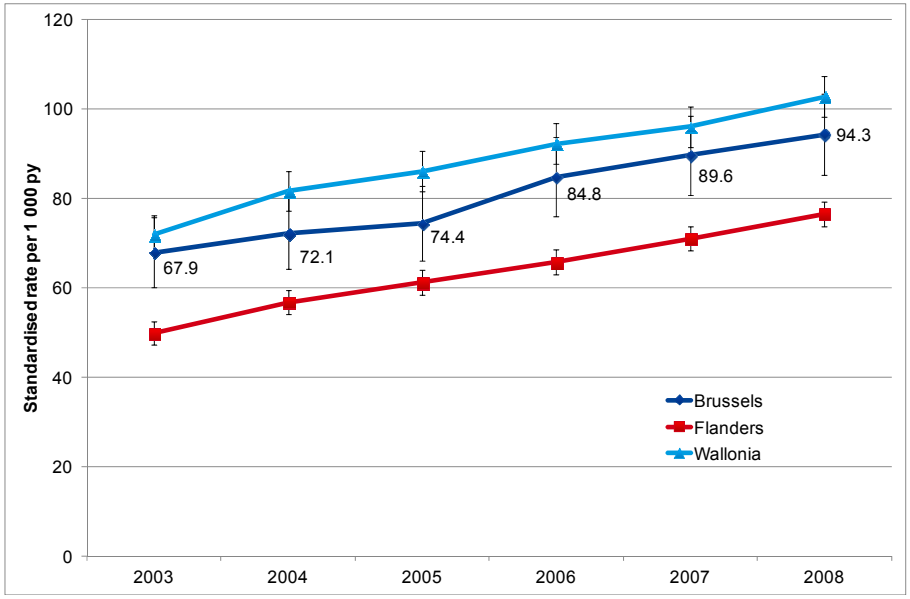


Table 11. Summary Table for standardized rates of high-tech imaging tests (combined or not with a TSH within 4-month period)

Parameter	Belgium	Brussels Capital Region (BxI)	Flemish Region (FI)	Walloon Region (W)	FI vs W IRR [95%CI] (p-value)	BxI vs W IRR [95%CI] (p-value)	FI vs BxI IRR [95%CI] (p-value)	Overall p-value for region effect
High-tech imaging tests								
Crude rate – Global Population	73.2 [72.3 ; 74.1]	80.6 [77.1 ; 84.1]	63.5 [62.4 ; 64.6]	88.5 [86.7 ; 90.3]				
Std. rate – Global Population	61.2 [60.9 ; 61.5]	75.9 [74.6 ; 77.3]	51.9 [51.5 ; 52.3]	74.9 [74.2 ; 75.6]	0.69 [0.63 ; 0.76] (p<.0001)	0.99 [0.88 ; 1.11] (p=0.8535)	0.70 [0.62 ; 0.79] (p<.0001)	p=0.0002
Std. rate – Restricted Population	58.8 [58.5 ; 59.2]	73.2 [71.9 ; 74.5]	50.5 [50.1 ; 50.9]	71.4 [70.7 ; 72.1]	0.71 [0.64 ; 0.78] (p<.0001)	1.00 [0.88 ; 1.13] (p=0.9422)	0.71 [0.63 ; 0.80] (p<.0001)	p=0.0002
High-tech imaging tests combined with a TSH within a 4-month period								
Crude rate – Global Population	45.5 [44.7 ; 46.2]	50.6 [47.8 ; 53.5]	39.4 [38.5 ; 40.3]	55.0 [53.5 ; 56.5]				
Std. rate – Global Population	36.6 [36.3 ; 36.8]	46.2 [45.2 ; 47.2]	30.8 [30.5 ; 31.1]	44.9 [44.4 ; 45.4]	0.68 [0.60 ; 0.78] (p<.0001)	0.98 [0.84 ; 1.14] (p=0.75)	0.70 [0.61 ; 0.81] (p<.0001)	p=0.0008
Std. rate – Restricted Population	34.1 [33.9 ; 34.4]	43.2 [42.2 ; 44.2]	29.3 [29.0 ; 29.6]	41.3 [40.8 ; 41.8]	0.71 [0.62 ; 0.82] (p<.0001)	0.98 [0.84 ; 1.15] (p=0.7959)	0.73 [0.63 ; 0.84] (p<.0001)	p=0.0018
Rates (per 1 000 PY) per Region (period 2003-2008) European Standard Population					**Statistical analyses results (GEE model) IRR : Incidence Rate Ratio**			

The rate of high tech imaging tests was similar regardless the population considered (global population or restricted population).

It was also planned to look at the rate of high tech imaging tests combined with a TSH testing within a 4-month period. For all regions, around 60% of the imaging tests were combined with a TSH testing within a 4-month period (before or after the imaging test) and excluding the cases involving a neck US performed in the 4-month preceding the imaging test. Same conclusions can be drawn both for imaging tests alone and for the combined high tech imaging tests and TSH testing.

Key points

- **Standardized rates of high-tech imaging tests (CT scan, PET scan or MRI) were moderately high (crude rate around 70 per 1 000 PY in Belgium).**
- **These exams are not specific to detect thyroid abnormalities but might disclose incidentalomas (incidental finding).**
- **The use of these exams clearly increased with age, higher rates being observed between 65 and 85 years old.**
- **A small increase in the standardized rates of high-tech imaging tests was observed over the years for all regions (from around 60 per 1 000 PY in 2003 to 90 per 1 000 PY in 2008).**
- **In the Walloon Region the standardized rates of high-tech imaging tests were higher than in the Flemish Region (23 tests per 1 000 PY in the global population).**
- **The indication for the ordering of high-tech imaging tests is not traceable in the present study and only global codes are used to identify CT scan and MRI in the administrative databases without knowledge of the anatomical region examined.**

4.5. Discussion

The standardized rates of diagnostic tests potentially leading to incidental or case findings are, for the tests investigated in the present research project, moderately higher in the Walloon Region or the Brussels-Capital Region compared to the Flemish Region. Apart from serum TSH testing, all the standardized rates in the Brussels-Capital Region were close to the rates reported for the Walloon Region. From a statistical point of view, the differences were, in most cases, statistically significant but they should be interpreted cautiously as small differences, even statistically significant, might not be clinically relevant.

As expected, measurement of serum TSH is a very frequently used screening test for thyroid dysfunction in the general population, as was observed from the rates in Belgium (around 400 per 1 000 PY). Remarkably, clear differences exist between regions, especially between the Walloon Region and the Flemish Region (difference in standardized rates of 34 tests per 1 000 PY). This difference is statistically significant, and also clinically relevant, due to the very high rate of TSH testing. Since TSH is a sensitive test for a highly prevalent disease as functional thyroid disease, an abnormal TSH could thus result in the ordering of additional diagnostic tests including imaging thereby revealing incidental thyroid nodules eventually leading to thyroid cancer diagnosis.

The number of patients detected with a history of thyroid disease (as defined by having received any thyroid-specific treatment before the performance of diagnostic tests) was slightly higher in the Walloon Region than in the Flemish Region (2% difference). After the exclusion of these patients, results suggested that the rate of TSH testing became similar between regions. In patients with history of thyroid disease, TSH testing is more intensive either for the follow-up of patients and the monitoring of their treatment. This was confirmed by investigating the intensity of TSH testing, evaluated by the proportion of patients who performed more than 5 TSH tests on the period 2003-2008. Whereas in the Walloon Region, the proportion of all patients in whom more than 5 TSH tests were performed was slightly higher than in the Flemish Region (11.4% [95%CI 11.2-11.7%] vs. 10.0% [95%CI 9.8-10.2%], such difference disappeared when looking at the subgroup without history of thyroid disease (8.3% [95%CI 8.1-8.5%] vs. 8.4% [95%CI 8.2-8.5%]). This might be suggestive for slightly more

TSH testing in patients with history of thyroid disease in the Walloon Region *versus* the Flemish Region.

As compared to rates of TSH testing, neck US was less frequently performed and mainly combined with a TSH testing within a 4-month time frame in each of the 3 regions. Difference in use of neck US between regions was statistically significant, in the global population (4.8, 12.0 and 15.1 per 1 000 PY in the Flemish, the Brussels-Capital and the Walloon Regions respectively) as well as in the population without history of thyroid disease (3.3, 7.6 and 9.1 per 1 000 PY in the Flemish, the Brussels-Capital and the Walloon Regions respectively). These differences are considered significant also from the clinical point of view but only hypotheses can be formulated to explain such differences since the indication for the ordering of neck US is not traceable in this type of study. Neck US could be more frequently used as a screening tool to detect thyroid abnormalities in the absence of clinical symptoms, but this hypothesis does not seem to be supported by clinicians, from the North and the South of Belgium. In general, different thresholds most probably exist for the ordering of US in case of neck discomfort, abnormal TSH,… but a different prevalence of palpable neck lesions (including thyroid nodules) can also not be ruled out[16].

For the duplex carotid US, findings were quite similar as for neck US, but differences between regions were smaller but still statistically significant (difference of 4 tests per 1 000 PY (11.3 in the Flemish Region *versus* 15 in the Walloon Region). The rate of duplex carotid US was similar regardless the population considered (overall population and population without history of thyroid dysfunction). This is not surprising since this exam is not specific nor required for the follow-up of patients with thyroid diseases and is therefore not expected to be more frequent in this subpopulation. From a clinical point of view, the findings might be relevant, as a duplex carotid US might unmask an occult thyroid cancer.

For the high-tech imaging tests (CT scan, PET scan or MRI), standardized rates of testing were moderately high (crude rate around 70 per 1 000 PY in Belgium)[d]. Higher standardized rates were observed in the Walloon Region as compared to the Flemish Region (difference of 23 tests per 1 000 PY, with 51.9 per 1 000 for the Flemish Region and 74.9 per 1 000 PY for the Walloon Region). This difference is also clinically relevant since imaging techniques are sensitive exams for the detection of subclinical thyroid nodules. The more frequent use of these imaging modalities might disclose more incidentalomas in one region as compared to another. According to the American Thyroid Association (ATA) guidelines (2009)[11], approximately 1–2% of persons undergoing ^{18}FDG-PET imaging for other reasons have thyroid nodules discovered incidentally. Moreover, ^{18}FDG-positive nodules have an increased risk of malignancy and the cancers may be more aggressive. Consequently, these lesions require prompt evaluation with subsequent diagnostic and therapeutic procedures (diagnostic thyroid US, FNA biopsy,…).

High-tech imaging was in 60% of the cases combined with a TSH testing within a 4-month time frame. This practice was observed for each of the 3 regions. It is plausible that when high-tech imaging is ordered in patients, this is most often accompanied by a broad biochemical evaluation usually

[d] To have an idea about the intensity of high-tech imaging exams in Belgium, data of medical technology use in other countries was retrieved from OECD HEALTH DATA 2011 for comparison (available on http://www.oecd.org/document/0,3746,en_2649_201185_46462759_1_1_1_1,00.html;March 12th 2012). OECD data were available both for MRI and CT scan exams per 1 000 population (year 2008, ambulatory and hospital settings). OECD data reported all MRI and CT scans exams whatever the anatomical site (head, neck, heart and vessels, spine, joints, thorax, abdomen, limbs) leading to higher global rates than those reported in our study (including only head, neck, and thorax and abdomen when combined with the neck. Globally, Belgium reported 52.8 MRI and 179.8 CT scan performed per 1 000 population in 2008. These rates were higher than those reported by Denmark (37.8 and 83.8 respectively), the Netherlands (38.8 and 60.3 respectively), Canada (40.6 and 119 respectively) and France (48.4 and 130 respectively) but lower than those reported by Luxemburg (64.6 and 181.5 respectively) and USA (91.2 and 227.9 respectively in 2007).

including serum TSH testing, especially in the older population. A limitation in the present study is that only global codes are used to identify CT scan and MRI in the administrative databases and are thus not specific for the anatomical region examined, including head, neck and thorax (whereas FDG-PET scan consists in whole body imaging).

Nevertheless, as the rates of testing are very elevated, from a clinical point of view it might be expected that this will also be reflected in rates of CT or MRI not ordered for thyroid imaging but in which the thyroid is potentially also visualized (neck, but also lung and cervical spine).

Of course, caution is needed when trying to establish a potential link between the variable use of diagnostic techniques and thyroid cancer incidence across regions. Aggregation of events observed at one geographical level, i.e. the region or the district, could lead to the observation of associations between different variables at this level of aggregation that would not be observed at the individual level or at other aggregation scales (e.g. comparison of eastern and western districts, comparison of urban and rural areas, comparison of coastal areas and remote areas). Neighbourhood to the land borders might also be of importance. For example, highest rates of TSH testing were observed both in Walloon districts and in some western districts in the Flemish Region, near the French border. Such observation could also reflect standard practice as learned during medical studies.

In conclusion, in Belgium and for the period studied (2003-2008), there is substantial geographical variation in the use of a panel of diagnostic tests potentially leading to the incidental detection of thyroid cancer, or to further investigations and treatments, that can eventually also lead to the detection of more cases. However, as in this study no clinical information was available on the indications for these diagnostic tests, nothing can be said on the degree of appropriateness of their use.

5. VARIABILITY OF TREATMENT STRATEGIES FOR THYROTOXICOSIS

5.1. Introduction

This chapter aimed to evaluate the association between the incidence of thyroid cancer and the intensity of use of thyroid surgery as a treatment strategy for *a priori* benign thyrotoxicosis across regions.

Thyrotoxicosis, defined as a state of increased serum T4 and/or T3, is a relatively prevalent disease that is most frequently caused by autoimmune disorders (Graves' disease) or by toxic nodular disease (one or more toxic nodules). As the condition of thyrotoxicosis is mostly symptomatic and induces the risk for serious complications, such as osteoporosis and atrial fibrillation, thyrotoxicosis is always treated. A conservative approach is thus not considered apart from selective very mild cases (so-called subclinical hyperthyroidism). In case of the most frequent aetiology (Graves' disease and toxic nodular disease), three main treatment options are available for thyrotoxicosis:

- Treatment with antithyroid drugs. In Belgium, two antithyroid drugs are currently available: thiamazole (Strumazol) and propylthiouracil (PTU). This option is less frequently chosen in case of toxic nodular disease. Indeed, this treatment option is only temporarily effective, while toxic nodular disease is slowly progressive and irreversible by nature.
- Treatment with radioiodine (^{131}I), at low doses (≤15 mCi per treatment).
- Treatment with surgery being total or partial thyroidectomy. Surgical resection is more frequently performed in case of a large goitre, pregnancy or child wish and pronounced ophthalmopathy[12]. Total thyroidectomy is the preferred surgical approach in view of the relapse rate after partial thyroidectomy (30% in one study)[13] and because the rate of complications is similar between both procedures in experienced hands[12]. Moreover, this option is more performed in case of toxic nodular disease in comparison to autoimmune thyrotoxicosis. Most thyrotoxic patients treated with surgery will have a medical pre-treatment with antithyroid drugs (Strumazol or PTU).

The choice of a specific treatment is determined by the aetiology of the thyrotoxicosis, the thyroid volume or coexisting medical conditions. The treatment choice will take into consideration a number of clinical and demographic factors as well as the patient's preference. Recently, clinical guidelines have been published to guide clinicians in the management of their patients[25].

Three main outcome measures for this research question were defined:

A. What is the proportion of thyrotoxic patients treated with surgery?
B. What is the proportion of thyrotoxicosis in patients treated with thyroid surgery?
C. What is the proportion of thyrotoxicosis in patients treated with thyroid surgery, within the group of cancer patients?

In addition, two secondary outcome measures were defined:

A1: What is the proportion of thyrotoxic patients treated with antithyroid drugs only?

A2: What is the proportion of thyrotoxic patients treated with ^{131}I?

5.2. Methodology

To answer these questions, several measures, formulated as proportions, have been defined. The results were calculated for Belgium as well as per region (the Flemish Region, the Walloon Region and the Brussels-Capital Region). Questions A, B, A1 and A2 were calculated on patients treated between 2003 and 2008 (all cases), while question C relied only on patients with thyroid cancer diagnosed between 2004 and 2006.

The whole procedure for data selection, the exploration of databases and the procedure for data linkage is available in Appendix 9. Descriptive statistics are presented in Appendix 10 for all cases and in Appendix 11 for cancer cases.

Results were reported by age groups (<40, 40-69, 70+). The 95% confidence interval for each proportion was calculated using the Wilson score method[38]. Such intervals should be interpreted cautiously when they are computed on less than 30 cases.

The age-standardized rates for surgery, thyrotoxicosis and surgery within thyrotoxicosis and the age-standardized proportions for each outcome measure were calculated using the direct method of standardisation using the European Standard Population. Such resulting age-standardized rate/proportion is a weighted average of the individual age-specific rates/proportions. Age categories for the age-standardization for surgery, thyrotoxicosis and surgery within thyrotoxicosis where defined by 5 year age groups. However, to avoid small numbers impact of younger age categories, the age-standardized proportions for each outcome were calculated on a basis of 7 age groups for age-standardization (< 35 years, 35-44 years, 45-54 years, 55-64 years, 65-74 years, 75-84 years, ≥ 85 years).

These age-standardized rates/proportions represent the results that would be observed if the population had the same age structure as this standard population. The advantage of using age-standardized rates/proportions instead of the crude rates/proportions is that they make comparisons between different regions independently of the age structure of the regions. The 95% confidence intervals on these rates/proportions were also reported.

It is possible that the confidence interval was large. This is due to wide variance in some age groups where the population at risk and the number of cases are low.

To allow comparison of age-standardized proportions (ASP) between two regions, the ratio of these proportions (named Comparative Incidence Figure or CIF) and its 95% confidence interval were computed using the following formula:

$$95\%CI = e^{\ln\left(\frac{ASP_1}{ASP_2}\right) \pm 1.96 \times \sqrt{\frac{Var(ASP_1)}{ASP_1^{\,2}} + \frac{Var(ASP_2)}{ASP_2^{\,2}}}}$$

Age-standardized proportions were considered significantly different if the value 1.0 was not included in the computed 95% confidence interval[39].

Finally, analyses per region were based on the residence of the patient and not on the location where they were treated.

5.2.1. Definition of thyrotoxic patients

Thyrotoxic patients were identified by the treatment they received. All patients that received at least once Strumazol or ^{131}I or a combination were considered thyrotoxic, but some arbitrary decisions needed to be made.

- ^{131}I

^{131}I can be prescribed for thyrotoxicosis at low doses (≤15 mCi) or for thyroid cancer at high doses (≥ 30 mCi). If nomenclature codes distinguish a hospital-based or an ambulatory treatment, they do not precise the administered dose of ^{131}I.

For the selection of cancer cases (incidence years 2004-2006), ^{131}I administered before or at the incidence date was considered as a treatment for thyrotoxicosis. Of note, two patients were identified with ^{131}I administered at the incidence day of the thyroid cancer.

For all other patients, ^{131}I administered during a hospitalisation was considered as a possible cancer treatment and not included in the thyrotoxicosis treatments. On the contrary ^{131}I administered to an outpatient was considered as treatment for thyrotoxicosis. Of note, in Belgium a maximum of 15 mCi ^{131}I is allowed to be administered to an outpatient.

- PTU

PTU is an antithyroid drug with mechanisms of action similar to Strumazol and therefore potentially used in thyrotoxicosis treatment. In Belgium, this drug is currently not reimbursed, which has important consequences for the reporting of this treatment in the administrative databases of the health Results

Table 12 reported the age-standardized rates for surgery and thyrotoxicosis, using the European Standard Population as a reference (ESR).

insurances. The prescription of PTU is largely underreported in these databases, as reporting has no financial consequences for the health insurance company. An exploration of the administrative databases showed that all health insurance companies registered at least some PTU administrations. However, when considering PTU in the definition of thyrotoxic patients (i.e. the patients who received at least once Strumazol or PTU or ^{131}I), the proportion of patients that would be added as thyrotoxic was higher in the Walloon Region than in the other regions (2.4% extra patients with thyrotoxicosis in the Walloon Region, versus 0.5% in the Brussels-Capital Region and 0.3% in the Flemish Region).Moreover, as the registration of PTU use in Belgium is neither systematic nor complete it was decided not to retain PTU in the analyses.

5.2.2. Definition of surgery

- Selection of nomenclature codes

Surgery was identified by specific nomenclature codes (see appendix for the complete list of codes).

- Choice of surgery

Based on the selected nomenclature codes, some patients underwent multiple thyroid surgeries. Only the first charged surgery was considered.

- Time frames for surgery

For both Strumazol and ^{131}I in relation with surgery, we considered the last administration of Strumazol or ^{131}I as the time point reference. It was investigated whether the first surgery was charged within 1 year after the last administration of Strumazol or ^{131}I.

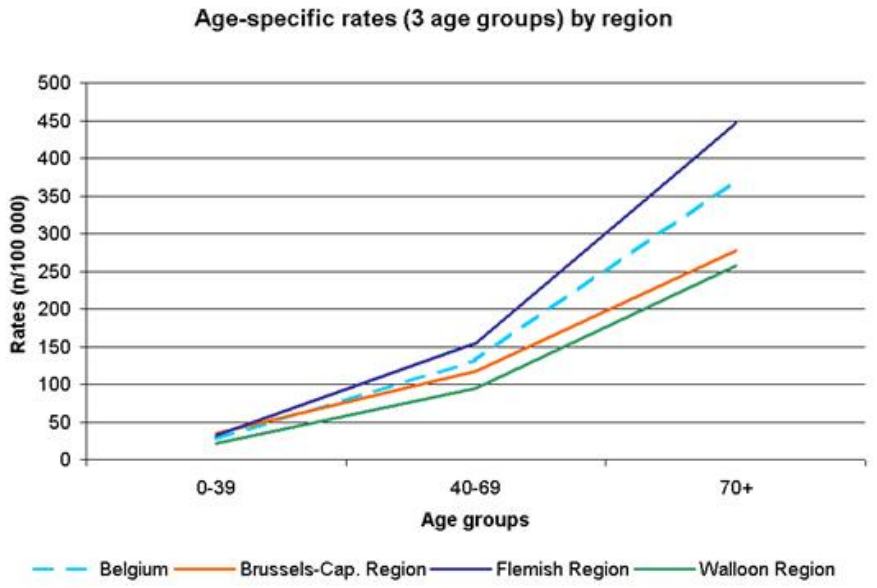
5.3. Results

Table 12. Age-standardized rates (n/100 000 PY) for surgery and thyrotoxicosis over the period 2003-2008, per region

2003-2008	Belgium		Brussels-Capital Region		Flemish Region		Walloon Region	
	ESR	95%CI	ESR	95%CI	ESR	95%CI	ESR	95%CI
Surgery	50.8	[50.3 ; 51.4]	56.6	[54.7 ; 58.5]	34.0	[33.4 ; 34.6]	80.3	[79.1 ; 81.5]
Thyrotoxicosis	87.4	[86.7 ; 88.1]	78.6	[76.4 ; 80.7]	101.9	[101.0 ; 102.9]	62.7	[61.7 ; 63.7]
Surgery within thyrotoxicosis	5.7	[5.5 ; 5.9]	6.5	[5.8 ; 7.1]	5.4	[5.2 ; 5.6]	6.0	[5.6 ; 6.3]

Age-standardized rates by region showed most surgical interventions per capita per year in the Walloon Region, followed by the Brussels-Capital Region and the Flemish Region. The age-standardized rate of thyrotoxicosis was highest in the Flemish Region, particularly after 70 years old (Figure 30) followed by the Brussels-Capital Region and the Walloon Region. Age-standardized rates for surgery within thyrotoxicosis showed only minor interregional differences.

Figure 30. Age-specific rates for thyrotoxicosis by region (2003-2008)



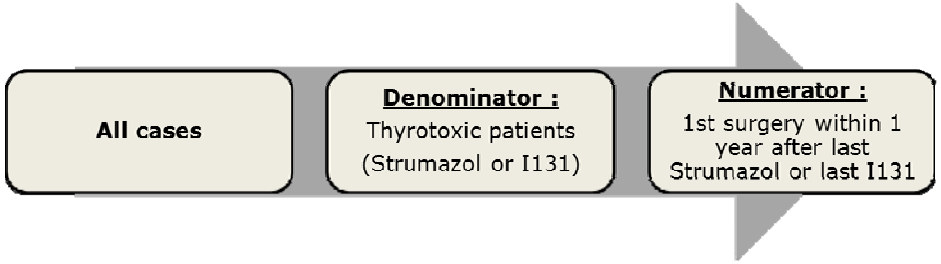
5.3.1. Main outcome measures

5.3.1.1. A: Proportion of thyrotoxic patients treated with surgery

Denominator: All thyrotoxic patients

Numerator: All thyrotoxic patients who were operated within one year after the last administration of ^{131}I or Strumazol

Figure 31. Flowchart A - Proportion of thyrotoxic patients treated with surgery



In Belgium 2003-2008, 4.6% of patients with thyrotoxicosis were treated with surgery (95%CI: 4.4; 4.7). In the Walloon Region, surgical intervention was performed relatively more frequently than in the other regions, and this observation was confirmed after age-standardization. Analyses by age group showed that younger patients (0-39 years) with thyrotoxicosis underwent surgical treatment more often (9.2% for Belgium [95%CI: 8.6; 9.8]) while this was rarely the case for patients of 70 years and older (1.6% for Belgium [95%CI: 1.5; 1.8]). This age-related trend was observed for all regions.

All interregional comparisons of age-standardized proportions showed significant differences (see Appendix 12).

Table 13. Crude and age-standardized proportions of thyrotoxic patients treated with surgery by region and age group

		Belgium	Brussels-Capital Region	Flemish Region	Walloon Region
Thyrotoxicosis	**(n)**	69 420	5 465	48 127	15 828
Surgery	**(n)**	3 172	301	1 843	1 028
% thyrotoxic patients with surgical treatment	**(%)**	4.6	5.5	3.8	6.5
	[95%CI]	[4.4 ; 4.7]	[4.9 ; 6.1]	[3.7 ; 4.0]	[6.1 ; 6.9]
% by age group					
0-39 years	**(%)**	9.2	10.3	8.1	11.4
	[95%CI]	[8.6 ; 9.8]	[8.7 ; 12.1]	[7.4 ; 8.8]	[10.2 ; 12.8]
40-69 years	**(%)**	5.9	6.4	4.9	8.8
	[95%CI]	[5.6 ; 6.2]	[5.5 ; 7.5]	[4.6 ; 5.2]	[8.2 ; 9.5]
70+ years	**(%)**	1.6	1.4	1.5	2.1
	[95%CI]	[1.5 ; 1.8]	[1.0 ; 2.0]	[1.4 ; 1.7]	[1.8 ; 2.5]
Age-Standardized Proportion	**(%)**	7.7	8.3	6.7	10.1
	[95%CI]	[7.3 ; 8.1]	[7.2 ; 9.4]	[6.2 ; 7.2]	[9.2 ; 11.0]

5.3.1.2. B: Proportion of patients with thyrotoxicosis within the surgical group

Denominator: All patients with thyroid surgery

Numerator: All patients with thyroid surgery, who were treated with Strumazol or ^{131}I within one year before the surgery

Considerations: Last Strumazol or last ^{131}I were considered

Figure 32. Flowchart B - Proportion of patients with thyrotoxicosis within the surgical group



Of all patients who underwent a thyroid surgery in Belgium during the period 2003-2008, 9.2% (95%CI: 8.9; 9.5) received a treatment for thyrotoxicosis within the year preceding the first surgical intervention. This proportion was highest in the Flemish Region (13.6% [95%CI: 13.0; 14.2]), followed by the Brussels-Capital Region (8.7% [95%CI: 7.7;9.6]) and the Walloon Region (5.9% [95%CI: 5.6;6.3]). However, after age-standardization, the Flemish Region was the region with most patients with thyrotoxicosis among surgical patients (14.4% [95%CI: 13.6; 15.3]), followed by the Brussels Capital Region (10.4% [95%CI: 9.0; 11.7]) and the Walloon Region (10.3% [95%CI: 9.8; 10.8]). In alignment with this observation, analyses of this outcome measure by age group showed remarkable differences between the regions. While in the Walloon Region, the proportions of patients undergoing thyroid surgery for at least thyrotoxicosis was equally distributed between the three defined age groups, a shift was noted towards younger (0-39 years) patients in the Brussels-Capital Region and older patients (70+ years) in the Flemish Region.

All interregional comparisons of age-standardized proportions showed significant differences (see Appendix 12).

Table 14. Crude and age-standardized proportions of patients with thyrotoxicosis within the surgical patients, by region and age group

		Belgium	Brussels-Capital Region	Flemish Region	Walloon Region
Thyroid surgery	**(n)**	34 435	3 474	13 553	17 408
Thyrotoxicosis	**(n)**	3 172	301	1 843	1 028
% of surgical patients with a history of thyrotoxicosis	**(%)**	9.2	8.7	13.6	5.9
	[95%CI]	[8.9 ; 9.5]	[7.7 ; 9.6]	[13.0 ; 14.2]	[5.6 ; 6.3]
% by age group					
0-39 years	**(%)**	10.2	11.9	13.5	6.8
	[95%CI]	[9.6 ; 10.9]	[10.0 ; 14.0]	[12.4 ; 14.7]	[6.0 ; 7.6]
40-69 years	**(%)**	8.3	7.3	12.5	5.5
	[95%CI]	[8.0 ; 8.7]	[6.2 ; 8.5]	[11.8; 13.2]	[5.1 ; 5.9]
70+ years	**(%)**	12.0	7.4	19.8	6.8
	[95%CI]	[11.0 ; 13.1]	[5.1 ; 10.5]	[17.9; 21.8]	[5.7 ; 7.9]
Age-Standardized Proportion	**(%)**	10.3	10.4	14.4	6.7
	[95%CI]	[9.8 ; 10.8]	[9.0 ; 11.7]	[13.6 ; 15.3]	[6.2 ; 7.3]

5.3.1.3. C: Proportion of operated thyroid cancer cases with history of thyrotoxicosis

Denominator: All thyroid cancer patients who were operated

Numerator: All thyroid cancer patients who were operated, and having received Strumazol or ^{131}I within one year before the surgery

Considerations: Last Strumazol or last ^{131}I were considered

Figure 33. Flowchart C - Proportion of operated thyroid cancer cases with history of thyrotoxicosis



Of all thyroid cancer patients who underwent thyroid surgery, a minority had evidence of thyrotoxicosis within the year before the first surgical intervention (4.8% [95%CI: 3.9; 5.9]). Estimations per region, both crude and age-standardized, showed highest proportions in the Flemish Region followed by the Brussels-Capital Region and the Walloon Region. Analyses by age group suggested that the proportion of thyroid cancer patients treated for thyrotoxicosis in the year preceding the first thyroid surgery was highest for elderly patients, both in the Flemish (9.7% [95%CI: 5.5; 16.6]) and the Walloon Region (8.1% [95%CI: 4.2; 15.1]. Given the low numbers, results for the Brussels-Capital Region should be interpreted with caution.

Age-standardized proportions were significantly different between the Flemish and the Walloon Region (see Appendix 12).

Table 15. Crude and age-standardized proportions of operated thyroid cancer cases with history of thyrotoxicosis by region and age group

		Belgium	Brussels-Capital Region	Flemish Region	Walloon Region
Thyroid surgery	**(n)**	1 750	216	712	822
Thyrotoxicosis	**(n)**	84	8	42	34
% of surgically treated cancer patients with a history of thyrotoxicosis	**(%)**	4.8	3.7	5.9	4.1
	[95%CI]	[3.9 ; 5.9]	[1.9 ; 7.1]	[4.4 ; 7.9]	[3.0 ; 5.7]
% by age group					
0-39 years	**(%)**	4.0	5.6	5.0	2.6
	[95%CI]	[2.5 ; 6.3]	[1.9 ; 15.1]	[2.6 ; 9.2]	[1.1 ; 6.0]
40-69 years	**(%)**	4.4	3.8	5.3	3.9
	[95%CI]	[3.4 ; 5.8]	[1.6 ; 8.5]	[3.5 ; 7.8]	[2.6 ; 6.0]
70+ years	**(%)**	7.9	0.0	9.7	8.1
	[95%CI]	[5.1 ; 12.0]	[0.0 ; 11.7]	[5.5 ; 16.6]	[4.2 ; 15.1]
Age-Standardized Proportion	**(%)**	4.6	4.8	6.2	3.0
	[95%CI]	[3.2 ; 5.9]	[2.0 ; 9.4]	[3.7 ; 8.7]	[1.6 ; 4.3]

It would be interesting to check the proportions of T1 tumours in patients who were operated for thyrotoxicosis (Figure 34 and Table 16). Age standardized proportions were slightly different between the Flemish and the Walloon Regions (a higher rate was reported in the Walloon Region).

Figure 34. Proportions of T1 tumours in patients operated for thyrotoxicosis

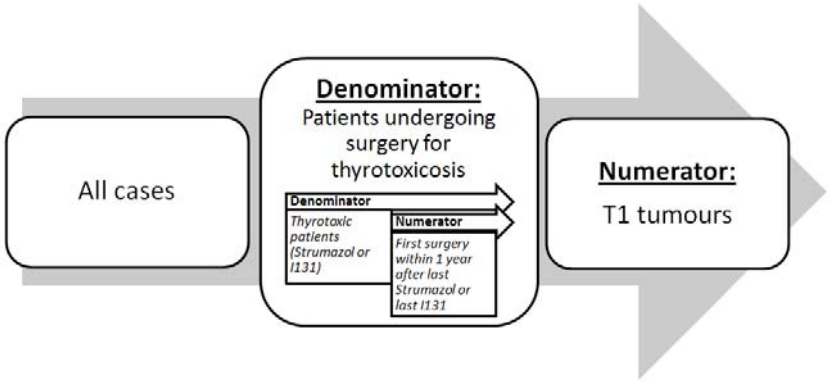


Table 16. Proportions of T1 tumours in patients operated for thyrotoxicosis

	Belgium	Brussels-Capital Region	Flemish Region	Walloon Region
Denominator (n)	3 172	301	1 843	1 028
Numerator (n)	54	7	19	28
Crude proportion (%)	1.70%	2.33%	1.03%	2.74%
Age standardized proportions (% [95%CI])	1.2 [0.8; 1.6]	1.7 [0.7; 3.4]	0.9 [0.6; 1.5]	1.7 [1.1; 2.5]

The proportion of small cancers in patients with surgery for thyrotoxicosis might be considered as a potential marker of incidental cancer findings in thyroid surgical specimens. This proportion is higher in the Walloon Region as compared to the Flemish Region. Although this could imply a true higher prevalence it could also point to a pathological bias with more incidental T1 cancers per surgical specimen. Different thresholds to label a small abnormality as a cancer, different levels of scrutiny (e.g. number and thickness of slices) could be present. Another potential confounder being variable proportions of lobectomy versus total thyroidectomy could be present as well, resulting in a different amount of thyroid tissue submitted to pathology and thus different risks of incidentally finding a small thyroid cancer.

Key points

- **The age-standardized rate of thyrotoxicosis reported in this study was around 87 per 100 000 PY for Belgium.**
- **The age-standardized rate of thyrotoxicosis was highest in the Flemish Region (around 102 per 100 000 PY) and lowest in the Walloon Region (around 63 per 100 000 PY).**
- **In Belgium 2003-2008, surgery was performed in a minority of thyrotoxic patients (7.7% for Belgium).**
- **In the Walloon Region, age standardized proportions of surgery for thyrotoxicosis were higher (10.1%) than in the Flemish Region (6.7%).**
- **Younger patients (0-39 years) with thyrotoxicosis underwent surgical treatment more often (9.2% for Belgium) than patients of 70 years and older (1.6% for Belgium).**
- **Among surgical patients, evidence of thyrotoxicosis was present in 14.4% in the Flemish Region and in 6.7% in the Walloon Region.**
- **The proportion of thyroid cancer patients with evidence of thyrotoxicosis in the year preceding their first surgery is low (4.6% in Belgium). Significant differences were reported between the Flemish (6.2%) and the Walloon Region (3.0%).**

5.3.2. *Secondary outcome measures*

5.3.2.1. *A.1: Proportion of thyrotoxic patients treated with antithyroid drugs only*

Denominator: All thyrotoxic patients

Numerator: All thyrotoxic patients who were treated with antithyroid drugs only

Considerations: These patients were not treated with ^{131}I, and did not undergo a first surgery within 1 year after the last administration of Strumazol.

Figure 35. Flowchart A.1 - Proportion of thyrotoxic patients treated with antithyroid drugs only

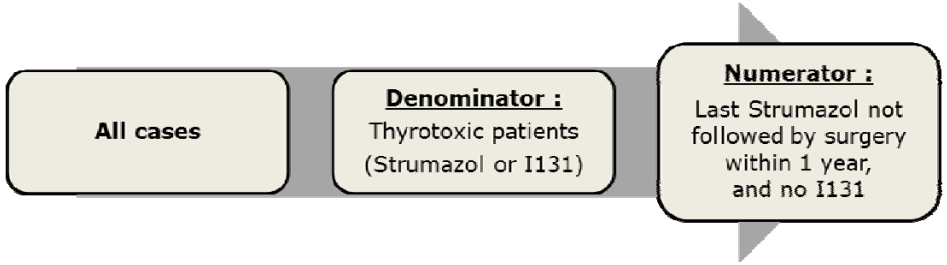


Table 17. Crude and age-standardized proportions of thyrotoxic patients treated with antithyroid drugs only by region and age group

		Belgium	Brussels-Capital Region	Flemish Region	Walloon Region
Thyrotoxicosis	**(n)**	69 420	5 465	48 127	15 828
Thyrotoxicosis treated by antithyroid drugs	**(n)**	44 762	3 717	32 268	8 777
% of thyrotoxic patients treated with antithyroid drugs	**(%)**	64.5	68.0	67.0	55.5
	[95%CI]	[64.1 ; 64.8]	[66.8 ; 69.2]	[66.6 ; 67.5]	[54.7 ; 56.2]
% by age group					
0-39 years	**(%)**	75.4	79.2	77.3	68.5
	[95%CI]	[74.6 ;76.3]	[76.9 ; 81.4]	[76.2 ; 78.4]	[66.5 ; 70.4]
40-69 years	**(%)**	55.8	61.6	57.5	48.9
	[95%CI]	[55.2 ; 56.3]	[59.6 ; 63.5]	[56.8 ; 58.1]	[47.7 ; 50.0]
70+ years	**(%)**	70.5	68.8	74.4	58.4
	[95%CI]	[70.0 ; 71.0]	[66.7 ; 70.8]	[73.8 ; 75.0]	[57.2 ; 59.7]
Age-Standardized Proportion	**(%)**	69.1	73.1	71.1	61.6
	[95%CI]	[68.5 ; 69.7]	[71.5 ; 74.6]	[70.5 ; 71.8]	[60.4 ; 62.9]

The majority of patients with thyrotoxicosis was treated with antithyroid drugs defined as Strumazol in this project (Belgium: 64.5% [95%CI: 64.1; 64.8]). While this observation was true in all Belgian regions, the proportion of thyrotoxic patients with antithyroid drugs was lower in the Walloon Region than elsewhere, independent of age-standardization. Analyses by age group showed in all three regions that antithyroid drugs were prescribed most frequently in either younger (0-39 years) or older (+70 years) patients.

Age-standardized proportions were significantly different between the Walloon and the Flemish Region and between the Walloon and the Brussels-Capital Region (see Appendix 12).

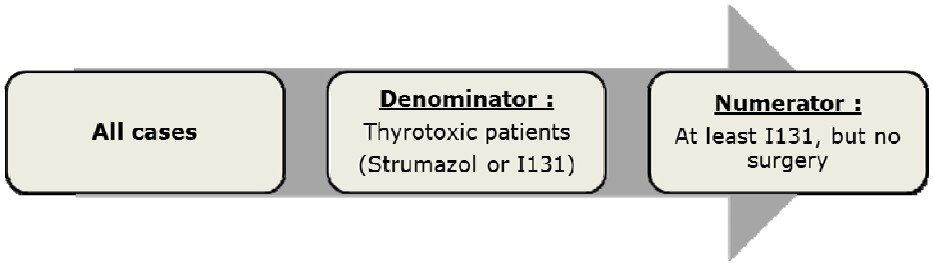
5.3.2.2. A.2: Proportion of thyrotoxic patients treated with ^{131}I

Denominator: All thyrotoxic patients

Numerator: All thyrotoxic patients who received at least once ^{131}I

Considerations: All patients with at least once ^{131}I were considered, regardless the administration of Strumazol. A selection of non-operated patients was performed.

Figure 36. Flowchart A.2 - Proportion of thyrotoxic patients treated with antithyroid drugs only



Of all Belgian patients with evidence of thyrotoxicosis during the period 2003-2008, radioiodine was administered in 30.4% of the patients ([95%CI: 30.1; 30.8]). Both crude and age-standardized proportions showed that this practice was most frequently performed in the Walloon Region, followed by the Flemish Region and the Brussels-Capital Region. The calculated proportions by age group suggested that the use of radioiodine in the treatment of thyrotoxicosis was the highest for patients of middle age (40-69 years: Belgium 37.6% [95%CI: 37.0; 38.1]), independent of the region.

All interregional comparisons showed significant differences for the age-standardized proportions (see Appendix 12).

Table 18. Crude and age-standardized proportions of thyrotoxic patients treated with ^{131}I by region and age group

		Belgium	Brussels-Capital Region	Flemish Region	Walloon Region
Thyrotoxicosis	**(n)**	69 420	5 465	48 127	15 828
^{131}I, no surgery	**(n)**	21 137	1 390	13 876	5 871
% of thyrotoxic patients treated with ^{131}I	**(%)**	30.4	25.4	28.8	37.1
	[95%CI]	[30.1 ; 30.8]	[24.3 ; 26.6]	[28.4 ; 29.2]	[36.3 ; 37.8]
% by age group					
0-39 years	**(%)**	14.6	9.0	14.2	18.6
	[95%CI]	[13.9 ; 15.3]	[7.5 ; 10.8]	[13.3 ; 15.1]	[17.0 ; 20.3]
40-69 years	**(%)**	37.6	30.6	37.2	40.9
	[95%CI]	[37.0 ; 38.1]	[28.8 ; 32.5]	[36.6 ; 37.8]	[39.8 ; 42.1]
70+ years	**(%)**	27.7	29.5	24.0	39.1
	[95%CI]	[27.2 ; 28.2]	[27.5 ; 31.6]	[23.4 ; 24.5]	[37.9; 40.3]
Age-Standardized Proportion	**(%)**	22.4	17.2	21.8	26.8
	[95%CI]	[22.0 ; 22.9]	[16.1 ; 18.3]	[21.2 ; 22.3]	[25.8 ; 27.8]

Key points

- **The majority of thyrotoxic patients were treated with antithyroid medication only (around 69%) or radioiodine (around 22%).**
- **Age-standardized proportions showed a relatively higher rate for antithyroid treatment in the Brussels-Capital Region and the Flemish Region. Surgery and radioiodine were more often chosen in the Walloon Region.**
- **Surgery was more often performed in younger patients (0-39 years: 9.2%) than in elderly patients (70+ years: 1.6%). Radioiodine was relatively more frequently administered in patients of middle age (40-69 years: 37.6%).**

5.3.3. Summary of results

Table 19. Summary of results for all cases

	Total	Brussels-Capital Region	Flemish Region	Walloon Region
Numbers of				
Thyrotoxicosis	69 420	5 465	48 127	15 828
Surgery	34 435	3 474	13 553	17 408
Surgery for thyrotoxicosis	3 172	301	1 843	1 028
Medication only for thyrotoxicosis	44 762	3 717	32 268	8 777
Radioiodine for thyrotoxicosis	21 137	1 390	13 876	5 871
Main outcome measures: Crude proportions % [95%CI]				
A. Thyrotoxicosis treated with surgery	4.6 [4.4 ; 4.7]	5.5 [4.9 ; 6.1]	3.8 [3.7 ; 4.0]	6.5 [6.1 ; 6.9]
B. Surgical patients with thyrotoxicosis	9.2 [8.9 ; 9.5]	8.7 [7.7 ; 9.6]	13.6 [13.0 ; 14.2]	5.9 [5.6 ;6.3]
Main outcome measures: Age-Standardized Proportion % [95%CI]				
A. Thyrotoxicosis treated with surgery	7.7 [7.3 ; 8.1]	8.3 [7.2 ; 9.4]	6.7 [6.2 ; 7.2]	10.1 [9.2 ; 11.0]
B. Surgical patients with thyrotoxicosis	10.3 [9.8 ; 10.8]	10.4 [9.0 ; 11.7]	14.4 [13.6 ; 15.3]	6.7 [6.2 ; 7.3]
Secondary outcome measures: Crude proportions % [95%CI]				
A.1 Thyrotoxicosis treated with medication only	64.5 [64.1 ; 64.8]	68.0 [66.8 ; 69.2]	67.0 [66.6 ; 67.5]	55.5 [54.7 ; 56.2]
A.2 Thyrotoxicosis treated with ^{131}I	30.4 [30.1 ; 30.8]	25.4 [24.3 ;26.6]	28.8 [28.4 ; 29.2]	37.1 [36.3 ; 37.8]
Secondary outcome measures: Age-Standardized Proportion % [95%CI]				
A.1 Thyrotoxicosis treated with medication only	69.1 [68.5 ; 69.7]	73.1 [71.5 ; 74.6]	71.1 [70.5 ; 71.8]	61.6 [60.4 ; 62.9]
A.2 Thyrotoxicosis treated with ^{131}I	22.4 [22.0 ; 22.9]	17.2 [16.1 ; 18.3]	21.8 [21.2 ; 22.3]	26.8 [25.8 ; 27.8]

Table 20. Treatment for thyrotoxic patients by region and age group

Treatment for thyrotoxic patients	Belgium	Brussels-Capital Region	Flemish Region	Walloon Region
0-39 years				
% surgery [95%CI]	9.2 [8.6 ; 9.8]	10.3 [8.7 ; 12.1]	8.1 [7.4 ; 8.8]	11.4 [10.2 ; 12.8]
% ^{131}I [95%CI]	14.6 [13.9 ; 15.3]	9.0 [7.5 ; 10.8]	14.2 [13.3 ; 15.1]	18.6 [17.0 ; 20.3]
% antithyroid drugs [95%CI]	75.4 [74.6 ; 76.3]	79.2 [76.9 ; 81.4]	77.3 [76.2 ; 78.4]	68.5 [66.5 ; 70.4]
40-69 years				
% surgery [95%CI]	5.9 [5.6 ; 6.2]	6.4 [5.5 ; 7.5]	4.9 [4.6 ; 5.2]	8.8 [8.2 ; 9.5]
% ^{131}I [95%CI]	37.6 [37.0 ; 38.1]	30.6 [28.8 ; 32.5]	37.2 [36.6 ; 37.8]	40.9 [39.8 ; 42.1]
% antithyroid drugs [95%CI]	55.8 [55.2 ; 56.3]	61.6 [59.6 ; 63.5]	57.5 [56.8 ; 58.1]	48.9 [47.7 ; 50.0]
70+ years				
% surgery [95%CI]	1.6 [1.5 ; 1.8]	1.4 [1.0 ; 2.0]	1.5 [1.4 ; 1.7]	2.1 [1.8 ; 2.5]
% ^{131}I [95%CI]	27.7 [27.2 ; 28.2]	29.5 [27.5 ; 31.6]	24.0 [23.4 ; 24.5]	39.1 [37.9; 40.3]
% antithyroid drugs [95%CI]	70.5 [70.0 ; 71.0]	68.8 [66.7 ; 70.8]	74.4 [73.8 ; 75.0]	58.4 [57.2 ; 59.7]

A life time risk of undergoing thyroid surgery in Belgium and by region based on age and gender-specific incidence rates reported between 2003 and 2008 was calculated (Table 21), according to the following equation:

$$Cum.rate\ (0-74) = \sum_{i=1}^{15} 5a_i$$

where a_i is the age-specific incidence rate in the i^{th} age class which is t_i years long

$$Cum.risk = 100\ x\ [1 - \exp\ (-cum.rate/100)]$$

Table 21. Cumulative risk for thyroid surgery in Belgium and by region (2003-2008)

Cumulative risk (%)	Belgium	Brussels-Cap. Region	Flemish Region	Walloon Region
0-24 years	0.13	0.17	0.10	0.18
0-29 years	0.31	0.36	0.23	0.43
0-34 years	0.57	0.65	0.43	0.81
0-39 years	0.91	1.02	0.67	1.29
0-44 years	1.29	1.46	0.93	1.88
0-49 years	1.74	1.96	1.23	2.60
0-54 years	2.25	2.54	1.55	3.40
0-59 years	2.76	3.09	1.87	4.23
0-64 years	3.25	3.64	2.20	5.05
0-69 years	3.69	4.11	2.47	5.81
0-74 years	4.07	4.47	2.71	6.46

5.4. Discussion

This part of the study evaluated geographical variations in the treatment of thyrotoxicosis. Thyrotoxicosis (defined by elevated serum levels of T4 and/or T3 and decreased serum TSH) is a prevalent condition and surgery represents one of the possible therapeutic options. More surgical treatment as a treatment option for thyrotoxicosis might lead to an increased uncovering of indolent thyroid cancer. The lifetime risk of overt hyperthyroidism has been reported as high as 6.5 % in a Danish study[40]. In a single centre reporting results of 3 114 surgical patients in Ankara, 25 infracentrimetric thyroid cancers were found among 869 thyrotoxic patients. In this study thyrotoxicosis was the indication for surgery in 27.9% of patients and an incidental thyroid cancer was described in 2.9% of this subgroup[41]. The risk of incidental thyroid cancer was higher in Graves' disease patients compared to patients operated for toxic multinodular goitre. This is in line with findings regarding auto-immune thyroid disease (and Graves' disease in particular) as a predisposing condition for thyroid cancer, although this is still a debated issue[42].

In order to evaluate geographical variations in (incidental) thyroid cancer in relation to thyroid disorders in which surgery represents one of the possible therapeutic options, the case load of thyrotoxicosis was therefore studied as well as the treatment approaches (medical treatment, radioiodine, surgery) with their geographical variations. As expected, surgery is used infrequently in the treatment of hyperthyroidism. Relative indications for surgery include large goitre (suspicion or diagnosis of coexisting thyroid cancer are absolute indications), pregnancy (if drug side-effects are serious or insufficient responsiveness to drug therapy) or desire for pregnancy, and pronounced ophthalmopathy[12]. Relapse after a course of antithyroid drugs is also a relative indication. Patient preference is another frequent driver for surgery[12]. Total thyroidectomy is the preferred surgical approach in view of the relapse rate after partial thyroidectomy (30% in

one study)[13] and because the rate of complications is similar between both procedures in experienced hands.

The age-standardized rate of thyrotoxicosis found in this study (87.4 per 100 000 PY [95%CI: 86.7; 88.1]) is within expectations for a mild iodine-deficient country as Belgium[14, 15]. Although retrieval of thyrotoxic patients by their treatment has limitations as described in the methodology section, the case load traced by the study method is a valuable approach resulting in age-standardized rates of thyrotoxicosis within expectations. The regional difference in age-standardized thyrotoxicosis rates with 101.9 per 100 000 PY in the Flemish Region compared to 78.6 per 100 000 PY in the Brussels-Capital Region and 62.7 per 100 000 PY in the Walloon Region represents however an unexpected finding (i.e. 61.5% higher rate of thyrotoxicosis in the Flemish as compared to the Walloon Region). Regional variability in the incidence of hyperthyroidism has been described with higher incidences in moderate iodine deficiency regions compared to mild iodine deficiency regions, due to more toxic nodular disease in moderate iodine deficiency[15]. However, mild iodine deficiency is present in all regions in Belgium[16]. Therefore the difference in thyrotoxicosis rate in the different regions in Belgium can most probably not be explained by variability in iodine status. As increasing evidence is becoming available on the inverse relation of serum TSH with thyroid cancer risk[43-45], the higher thyrotoxicosis rate in the Flemish Region might be protective for thyroid cancer. However future studies would be needed to test this hypothesis.

Hypothetical contributing factors include a variability in prevalence of auto-immune thyroid disease or a variability in detection and/or treatment of thyrotoxicosis. Indeed a different threshold to detect and/or treat mild thyrotoxicosis could shift persons from being untraceable to traceable by their treatment and thus include them in the thyrotoxicosis group. Management guidelines of the ATA and AACE give level 2 recommendations regarding the threshold for treatment of subclinical hyperthyroidism implying 'best action' in the difficult field of mild or subclinical hyperthyroidism (abnormal TSH but normal T4/T3) depending on circumstances or patient values[25]. A variable use of propylthiouracil between regions could also contribute to a variable underestimation of the number of patients treated by antithyroid drugs. As PTU is not currently reimbursed in Belgium, its use is not systematically registered by all sickness funds. According to available data on PTU prescriptions, this drug might be more prescribed in the Walloon Region, thereby potentially underestimating the rate of thyrotoxicosis in this region. Finally, a variable approach to thyroid disease in general can influence the number of persons at risk for hyperthyroidism i.e. in a population with a high surgical rate the number at risk for toxic multinodular disease in the older age categories will decrease (as they might already have undergone thyroid surgery).

The cumulative risk of undergoing thyroid surgery in Belgium and by region based on age and gender-specific incidence rates reported between 2003 and 2008 increases throughout the life. However, whatever the age category, this cumulative risk is always higher in the Walloon Region compared with the other two Regions. Before the age of 50 years, the risk to undergo such thyroid surgery is two times higher in the Walloon Region (2.6%) than in the Flemish Region (1.2%). Before the age of 75 years, the cumulative risk rises to 6.5% in the Walloon Region, 4.5% in the Brussels Capital Region and only to 2.7% in the Flemish Region.

As expected, surgery was performed in a minority of thyrotoxic patients (7.7% for Belgium [95%CI: 7.3; 8.1]). The majority of thyrotoxic patients was treated with antithyroid medication only (69.1% [95%CI: 68.5; 69.7]) or radioiodine (22.4% [95%CI: 22.0; 22.9]). However, there were some differences between the regions and age groups. At the regional level, age-standardized proportions showed a relatively higher rate for antithyroid treatment in the Brussels-Capital Region and in the Flemish Region. On the other hand, surgery and radioiodine were more often chosen as treatment for thyrotoxicosis in the Walloon Region. Regarding the different age groups, surgery was most often performed in younger patients (0-39 years: 9.2%) and hardly used to treat thyrotoxicosis in elderly patients (70+ years: 1.6%). For middle aged patients (40-69 years), radioiodine was relatively more frequently administered in comparison to other age categories (37.6%). Finally, while the incidence of thyrotoxicosis was higher in the Flemish Region, the proportion of thyroid surgeries was higher in the Walloon Region (10.1% [95%CI: 9.2; 11.0] vs. 6.7% [95%CI: 6.2; 7.2] in the Flemish region).

When focusing on patients with thyroid cancer, the proportion of patients with evidence of thyrotoxicosis in the year preceding their first surgery is low (4.6% in Belgium) but significant differences were reported between the Flemish (6.2%; 95%CI [3.7 ; 8.7]) and the Walloon Region (3.0%; 95%CI [1.6 ; 4.3]).

In conclusion, an interplay of geographical variations in incidence of thyrotoxicosis and its treatment approach makes that the number of patients in whom thyroid surgery is performed and in whom incidental thyroid cancers can potentially be detected are slightly higher in the Walloon Region than in the Flemish Region. Given the inability to control for potential confounding factors in this study, these results should be interpreted with caution.

6. VARIABILITY OF TREATMENT STRATEGIES FOR NODULAR DISEASE

6.1. Introduction

This chapter aimed to evaluate the association between the incidence of thyroid cancer and the intensity of use of thyroid surgery as treatment strategy for structural (nodular) disease across regions. A more intensive use of surgery for nodular disease could be explained by a less frequent use of FNAC to exclude thyroid cancer. As for thyrotoxicosis management, the probability to discover an indolent thyroid tumour is higher after a surgical resection than with other therapeutic options.

Nodular disease is defined as the presence of one or more nodules in the thyroid diagnosed after clinical examination or imaging (US, scintigraphy or other).

Three main treatment options are available for nodular disease:

- Conservative approach. If thyroid functions tests show no abnormalities and there is no volume problem or suspicion for cancer, a conservative approach and regular follow-up are preferred (consisting of clinical follow-up, ultrasound follow-up combined or not with FNAC follow-up).
- Treatment with surgery (total or partial thyroidectomy). This option is chosen in the presence of a volume problem and/or suspicion of cancer.
- Treatment with radioiodine (^{131}I), at low doses (≤15 mCi per treatment), is most often performed in case of concomitant thyrotoxicosis that is not accompanied by a major volume problem or by suspicion of cancer (mixed functional and structural thyroid disease). Only in rare cases of euthyroid (or non-thyrotoxic) goitre with volume problems and contra-indication for surgery ^{131}I can also be chosen as treatment aiming at volume reduction.

Eight outcomes measures were defined, grouped in 4 clusters, and listed below.

Among patients with nodular disease:

A. What is the proportion of patients treated with thyroid surgery?
B. What is the proportion of patients with a conservative approach (only FNAC)?
C. What is the proportion of patients treated with surgery preceded by FNAC?

Among surgical patients:

D. What is the proportion of surgery with preoperative cytological diagnosis by FNAC?

Among surgical patients within the period 2004-2006:

E. What is the proportion of surgery with final diagnosis of thyroid cancer?
F. What is the proportion of surgery with only a postoperative diagnosis of thyroid cancer (without prior FNAC)?

Among surgically treated thyroid cancer patients within the period 2004-2006:

G. What is the proportion of cases with intermediate or high probability of thyroid cancer (surgery preceded by FNAC)?
H. What is the proportion of cases with very high probability of thyroid cancer (lymph node dissection at the same time as surgery)?

6.2. Methodology

To answer these questions, each proportion was calculated for Belgium as well as per region (Flemish Region, Walloon Region and Brussels-Capital Region). Outcome measures A to D were calculated on patients treated between 2003 and 2008 (all cases), outcome measures E and F compared patients with thyroid cancer diagnosed between 2004 and 2006 with all surgical patients operated between 2004-2006 and outcome measures G and H relied only on patients with thyroid cancer diagnosed between 2004 and 2006.

The whole procedure for data selection, the exploration of databases and the procedure for data linkage is available in Appendix 9. Descriptive statistics are presented in Appendix 10 for all cases and in Appendix 11 for cancer cases.

Results were reported by age groups (<40, 40-69, 70+). The 95% confidence interval for each proportion was calculated using the Wilson score method[38]. Such intervals should be interpreted cautiously when they are computed on less than 30 cases.

The age-standardized rates for surgery, FNAC and nodular disease and the age-standardized proportions for each outcome measure were calculated using the direct method of standardisation using the European Standard Population. Such resulting age-standardized rate/proportion is a weighted average of the individual age-specific rates/proportions. Age categories for the age-standardization for FNAC and nodular disease where defined by 5 year age groups. However, to avoid small numbers impact of younger age categories, the age-standardized proportions for each outcome were calculated on a basis of 7 age groups for age-standardization (< 35 years, 35-44 years, 45-54 years, 55-64 years, 65-74 years, 75-84 years, ≥ 85 years).

These age-standardized rates/proportions represent the results that would be observed if the population had the same age structure as this standard population. The advantage of using age-standardized rates/proportions instead of the crude rates/proportions is that they make comparisons between different regions independently of the age structure of the regions. The 95% confidence intervals on these rates/proportions were also reported.

It is possible that the confidence interval was large. This is due to wide variance in some age groups where the population at risk and the number of cases are low.

To allow comparison of age-standardized proportions (ASP) between two regions, the ratio of these proportions (named Comparative Incidence Figure or CIF) and its 95% confidence interval were computed using the following formula:

$$95\%CI = e^{\ln\left(\frac{ASP_1}{ASP_2}\right) \pm 1.96 \times \sqrt{\frac{Var(ASP_1)}{ASP_1^{\,2}} + \frac{Var(ASP_2)}{ASP_2^{\,2}}}}$$

Age-standardized proportions were considered significantly different if the value 1.0 was not included in the computed 95% confidence interval[39].

Finally, analyses per region were based on the residence of the patient and not on the location where they were treated.

6.2.1. Definition of patients with nodular disease

Patients with nodular disease were identified by diagnostic or treatment procedures they received. Excluding cases with thyrotoxicosis (Strumazol or ^{131}I within one year before surgery, without prior FNAC), all patients that underwent at least once FNAC or thyroid surgery only or in combination were considered as having (non-toxic) nodular disease.

This definition underestimated the patient group with nodular thyroid disease, as patients with nodular disease and conservative approach that did not undergo FNAC were not included. It was chosen not to include neck US (often the only diagnostic test used, not followed by FNAC when the nodule(s) do not meet the criteria for FNAC) in the denominator since the specificity of this diagnostic test (and code) is considered too low for nodular thyroid disease.

- FNAC

Selected nomenclatures codes for FNAC (see appendix for the complete list of codes) included two codes for biopsy. However, given the small number of cases they cover, they were grouped with specific FNAC codes.

6.2.2. Definition of surgery

- Selection of nomenclature codes

Surgery was identified by 4 specific nomenclature codes (see appendix for the complete list of codes).

- Choice of surgery

Some patients underwent multiple thyroid surgeries. Only the first charged surgery was considered.

For outcome measures A to D, the first surgery for the period 2003-2008 was considered. For outcome measures E and F, the surgery closest to incidence was selected for numerator (cancer cases), and the first surgery for the period 2004-2006 for denominator (all cases), as selected cancer cases were diagnosed between 2004 and 2006. Finally, for outcome measures G and H, the surgery closest to incidence was selected.

- Time frames for surgery

When we looked at FNAC followed by surgery, we considered the first FNAC as the time point reference, and no time frame between FNAC and surgery.

6.3. Results

The age-standardized rates for surgery, FNAC and nodular disease were calculated, using the European Standard Population as a reference (Table 22). For these age-standardized rates, all FNAC were considered, followed or not by a surgical procedure.

Table 22. Age-standardized rates (n/100 000 PY) for surgery and FNAC over the period 2003-2008, per region

2003-2008	Belgium		Brussels-Capital Region		Flemish Region		Walloon Region	
	ESR	*95%CI*	ESR	*95%CI*	ESR	*95%CI*	ESR	*95%CI*
Surgery	50.8	[50.3 ; 51.4]	56.6	[54.7 ; 58.5]	34.0	[33.4 ; 34.6]	80.3	[79.1 ; 81.5]
FNAC	51.7	[51.1; 52.2]	78.6	[76.3 ; 80.8]	49.9	[49.2 ; 50.6]	47.6	[46.7 ; 48.5]
Nodular disease	84.5	[83.8 ; 85.2]	112.9	[110.2 ; 115.6]	66.3	[65.5 ; 67.1]	110.2	[108.8 ; 111.6]

Age-standardized rates by region showed most surgical interventions per year in the Walloon Region, followed by the Brussels-Capital Region and the Flemish Region. The number of patients who underwent FNAC per year was highest in the Brussels-Capital Region than in the other two regions that both reported similar rates. Age-standardized rate for nodular disease was highest in the Brussels-Capital Region and the Walloon Region, followed by the Flemish Region.

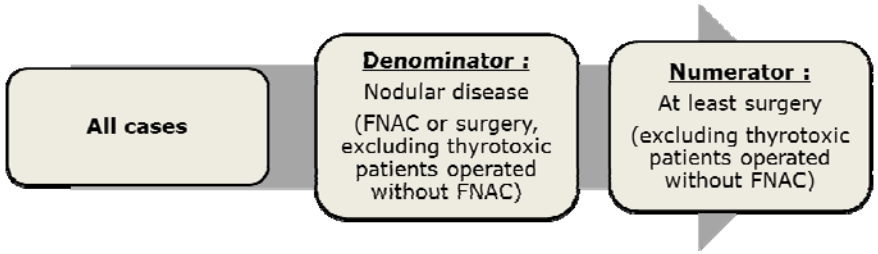
6.3.1. Outcomes measures

6.3.1.1. A: Proportion of patients with nodular disease treated with surgery, regardless of FNAC

Denominator: All patients with nodular disease

Numerator: All patients with nodular disease undergoing surgery, with or without FNAC (proportion of surgical approach), excluding thyrotoxic patients operated without FNAC

Figure 37. Flowchart outcome measure A



In Belgium for the period 2003-2008, more than half of patients with nodular disease were treated with surgery (54.7% [95%CI: 54.3; 55.1]). In the Walloon Region, surgical intervention was performed more frequently than in other regions. This observation was confirmed after age-standardization. Analyses by age group showed a gradient from younger patients (0-39 years) that underwent more surgery (58.6% for Belgium [95%CI: 57.7; 59.4]) to patients of 70 years and older, for whom surgery was less frequent (44.2% for Belgium [95%CI: 43.1; 45.3]). The same gradient was observed within the regions, with the highest rates for each age group reported in the Walloon Region.

Age-standardized proportions were significantly different between the Brussels-Capital Region and the Walloon Region and between the Flemish and the Walloon Region (see Appendix 13).

Table 23. Crude and age-standardized proportions of patients with nodular disease treated with surgery by region and age group

		Belgium	Brussels-Capital Region	Flemish Region	Walloon Region
Nodular disease	**(n)**	57 935	6 995	26 875	24 065
Surgery	**(n)**	31 678	3 203	12 035	16 440
% patients with nodular disease treated with surgery	**(%)**	54.7	45.8	44.8	68.3
	[95%CI]	[54.3 ; 55.1]	[44.6 ; 47.0]	[44.2 ; 45.4]	[67.7 ; 68.9]
% by age group					
0-39 years	**(%)**	58.6	51.8	50.7	70.6
	[95%CI]	[57.7 ; 59.4]	[49.5 ; 54.1]	[49.4 ; 51.9]	[69.4 ; 71.9]
40-69 years	**(%)**	55.6	46.8	45.0	69.2
	[95%CI]	[55.1 ; 56.1]	[45.3 ; 48.3]	[44.3 ; 45.8]	[68.5 ; 70.0]
70+ years	**(%)**	44.2	32.2	34.7	60.0
	[95%CI]	[43.1 ; 45.3]	[29.5 ; 35.0]	[33.2 ; 36.2]	[58.2 ; 61.7]
Age-Standardized Proportion	**(%)**	56.1	48.0	47.1	69.1
	[95%CI]	[55.5 ; 56.7]	[46.4 ; 49.6]	[46.3 ; 48.0]	[68.2 ; 70.0]

6.3.1.2. B: Proportion of patients with nodular disease with conservative approach

Denominator: All patients with nodular disease

Numerator: All patients with nodular disease undergoing FNAC not followed by surgery

Considerations: First FNAC and first surgery were considered

Figure 38. Flowchart outcome measure B

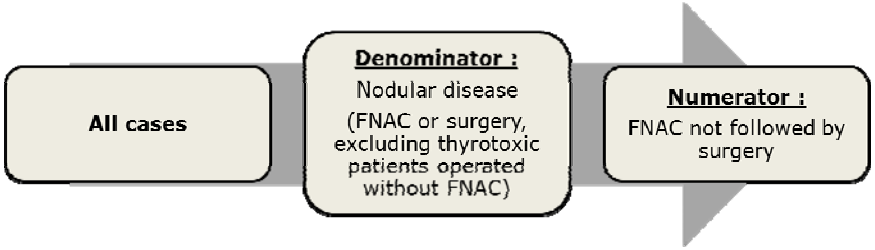


Table 24. Crude and age-standardized proportions of patients with nodular disease with conservative approach by region and age group

		Belgium	Brussels-Capital Region	Flemish Region	Walloon Region
Nodular disease	**(n)**	57 935	6 995	26 875	24 065
Conservative approach	**(n)**	26 387	3 813	14 895	7 679
% patients with nodular disease with conservative approach	**(%)**	45.3	54.5	55.4	31.9
	[95%CI]	[45.1 ; 46.0]	[53.3 ; 55.7]	[54.8 ; 56.0]	[31.3 ; 32.5]
% by age group					
0-39 years	**(%)**	41.6	48.4	49.5	29.6
	[95%CI]	[40.8 ; 42.5]	[46.1 ; 50.7]	[48.2 ; 50.8]	[28.4 ; 30.9]
40-69 years	**(%)**	44.6	53.6	55.2	31.0
	[95%CI]	[44.1 ; 45.1]	[52.1 ; 55.1]	[54.5 ; 56.0]	[30.3 ; 31.7]
70+ years	**(%)**	56.0	68.0	65.5	40.2
	[95%CI]	[54.9 ; 57.1]	[65.2 ; 70.7]	[64.0 ; 67.0]	[38.5 ; 42.0]
Age-Standardized Proportion	**(%)**	44.1	52.3	53.1	31.2
	[95%CI]	[43.5 ; 44.7]	[50.7 ; 53.8]	[52.2 ; 53.9]	[30.3 ; 32.1]

Of all Belgian patients with evidence of nodular disease during the period 2003-2008, a conservative approach was preferred in 45.3% of patients (95%CI: 45.1; 46.0). Both crude and age-standardized proportions showed that this approach was more frequent in the Flemish Region or in the Brussels-Capital Region than in the Walloon Region, where the proportion of FNAC was the lowest. Moreover, analyses by age group suggested that a conservative approach was more common in patients of 70 years and older (56.0% for Belgium [95%CI: 54.9; 57.1]), while it was less frequently the case for patients up to 39 years (41.6% [95%CI: 40.8; 42.5]). This age-related trend was observed in all regions.

Age-standardized proportions were significantly different between the Brussels-Capital Region and the Walloon Region and between the Flemish and the Walloon Region (see Appendix 13).

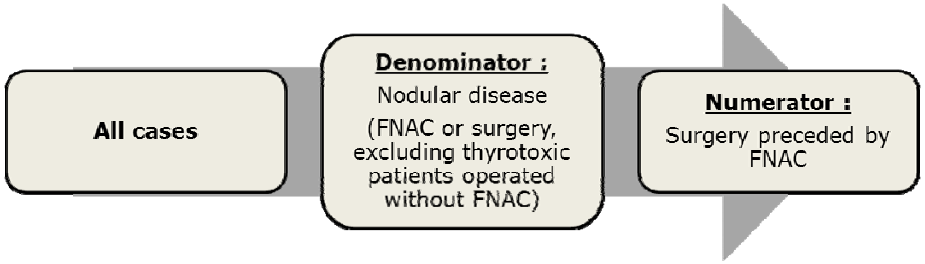
6.3.1.3. C: Proportion of patients with nodular disease treated with surgery preceded by FNAC

Denominator: All patients with nodular disease

Numerator: All patients with nodular disease undergoing surgery preceded by FNAC

Considerations: First FNAC and first surgery were considered

Figure 39. Flowchart outcome measure C



Of all Belgian patients with evidence of nodular disease during the period 2003-2008, only 15.9% [95%CI: 15.6; 16.2] underwent thyroid surgery preceded by FNAC. This proportion was highest in the Flemish Region (20.0% [95%CI: 19.5; 20.5]), followed by the Brussels-Capital Region (15.3% [95%CI: 14.5; 16.2]) and the Walloon Region (11.5% [95%CI: 11.1; 12.0]). After age-standardization, this observation was confirmed. Analyses by age group showed that younger patients (0-39 years) with nodular disease underwent surgical treatment preceded by FNAC about two times more often (20.3% for Belgium [95%CI: 19.6; 21.0]), than patients of 70 years and older (10.0% [95%CI: 9.3; 10.6]). This age-related trend was also observed within each region.

All interregional comparisons of age-standardized proportions showed significant differences (see Appendix 13)

Table 25. Crude and age-standardized proportions of patients with nodular disease treated with surgery preceded by FNAC by region and age group

		Belgium	Brussels-Capital Region	Flemish Region	Walloon Region
Nodular disease	**(n)**	57 935	6 995	26 875	24 065
Surgery preceded by FNAC	**(n)**	9 218	1 072	5 368	2 778
% patients with nodular disease undergoing FNAC before surgery	**(%)**	15.9	15.3	20.0	11.5
	[95%CI]	[15.6 ; 16.2]	[14.5 ; 16.2]	[19.5 ; 20.5]	[11.1 ; 12.0]
% by age group					
0-39 years	**(%)**	20.3	17.5	25.4	15.1
	[95%CI]	[19.6 ; 21.0]	[15.8 ; 19.3]	[24.3 ; 26.5]	[14.1 ; 16.1]
40-69 years	**(%)**	15.7	15.6	19.9	11.3
	[95%CI]	[15.3 ; 16.1]	[14.5 ; 16.8]	[19.3 ; 20.5]	[10.8 ; 11.8]
70+ years	**(%)**	10.0	10.6	12.0	7.2
	[95%CI]	[9.3 ; 10.6]	[8.9 ; 12.6]	[11 ; 13.1]	[6.4 ; 8.2]
Age-Standardized Proportion	**(%)**	18.0	16.6	22.5	13.4
	[95%CI]	[17.6 ; 18.5]	[15.4 ; 17.8]	[21.7 ; 23.2]	[12.7 ; 14.1]

6.3.1.4. *D: Proportion of surgical patients with preoperative cytological diagnosis by FNAC*

Denominator: All patients with thyroid surgery

Numerator: All patients with thyroid surgery preceded by FNAC

Considerations: First FNAC and first surgery were considered

Figure 40. Flowchart outcome measure D



Table 26. Crude and age-standardized proportions of surgical patients with preoperative cytological diagnosis by FNAC by region and age group

		Belgium	Brussels-Capital Region	Flemish Region	Walloon Region
Thyroid surgery	**(n)**	34 435	3 474	13 553	17 408
Surgery preceded by FNAC	**(n)**	9 218	1 072	5 368	2 778
% surgical patients with preoperative cytological diagnosis	**(%)**	26.8	30.9	39.6	16.0
	[95%CI]	[26.3 ; 27.2]	[29.3 ; 32.4]	[38.8 ; 40.4]	[15.4 ; 16.5]
% by age group					
0-39 years	**(%)**	31.4	29.9	44.1	20.0
	[95%CI]	[30.4 ; 32.4]	[27.2 ; 32.8]	[42.5 ; 45.8]	[18.7 ; 21.3]
40-69 years	**(%)**	26.2	31.3	39.7	15.5
	[95%CI]	[25.6 ; 26.8]	[29.3 ; 33.3]	[38.7 ; 40.8]	[14.8 ; 16.1]
70+ years	**(%)**	20.3	31.1	29.2	11.3
	[95%CI]	[19.0 ; 21.6]	[26.5 ; 36.0]	[27.0 ; 31.5]	[10.0 ; 12.7]
Age-Standardized Proportion	**(%)**	28.9	31.0	41.3	18.0
	[95%CI]	[28.2 ; 29.6]	[29.0 ; 32.9]	[40.2 ; 42.5]	[17.1 ; 18.9]

In Belgium during the period 2003-2008, about a quarter of patients who underwent thyroid surgery had a preoperative cytological diagnosis by FNAC (26.8% [95%CI: 26.3; 27.2]). In the Flemish Region, patients had a cytological diagnosis before their surgery 2.5 times more often (39.6% [95%CI: 38.8; 40.4]) than in the Walloon Region (16.0% [95%CI: 15.4; 16.5]). The Brussels-Capital Region presented intermediate results (30.9% [95%CI: 29.3; 32.4]). This observation was confirmed after age-standardization.

Given the lower than anticipated proportion of FNAC in surgical patients in Belgium, an additional analysis investigating the proportion of patients with preoperative FNAC, neck US or scintigraphy was performed. This showed age-standardized proportions of 65% (95%CI: [64.3; 65.7]) in Belgium for all thyroid surgical patients, with variations between regions. Higher proportions were reported in the Flemish Region (70.0% [95%CI: 68.9%; 71.1%] followed by the Brussels Capital Region (65.8% [95%CI: 63.8; 67.8]) and a lower proportion in the Walloon Region (60.6% [95%CI: 59.6; 61.7]).

The analyses by age group showed that patients of 70 years and older are less frequently operated with preoperative cytological diagnosis by FNAC than by patients of 40-69 years and patients of 40 years or younger in the Walloon Region and the Flemish Region. This trend was clearer in the Flemish Region. In the Brussels-Capital Region, the proportions were equally distributed between the three age groups.

All interregional comparisons of age standardized proportions showed significant differences (see Appendix 13).

Key points

- **The age-standardized rate of nodular disease reported in this study was around 85 per 100 000 PY for Belgium.**
- **The age-standardized rate of nodular disease was lowest in the Flemish Region (around 66 per 100 000 PY) compared to the Brussels-Capital and the Walloon Region (around 110 per 100 000 PY).**
- **In Belgium (2003-2008), more than half of patients with nodular disease (in whom a diagnostic or therapeutic procedure was performed) were treated with surgery whereas a conservative approach was preferred in 44.1% of the patients.**
- **A conservative approach was more common in patients of 70 years and older (56.0% for Belgium) than for patients up to 39 years (around 42% for Belgium).**
- **In Belgium (2003-2008), similar age-standardized proportions of surgery and FNAC were reported (around 51 procedures per 100 000 PY). However, the use of these two procedures was variable according to the Regions:**
  - **the Walloon Region reported the highest proportion of surgery (around 80 per 100 000 PY) compared with the Brussels-Capital Region (around 57 per 100 000 PY) and the Flemish Region (around 34 per 100 000 PY)**
  - **the Brussels-Capital Region reported the highest proportion of all FNAC followed or not by a surgical procedure (around 79 per 100 000 PY) compared with the Flemish Region (around 50 per 100 000 PY) and the Walloon Region (around 48 per 100 000 PY).**
- **Of all Belgian patients with evidence of nodular disease during the period 2003-2008, only 18% underwent thyroid surgery preceded by FNAC. The age standardized proportions for this sequential procedures were higher for the Flemish Region (around 23%) than for the Brussels-Capital Region (around 17%) and for the Walloon Region (around 13%).**
- **Considering pre-operative exams, 65% of Belgian patients underwent a preoperative FNAC, neck US or scintigraphy; variations were reported between regions, since 70%, 66% and around 61% of patients underwent such preoperative exams in the Flemish, the Brussels Capital and the Walloon Regions respectively.**
- **In the Flemish Region, patients had a cytological diagnosis before their surgery 2.5 times more often (around 40%) than in the Walloon Region (18.0%).**

6.3.1.5. *E: Proportion of surgical patients with final diagnosis of thyroid cancer*

Denominator: All patients with thyroid surgery within the period 2004-2006

Numerator: Cancer patients with thyroid surgery around incidence

Figure 41. Flowchart outcome measure E



Table 27. Crude and age-standardized proportions of surgical patients with final diagnosis of thyroid cancer by region and age group

		Belgium	Brussels-Capital Region	Flemish Region	Walloon Region
Thyroid surgery (all cases, 2004-2006)	**(n)**	17068	1656	6747	8665
Thyroid surgery (cancer cases)	**(n)**	1693	206	679	808
% surgical patients with final diagnosis of thyroid cancer	**(%)**	9.9	12.4	10.1	9.3
	[95%CI]	[9.5 ; 10.4]	[10.9 ; 14.1]	[9.4 ; 10.8]	[8.7 ; 10.0]
% by age group					
0-39 years	**(%)**	10.7	10.6	10.6	10.8
	[95%CI]	[9.7 ; 11.7]	[8.1 ; 13.6]	[9.2 ; 12.2]	[9.4 ; 12.3]
40-69 years	**(%)**	9.4	12.9	9.4	8.9
	[95%CI]	[8.9 ; 10.0]	[10.9 ; 15.1]	[8.5 ; 10.3]	[8.2 ; 9.6]
70+ years	**(%)**	11.1	15.1	12.5	9.3
	[95%CI]	[9.9 ; 12.6]	[10.7 ; 21.0]	[10.4 ; 14.9]	[7.7 ; 11.3]
Age-Standardized Proportion	**(%)**	10.6	11.5	10.8	10.3
	[95%CI]	[9.9 ; 11.3]	[9.6 ; 13.4]	[9.7 ; 11.9]	[9.3 ; 11.3]

Of all patients who underwent thyroid surgery in Belgium during the period 2004-2006, 9.9% were diagnosed as cancer cases (95%CI: [9.5; 10.4]). This proportion was highest in the Brussels-Capital Region (12.4% [95%CI: 10.9; 14.1]), followed by the Flemish Region (10.1% [95%CI: 9.4; 10.8]) and the Walloon Region (9.3% [8.7; 10.0]). However, after age-standardization, these differences did not appear anymore. Analyses by age group did not show remarkable differences.

All interregional comparisons of age-standardized proportions showed non-significant differences (see Appendix 13).

6.3.1.6. F: Proportion of surgical patients with only postoperative diagnosis of thyroid cancer

Denominator: All patients with surgery within the period 2004-2006

Numerator: All thyroid cancer patients with surgery around incidence, not preceded by FNAC

Considerations: For cancer cases, the surgery closest to incidence within 3 months around incidence and the first FNAC were considered

Figure 42. Flowchart outcome measure F

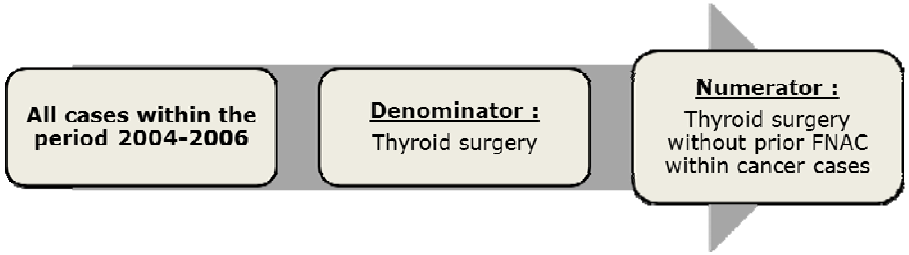


Table 28. Crude and age-standardized proportions of surgical patients with only postoperative diagnosis of thyroid cancer by region and age group

		Belgium	Brussels-Capital Region	Flemish Region	Walloon Region
Thyroid surgery (2004-2006)	**(n)**	17 068	1 656	6 747	8 665
Surgery not preceded by FNAC	**(n)**	1 000	113	282	605
% patients with nodular disease undergoing surgery without prior FNAC	**(%)**	5.9	6.8	4.2	7.0
	[95%CI]	[5.5 ; 6.2]	[5.7 ; 8.1]	[3.7 ; 4.7]	[6.5 ; 7.5]
% by age group					
0-39 years	**(%)**	6.1	5.8	4.3	8.0
	[95%CI]	[5.4 ; 6.9]	[4.0 ; 8.3]	[3.4 ; 5.4]	[6.8 ; 9.3]
40-69 years	**(%)**	5.6	7.3	3.9	6.6
	[95%CI]	[5.2 ; 6.1]	[5.8 ; 9.1]	[3.4 ; 4.5]	[6.0 ; 7.3]
70+ years	**(%)**	6.6	7.0	5.4	7.5
	[95%CI]	[5.6 ; 7.7]	[4.2 ; 11.7]	[4.0 ; 7.1]	[6.1 ; 9.3]
Age-Standardized Proportion	**(%)**	6.1	6.5	4.4	7.4
	[95%CI]	[5.5 ; 6.6]	[5.0 ; 8.0]	[3.7 ; 5.1]	[6.5 ; 8.2]

Of all patients who underwent thyroid surgery without prior FNAC in Belgium during the period 2004-2006, 5.9% were diagnosed as cancer cases (95%CI: [5.5; 6.2]). The Walloon Region and the Brussels-Capital Region had higher rates (respectively 7.0% [95%CI: 6.5; 7.5] and 6.8% [95%CI: 5.7; 8.1]) compared to the Flemish Region (4.2% [95%CI: 3.7; 4.7]). After age-standardization, the highest proportion was reported for the Walloon Region, followed by the Brussels-Capital Region and the Flemish Region. Analyses by age group did not show remarkable differences between the regions.

Age-standardized proportions were significantly different between the Brussels-Capital Region and the Flemish Region and between the Walloon and the Flemish Region (see Appendix 13).

6.3.1.7. G: Proportion of operated thyroid cancer cases with intermediate or high presurgical probability of thyroid cancer

Denominator: All thyroid cancer patients with surgery around incidence

Numerator: All thyroid cancer patients with surgery around incidence, preceded by FNAC

Considerations: The surgery the closest to incidence within 3 months around incidence and the first FNAC were considered.

Figure 43. Flowchart outcome measure G



Table 29. Crude and age-standardized proportions of cancer patients surgically treated with intermediate or high pre-surgical probability of thyroid cancer by region and age group

		Belgium	Brussels-Capital Region	Flemish Region	Walloon Region
Thyroid surgery (cancer cases)	**(n)**	1 693	206	679	808
Thyroid surgery (cancer cases) preceded by FNAC	**(n)**	693	93	397	203
% surgically treated cancer patients with intermediate or high pre-surgical probability of thyroid cancer	**(%)** **[95%CI]**	40.9 [38.6 ; 43.3]	45.1 [38.5 ; 52.0]	58.5 [54.7 ; 62.1]	25.1 [22.3 ; 28.2]
% by age group					
0-39 years	**(%)** **[95%CI]**	42.5 [37.8 ; 47.3]	45.1 [32.3 ; 58.6]	59.4 [52 ; 66.4]	26.1 [20.3 ; 32.8]
40-69 years	**(%)** **[95%CI]**	40.3 [37.4 ; 43.3]	43.3 [35 ; 52.0]	58.4 [53.5 ; 63.1]	25.8 [22.2 ; 29.7]
70+ years	**(%)** **[95%CI]**	40.9 [34.7 ; 47.3]	53.6 [35.8 ; 70.5]	57.1 [47.6 ; 66.2]	19.6 [12.9 ; 28.6]
Age-Standardized Proportion	**(%)** **[95%CI]**	42.6 [39.3 ; 45.9]	43.4 [33.9 ; 52.98]	59.5 [54.5 ; 64.4]	27.8 [23.4; 32.3]

Of all thyroid cancer patients diagnosed in Belgium between 2004 and 2006 who underwent surgery, there was an intermediate or high pre-surgical probability of thyroid cancer (FNAC performed before surgery) for 40.9% of patients (95%CI: [38.6; 43.3]). For both crude and age-standardized proportions, estimations per region showed highest proportions in the Flemish Region, followed by the Brussels-Capital Region and the Walloon Region. In the Flemish Region, these proportions were more than 2 times higher than in the Walloon Region. The proportions were relatively equally distributed between the three age groups. No major trend can therefore be observed.

Given the lower than anticipated proportion of FNAC in cancer surgical patients in Belgium an additional analysis investigating the proportion of patients with preoperative FNAC, neck US or scintigraphy was performed. This showed age-standardized proportions of 78.2% (95%CI: [75.5; 80.8]) for the thyroid cancer surgical patients, with variations between regions. Higher proportions were reported by the Flemish Region (84.2% [95%CI: 80.5%; 88.0%] followed by the Brussels Capital Region (77.5% [95%CI: 69.1; 85.8]) and a lower proportion in the Walloon Region (73.3% [95%CI: 69.1; 77.4]).

All interregional comparisons of age-standardized proportions showed significant differences (see Appendix 13).

6.3.1.8. H: Proportion of operated thyroid cancer cases with very high pre-surgical probability of thyroid cancer

Denominator: All thyroid cancer patients with surgery around incidence

Numerator: All thyroid cancer patients with surgery around incidence the same day as lymph node dissection

Considerations: The surgery the closest to incidence within 3 months around incidence and the first lymph node dissection were considered.

Figure 44. Flowchart outcome measure H



In Belgium, for all thyroid cancers diagnosed between 2004 and 2006 who underwent surgery, 15.1% [95%CI: 13.4; 16.8] had very high pre-surgical probability of thyroid cancer, since a lymph node dissection was performed the same day as thyroid surgery suggesting the very high probability of papillary or medullary thyroid cancer. The highest proportion was observed in the Flemish Region (20.5% [95%CI: 17.6; 23.7]), followed by the Brussels-Capital Region (16.0% [95%CI: 11.6; 21.6]) and the Walloon Region (10.3% [95%CI: 8.4; 12.6]). After age-standardization, the Flemish and the Brussels-Capital Region showed similar proportions while the Walloon Region had the lowest proportion. The calculated proportions by age group suggested that for middle aged patients (40-69 years), a lymph node dissection performed the same day as surgery was less frequent (13.3% for Belgium [95%CI: 11.3; 15.4]) than for other age groups, independent of the region. Given the low numbers, results for the Brussels-Capital Region should be interpreted with caution.

Taking a time frame of 7 days around surgery for lymph node dissection (in place of the same day) did not change the conclusions (only 9 patients were added to the numerator).

Interregional comparisons of age-standardized proportions showed significant differences between the Walloon Region and the other two regions (see Appendix 13).

Table 30. Crude and age-standardized proportions of cancer patients surgically treated with very high pre-surgical probability of thyroid cancer by region and age group

		Belgium	Brussels-Capital Region	Flemish Region	Walloon Region
Thyroid surgery (cancer cases)	**(n)**	1 693	206	679	808
Thyroid surgery (cancer cases) same day as lymph node dissection	**(n)**	255	33	139	83
% surgically treated cancer patients with high pre-surgical probability of thyroid cancer	**(%)**	15.1	16.0	20.5	10.3
	[95%CI]	[13.4 ; 16.8]	[11.6 ; 21.6]	[17.6 ; 23.7]	[8.4 ; 12.6]
% by age group					
0-39 years	**(%)**	17.4	19.6	20.6	13.8
	[95%CI]	[14.0 ; 21.3]	[11.0 ; 32.5]	[15.2 ; 27.2]	[9.6 ; 19.5]
40-69 years	**(%)**	13.3	14.2	19.0	8.6
	[95%CI]	[11.3 ; 15.4]	[9.2 ; 21.3]	[15.5 ; 23.2]	[6.5 ; 11.3]
70+ years	**(%)**	19.1	17.9	25.7	12.4
	[95%CI]	[14.6 ; 24.7]	[7.9 ; 35.6]	[18.3 ; 34.8]	[7.2 ; 20.4]
Age-Standardized Proportion	**(%)**	17.2	20.2	22.3	12.0
	[95%CI]	[14.5 ; 19.8]	[11.9 ; 28.5]	[17.9 ; 26.6]	[8.6 ; 15.3]

Key points

- **The proportion of operated thyroid carcinoma patients among all surgical patients was quite similar in the three regions (between 10.3% and 11.5%).**
- **Among thyroid cancer patients, FNAC preceding the surgery had been performed in 59.5% of thyroid cancer patients in the Flemish Region, in 43.4% of thyroid cancer patients in the Brussels-Capital Region and in 27.8% of thyroid cancer patients in the Walloon Region (intermediate or high pre-surgical probability of thyroid cancer).**
- **Considering pre-operative exams, 78% of Belgian cancer patients underwent a preoperative FNAC, neck US or scintigraphy; variations were reported between regions, since 84%, 78% and 73% of cancer patients underwent such preoperative exams in the Flemish, the Brussels Capital and the Walloon Regions respectively.**
- **Among thyroid cancer patients, a first extensive surgery including lymph node resection had been performed in 17% of thyroid cancer patients(very high pre-surgical probability of thyroid cancer). These proportions were lower in the Walloon Region (12%) than in the Brussels Capital and the Flemish Region (20.2 and 22.3% respectively).**

6.3.2. Summary of results

Table 31. Summary of results for all cases

	Belgium	Brussels-Capital Region	Flemish Region	Walloon Region
Numbers of				
Nodular disease	57 935	6 995	26 875	24 065
Surgery	34 435	3 474	13 553	17 408
Surgery for nodular disease	31 678	3 203	12 035	16 440
Surgery preceded by FNAC	9 218	1 072	5 368	2 778
Conservative approach for nodular disease	26 387	3 813	14 895	7 679
Outcome measure on all cases: Crude Proportions % [95%CI]				
A. Nodular disease treated with surgery	54.7 [54.3 ; 55.1]	45.8 [44.6 ; 47.0]	44.8 [44.2 ; 45.4]	68.3 [67.7 ; 68.9]
B. Nodular disease with conservative approach	45.3 [45.1 ; 46.0]	54.5 [53.3 ; 55.7]	55.4 [54.8 ; 56.0]	31.9 [31.3 ; 32.5]
C. Nodular disease treated with surgery preceded by FNAC	15.9 [15.6 ; 16.2]	15.3 [14.5 ; 16.2]	20.0 [19.5 ; 20.5]	11.5 [11.1 ; 12.0]
D. Surgical patients with preoperative cytological diagnosis	26.8 [26.3 ; 27.2]	30.9 [29.3 ; 32.4]	39.6 [38.8 ; 40.4]	16.0 [15.4 ; 16.5]
Outcome measures on all cases: Age-Standardized Proportions % [95%CI]				
A. Nodular disease treated with surgery	56.1 [55.5 ; 56.7]	48.0 [46.4 ; 49.6]	47.1 [46.3 ; 48.0]	69.1 [68.2 ; 70.0]
B. Nodular disease with conservative approach	44.1 [43.5 ; 44.7]	52.3 [50.7 ; 53.8]	53.1 [52.2 ; 53.9]	31.2 [30.3 ; 32.1]
C. Nodular disease treated with surgery preceded by FNAC	18.0 [17.6 ; 18.5]	16.6 [15.4 ; 17.8]	22.5 [21.7 ; 23.2]	13.4 [12.7 ; 14.1]
D. Surgical patients with preoperative cytological diagnosis	28.9 [28.2 ; 29.6]	31.0 [29.0 ; 32.9]	41.3 [40.2 ; 42.5]	18.0 [17.1 ; 18.9]

Table 32. Summary of results for cancer cases (2004-2006)

	Belgium	Brussels-Capital Region	Flemish Region	Walloon Region
Numbers of				
Surgery (all cases, 2004-2006)	17 068	1 656	6 747	8 665
Surgery (cancer cases)	1 693	206	679	808
Only postoperative diagnosis of thyroid cancer	1 000	113	282	605
Intermediate or high preoperative probability of thyroid cancer	693	93	397	203
Very high preoperative probability of thyroid cancer	255	33	139	83
Outcome measure on cancer cases: Crude Proportions % [95%CI]				
E. Surgical patients with final diagnosis of thyroid cancer	9.9 [9.5 ; 10.4]	12.4 [10.9 ; 14.1]	10.1 [9.4 ; 10.8]	9.3 [8.7 ; 10.0]
F. Surgical patients with only postoperative diagnosis of thyroid cancer	5.9 [5.5 ; 6.2]	6.8 [5.7 ; 8.1]	4.2 [3.7 ; 4.7]	7.0 [6.5 ; 7.5]
G. Cancer patients with intermediate or high preoperative probability of thyroid cancer	40.9 [38.6 ; 43.3]	45.1 [38.5 ; 52.0]	58.5 [54.7 ; 62.1]	25.1 [22.3 ; 28.2]
H. Cancer patients with a very high probability of thyroid cancer	15.1 [13.4 ; 16.8]	16.0 [11.6 ; 21.6]	20.5 [17.6 ; 23.7]	10.3 [8.4 ; 12.6]
Outcome measures on cancer cases: Age-Standardized Proportions % [95%CI]				
E. Surgical patients with final diagnosis of thyroid cancer	10.6 [9.9 ; 11.3]	11.5 [9.6 ; 13.4]	10.8 [9.7 ; 11.9]	10.3 [9.3 ; 11.3]
F. Surgical patients with only postoperative diagnosis of thyroid cancer	6.1 [5.5 ; 6.6]	6.5 [5.0 ; 8.0]	4.4 [3.7 ; 5.1]	7.4 [6.5 ; 8.2]
G. Cancer patients with intermediate or high preoperative probability of thyroid cancer	42.6 [39.3 ; 45.9]	43.4 [33.9 ; 52.9]	59.5 [54.5 ; 64.4]	27.8 [23.4; 32.3]
H. Cancer patients with a very high probability of thyroid cancer	17.2 [14.5 ; 19.8]	20.2 [11.9 ; 28.5]	22.3 [17.9 ; 26.6]	12.0 [8.6 ; 15.3]

Table 33. Treatment for nodular disease by region and age group

Treatment for nodular disease	Belgium	Brussels-Capital Region	Flemish Region	Walloon Region
0-39 years				
% surgery [95%CI]	58.6 [57.7 ; 59.4]	51.8 [49.5 ; 54.1]	50.7 [49.4 ; 51.9]	70.6 [69.4 ; 71.9]
% conservative approach [95%CI]	41.6 [40.8 ; 42.5]	48.4 [46.1 ; 50.7]	49.5 [48.2 ; 50.8]	29.6 [28.4 ; 30.9]
% surgery preceded by FNAC [95%CI]	20.3 [19.6 ; 21.0]	17.5 [15.8 ; 19.3]	25.4 [24.3 ; 26.5]	15.1 [14.1 ; 16.1]
40-69 years				
% surgery [95%CI]	55.6 [55.1 ; 56.1]	46.8 [45.3 ; 48.3]	45.0 [44.3 ; 45.8]	69.2 [68.5 ; 70.0]
% conservative approach [95%CI]	44.6 [44.1 ; 45.1]	53.6 [52.1 ; 55.1]	55.2 [54.5 ; 56.0]	31.0 [30.3 ; 31.7]
% surgery preceded by FNAC [95%CI]	15.7 [15.3 ; 16.1]	15.6 [14.5 ; 16.8]	19.9 [19.3 ; 20.5]	11.3 [10.8 ; 11.8]
70+ years				
% surgery [95%CI]	44.2 [43.1 ; 45.3]	32.2 [39.5 ; 35.0]	34.7 [33.2 ; 36.2]	60.0 [58.2 ; 61.7]
% conservative approach [95%CI]	56.0 [54.9 ; 57.1]	68.0 [65.2 ; 70.7]	65.5 [64.0 ; 67.0]	40.2 [38.5 ; 42.0]
% surgery preceded by FNAC [95%CI]	10.0 [9.3 ; 10.6]	10.6 [8.9 ; 12.6]	12.0 [11 ; 13.1]	7.2 [6.4 ; 8.2]

6.4. Discussion

This part of the study evaluated geographical variations in the diagnostic and treatment approaches of thyroid nodular disease, first at the level of thyroid nodular disease in whom a diagnostic or therapeutic procedure was performed, second at the level of all patients that underwent thyroid surgery, third at the level of patients with a final diagnosis of thyroid cancer.

In absence of the exact diagnosis, the definition of thyroid nodular disease included all patients who underwent at least once FNAC (or a thyroid biopsy) or thyroid surgery, excluding cases with thyrotoxicosis and no FNAC in order to obtain a stricter definition of (non-toxic) nodular disease. This definition did not include patients with thyroid nodules diagnosed clinically or after imaging (ultrasound, scintigraphy or other) in whom further diagnostic or therapeutic procedures were considered unnecessary (e.g. absence of suspicious features of the nodule(s) at US, small diameter of the nodule, absence of symptoms related to the thyroid volume). Moreover, the definition of nodular disease used for the present study does not allow to distinguish between uni- and multi nodular disease. However, despite these limitations, this definition offers the most accurate estimate of patients with thyroid nodules in whom a more invasive diagnostic or therapeutic strategy was used.

A broader definition of thyroid nodular disease was also considered, as patients having had surgery or FNAC. An advantage was the inclusion of all surgically treated autonomous or toxic multinodular goitres (regardless of a FNAC prior to surgery). A disadvantage was the inadvertent inclusion of non-nodular auto-immune thyrotoxicosis into this general definition. Whatever definition used, the results of the analyses were similar (the results for the broader definition are presented in Appendix 13).

Age-standardized rates for surgical and FNAC approaches varied between the regions. The most pronounced regional difference was present for the rate of thyroid surgery which was twice higher in the Walloon Region as compared to the Flemish Region (age-standardized rate of 80.3 *versus* 34.0 per 100 000 PY). Concerning FNAC however, no clear difference in age-standardized rates was noticed between the Walloon and the Flemish Region (47.6 *versus* 49.9 per 100 000 PY respectively), but remarkably in the Brussels-Capital Region almost twice more FNAC procedures were performed (78.6 per 100 000 PY).

The age-standardized proportion of patients with nodular thyroid disease treated with thyroid surgery was more or less 30% higher in the Walloon Region (69.1% [95%CI: 68.2; 70.0] as compared to the Flemish Region (47.1% [95%CI: 46.3; 48.0]) and the Brussels-Capital Region (48.0% [95%CI: 46.4; 49.6]). As expected, the proportion of patients in which a conservative approach was chosen was highest in the Flemish and the Brussels-Capital Regions followed by the Walloon Region (53.1%, 52.3% and 31.2% respectively). Although the proportion of surgery for nodular disease was higher in the Walloon Region, the proportion of surgery preceded by FNAC was highest in the Flemish Region followed by the Brussels-Capital and the Walloon Region (22.5% [95%CI: 21.7; 23.2], 16.6% [95%CI: 15.4; 17.8] and 13.4% [95%CI: 12.7; 14.1] respectively) pointing towards a geographical variation in the approach to the thyroid nodular disease patient in whom further invasive diagnosis or therapy is performed.

In the group of patients treated with thyroid surgery, preoperative FNAC has been performed in 41.3% (95%CI: 40.2; 42.5) of the cases in the Flemish Region, as compared to 31.0% (95%CI:29.0; 32.9) in the Brussels-Capital and 18.0% (95%CI: 17.1; 18.9) in the Walloon Region, suggesting a lower probability of finding an undiagnosed and/or occult cancer in the Flemish Region as compared to the Brussels-Capital and the Walloon Region. However, no interregional differences were observed in the proportion of operated thyroid carcinoma patients among all surgical patients (11.5% [95%CI: 9.6; 13.4] in the Brussels-Capital Region, 10.8% [95%CI: 9.7; 11.9] in the Flemish Region and 10.3% [95%CI: 9.3; 11.3] in the Walloon Region). This is not surprising for the following reasons: 1/ with this particular sub-analysis, no difference can be made between high and low preoperative probability for thyroid cancer; 2/ all thyroid surgery types are pooled including lobectomy and surgery for thyrotoxicosis. Therefore a future study focusing on the proportion of thyroid cancer in surgery for nodular disease (with exclusion of surgery for thyrotoxicosis only) as well as on the proportion of thyroid cancer in total thyroidectomy and lobectomy separately would be of value.

In line with the finding of more preoperative FNAC in the Flemish and the Brussels-Capital Region, the proportion of surgical patients with only a postoperative diagnosis of thyroid carcinoma (without prior FNAC) suggestive for an increased probability of undiagnosed and/or occult cancer finding was twice higher in the Walloon Region as compared to the Brussels-Capital and the Flemish Region.

Among thyroid cancer patients, FNAC had been performed in the majority of patients in the Flemish Region (59.5% [95%CI: 54.5; 64.4]) and in a minority of patients in the Walloon Region and the Brussels-Capital Region (respectively 27.8% [95%CI: 23.4; 32.3] and 43.4% [95%CI: 33.9; 52.9]) suggesting a lower pre-surgical probability for thyroid cancer in the Walloon and the Brussels-Capital Regions. The proportion of thyroid cancer patients with a first extensive surgery including lymph node resection was also particularly lower in the Walloon Region (12% [95%CI 8.6; 15.3]) compared to the two other regions, reaching 20-22%.

Concerning the use of FNAC, the proportion of FNAC in surgical patients in Belgium (28.9% [95%CI: 28.2; 29.6]) is lower than anticipated. Indeed FNAC is considered as the single most valuable, cost-effective, and accurate method in the evaluation of the patient with thyroid nodules or a nodular goitre[11, 17-19]. As such, FNAC reduces the rate of unnecessary thyroid surgeries for patients with benign asymptomatic nodules[20] and allows appropriate surgery in patients (presurgically) diagnosed with thyroid cancer. In a surgical series of 1 291 consecutive patients 797 had FNAC prior to surgery[46]. On the other hand, not every nodule that is clinically or radiologically diagnosed deserves an examination by FNAC. For example, FNAC is not routinely recommended for subcentimeter nodules, except for patients having a high risk history (family history of papillary tumour carcinoma, history of external beam radiation exposure as a child, exposure to ionizing radiation in childhood or adolescence, history of prior hemithyroidectomy with discovery of thyroid cancer; and ^{18}FDG-PET–positive thyroid nodules[11]. Moreover, an additional analysis investigating the proportion of patients with preoperative FNAC, neck US or scintigraphy showed age-standardized proportions of 65% (95%CI: [64.3; 65.7]) in Belgium for all thyroid surgical patients, with variations between regions. Higher proportions were reported by the Flemish Region (70.0% [95%CI: 68.9%; 71.1%] followed by the Brussels Capital Region (65.8% [95%CI: 63.8; 67.8]) and a lower proportion in the Walloon Region (60.6% [95%CI: 59.6; 61.7]).

As to the limitations of the study potential confounders cannot be taken into account e.g. differences in iodine status between regions. However both in the Flemish and the Walloon Region, mild iodine deficiency of a similar degree has been reported[16]. Another limitation of the present study is that no data are available on the thyroid weight after surgery, or on the presence of symptoms related to the thyroid volume and leading to the decision of thyroid surgery instead of a conservative approach.

In conclusion, the rate for nodular disease, estimated through the performance of an invasive procedure (FNAC or surgery) was largely higher in the Walloon Region (around 110 per 100 000 PY) than in the Flemish Region (around 66 per 100 000 PY). Higher procedural rates for surgery were recorded in the Walloon Region compared to the Flemish Region, with same rates of all FNAC but lower proportions of surgical interventions *preceded* by FNAC. The Walloon Region is characterized by a higher thyroid cancer incidence which is mainly explained by T1 (mostly infracentrimetric, T1a) thyroid papillary carcinoma. A different prevalence of thyroid nodular disease / thyroid cancer as well as different thresholds for FNAC and/or surgery are potential explanations. The present study of an ecological type does not allow to conclude on their precise/relative contribution, due to potential confounders and abovementioned limitations. However it points to room for improvement regarding optimal use of US and FNAC in selecting patients for appropriate surgery. Additional studies evaluating possible reasons of underuse of (US guided) FNAC as a pre-surgical strategy could be of benefit.

7. INTERNATIONAL TRENDS IN THYROID CANCER INCIDENCE

7.1. Introduction

In order to feed the conclusions and recommendations of the present report the patterns and trends in incidence rates reported in other countries were evaluated.

7.2. Methodology

A search was conducted in Medline with the following MeSH/*key* terms used in combination: thyroid neoplasm, *thyroid cancer*, epidemiology, *incidence, time trend,* registries, survival. Above this, a Google search for grey literature was done with the search terms used for the Medline search, and websites of specific agencies were searched (e.g. Institut de Veille Sanitaire in France). It was decided to include neighbouring and Central-European countries such as France, Grand-Duchy of Luxemburg, the Netherlands, Germany and Switzerland, Northern countries such as Sweden, Scotland, and a distant country such as Canada to obtain a global picture from countries sharing similar medical practices but different environments (climate, diversity, mountains and sea, pollution, Chernobyl fallout…). The extensive description of each country can be found in Appendix 15.

7.3. Overview of international data and epidemiological surveys

7.3.1. World adjusted incidence rates

Thyroid cancer is a relatively rare neoplasm worldwide. In 2008, the estimated age-standardized thyroid cancer incidence rates were 4.7 and 1.5 per 100 000 women and men, respectively[47]. However, it represents more than 95% of all cancers of the endocrine system[1]. Incidence rates vary considerably across geographical regions, and tend to be higher in more developed regions than less developed ones[48]. The highest rates were reported in the US and Israel for males (3.5 per 100 000 for both countries) and females (10.0 per 100 000 and 12.1 per 100 000, respectively), and the lowest rates in Uganda for males (0.5 per 100 000) and females (1.5 per 100 000)[7]. Neither the highest nor the lowest rates were concentrated in only one continent for both genders. Based on the rates from 1998 to 2002, the incidence of papillary carcinoma was the highest (85%), followed by follicular, medullar and anaplastic subtypes.

Well-differentiated thyroid cancers often present low morbidity and mortality. According to the SEER database, the age-adjusted death rate was 0.5 per 100 000 men and women per year between 2004 and 2008. The epidemiological studies conducted in France reported highest five-year overall and relative survival rates for papillary carcinomas (95% and 99% respectively) followed by follicular subtypes (85% and 95% respectively) and medullary subtypes (82% and 88% respectively). Five-year overall and relative survival rates were the lowest for anaplastic carcinomas (10% and 15% respectively)[3]. Survival also differed between sexes. For papillary subtypes, 5-year overall and relative survival rates were 88% and 95% in men and 96% and 99% in women respectively)[3]. Mortality rates are significantly higher in men compared with women, largely due to late diagnosis and more advanced disease in men at the time of initial diagnosis[1].

7.3.2. Increasing trends

7.3.2.1. Worldwide increase in incidence rates

Thyroid cancer rates increased from 1973–1977 to 1998–2002 for most populations (Table 5). This trend has been observed in many countries across Europe, Asia, Oceania, USA and South America. There has been, however, a levelling off for trends in the Scandinavian countries[7]. The only countries to report a decline in thyroid cancer were Sweden (18% reduction for both men and women), Norway (5.8% reduction for women) and Spain (25.9% reduction for women)[7]. The other European countries reported increases in incidence between 5.3% (Switzerland) and 155.6% (France)[7]. No explanation for the decreasing trend was reported in the literature. In Scotland, the incidence of thyroid cancer has almost doubled between 1960 and 2000 from 1.76 to 3.54 per 100 000 in females and from 0.83 to 1.25 per 100 000 in males[5]. In the Netherlands, fairly stable ESR were reported in the period 1989-2001 (between 1.9 and 2.1 per 100 000 persons). Afterwards clear increase to 2.7 per 100 000 persons in 2008[4].

Survival is improving over time: considering all subtypes, the 5-year overall survival increased from 81% between 1989-1991 and 91% between 1995-1997 in France[3]. A possible reason for the improved survival is the rise of incidence of histological types (papillary and follicular) with good prognosis combined with the decrease in incidence of anaplastic cancers with a worse prognosis. Another explanation could be the increased diagnosis of very small cancers (≤1cm and ≤2 cm) that have little risk of progression. More effective treatment delivered without delay was also invoked to explain the improvement in survival rates[1].

7.3.2.2. Incidence trends by gender

Increases were generally stronger for females. A consistent female-to-male ratio of 3:1 is observed in most countries included in both the earlier (seventies') and more recent (nineties') data[5, 49-51].

Hypotheses for the disparity between males and females include biological sex differences (production of increased levels of female hormones during reproductive years, such as TSH), differential screening patterns, or gender-specific behavioural differences[7].

7.3.2.3. Incidence trends by histological types

The global increase of the incidence of thyroid cancer mainly concerned papillary cancer[3-6]. For example, in France, the WSR incidence increased from 0.53 to 2.77 in men (multiplied by 5.2) and from 1.76 to 10.0 (multiplied by 5.7) in women. Between 1985-1989 and 2000-2004, the percentages of the papillary subtype relative to all thyroid cancer types evolved from 55% to 73% in men and from 62% to 84% in women[3]. In the meanwhile, the incidence of other subtypes such as follicular (from 0.28 to 0.50 in men; from 1.02 to 1.18 in women) and medullary carcinoma (from 0.15 to 0.33 in men; from 0.19 to 0.33 in women) only slightly increased, and that of the anaplastic subtype even decreased (from 0.12 to 0.08 in men; from 0.16 to 0.10 in women)[3]. Similar observations were reported in Switzerland, where an increase of papillary cases, a decrease of non-papillary cases and stable trends when all morphologies were combined were observed for the period 1980–1999[52]. In Scotland, the incidence of follicular thyroid cancer also increased between 1975 and 2000 in both females and males (females 67.6%, p=0.001 and males 72.0%, p=0.051), whereas the incidence of anaplastic and medullary thyroid cancer did not change significantly[5].

7.3.2.4. Incidence trends by tumour size

In France, between 1983 and 2000, the sharpest increase was observed for cancers < 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[49]. These very little tumours represented 27% of all cases for the period 2000-2004[8].

A study conducted on the incidence of thyroid cancer over a 12-year period in Ontario reported that the incidence of medium-sized tumours (2–4 cm) remained stable over time, but a slight increase in large tumours (> 4 cm) among patients 45 years and younger was reported in the same time frame[53].

Table 34. International comparison of epidemiological data

	The Netherlands	France	Germany	Luxembourg	Switzerland	Scotland	Sweden	Canada
Periods								
	1989 - 2003	1980 - 2005	1980 - 2006	1990 - 1999	1980-1999a	1960 - 2000		1970 - 1996
					2003-2006[b]			
Epidemiological data								
Incidence rates	***Year: 2008 (ESR)***	***Year: 2005***	***Year: 2006 (ESR)***	***Year: 1999***	***Two periods***	***Year: 2000 (ESR)***	***Year: 2008 (WSR)***	***1996 (WSR)***
Men / 10^5	1.7	4.2	3.4	3.0	2.5[a] – 3.3[b]	1.2	1.5	2.2
Women / 10^5	3.8	12.7	7.5	8.8	5.6[a] – 8.2[b]	3.5	3.8	6.6
Time trend	1989 - 2003	1980 - 2005	1980 - 2006	1990 - 1999	1998 - 2007	1975 - 2000	1999 - 2008	1970 - 1996
Annual rate of increase	0.4%	± 6%	± 3.7%	3% (M) - 5% (F)	3% (M) - 6% (F)		2.8% (M) - 2.5% (F)	
Higher increases	Papillary cancer (2% per year)	Women	Women	Women		Papillary cancer (165.9% in F;331.3% in M)		Papillary: 1.4 to 5.4 in F;0.4 to 1.4 in M
	Stage I (2.3% per year)	Papillary	< 60 years		Papillary	Follicular cancer (67.6% in F;72% in M)		Slight increase in large tumours (>4 cm)
		Microcarcinomas (≤ 1 cm)		Microcarcinomas (≤ 1 cm)				Women <45 years
Geographical variations	Lowest: 2.5 (Amsterdam region)	Lowest: 5.7	Lowest: 2.8 (F) and 1.2 (M) in Hamburg		Lowest: ± 2.0 (Graubünden–Glarus)			
/10^6 p.y.	Highest: 3.1 (Leiden region)	Highest: 15.9	Highest: 10 (F) and 3.8 (M) in Bavaria		Highest: 8.0 (F) (Basel)			
Sex ratio (M/F)	1/2	1/3		1/3	1/2	1/3	1/2.5	
Histologic types		Year : 2005			period: 1980 - 1999			Papillary : 60%
		± 80% papillary		80% papillary	58% papillary			Follicular: 15%

	The Netherlands	France	Germany	Luxembourg	Switzerland	Scotland	Sweden	Canada
5-y survival		Better survival in women				Highest for women and recent diagnoses: 82.7% in 1991-1995 compared to 63.8% in 1976-80	79% (95%CI 75-84%) in males, 85% (83-87%) in females	
Papillary		- 95%				10-year : 88.9% (M) ;96.6% (F)		
Follicular		- 85%				10-year : 80.9% (M) ;88.6% (F)		
Medullary		- 82%				10-year: 47.2% (M);67.0% (F)		
Anaplastic		- 10%				10-year : 4.2% (M);10.4% (F)		
WSR mortality		0.3 (↓)	0.5 (M) - 0.6 (F)		0.7 (M) – 1.0 (F) (↓)	Females: 1.05 to 0.28; males: 0.73 to 0.34	0.3/10^5;annual change: +1.6% (M);-1.0% (F)	

7.3.3. *Spatial disparities in thyroid cancer incidence rates in countries*

In many European countries under study (France, Germany, Switzerland, the Netherlands), high spatial disparities in incidence rates are observed between regions or departments. For example, in France, incidence rates vary by a factor between 1 and 3 for women and between 1 and 2 for men. The highest incidence rate was observed in Tarn (15.9/100 000 persons-years) whereas the lowest incidence rate was observed in Bas-Rhin (5.7/100 000 PY)[8]. Lower rates were reported in Alsace, being more exposed to the Chernobyl Fallout, whereas less exposed areas reported higher rates for thyroid cancer. In young people (0-19 years), geographical disparities were also reported between the Western (4.7/10^6 persons-years; 95% CI 3.9-5.3) and the Eastern (6.3/10^6 PY; 95% CI 5-7.6) part of the country during the period 1999-2001. In France, the rural/urban ratio of thyroid cancer was significant: 0.72 (95% CI: 0.62–0.84) in men and 0.82 (95% CI: 0.73–0.93) in women. Whereas general practitioner density did not appear to have a significant effect on incidence, differences in care offered and accessibility to specialists involved in thyroid cancer, namely endocrinologists and surgeons who are more likely to have their practice in urban zones could offer an explanation[54].

In the Nordic countries, age-standardized incidence rates of thyroid cancer have been slightly increasing in both sexes during the 1960s and 1970s, with the exception of Denmark. Trends thereafter tend to diverge. In Finland and Denmark, incidence rates increased during the 1980s but seem to have stabilized more recently. In contrast, rates in Norway and Sweden have been in long-term decline over the last 25 years[55]. Icelandic men and women have incidence rates three times higher than in other countries[55].

It seems interesting to compare thyroid cancer incidence rates of the Walloon and the Flemish Regions with those reported by the bordering regions from neighbouring countries, i.e. the Departments of Marne-Ardennes in France and the Province of Limburg in the Netherlands. Incidence rates were more comparable between bordering regions both for males and for females than between Belgian Regions (Table 35).

Table 35. Comparisons of thyroid cancer incidence in bordering regions from France, Belgium and the Netherlands

Regions	Males (n / 100 000 PY)	Females (n / 100 000 PY)
Northern Regions		
Limburg in The Netherlands (2004-2006)	2.1	3.6
The Flemish Region in Belgium (2004-2006)	2.1	6.1
Southern Regions		
The Walloon Region in Belgium (2004-2006)	4.4	12.2
Departments Marne and Ardennes in France (2000-2004)	4.7	14.0

In the Netherlands, incidence rates reported for the whole country remain particularly low compared to other countries. Fairly stable ESR (between 1.9 and 2.1 per 100 000 persons) were reported in the period 1989-2001 before an increase to 3.1 per 100 000 persons in 2010. However, there was a slight increase in incidence of papillary tumours of 2.1% per year ($p<0.001$) particularly in stage I tumours, possibly, in part, because of a marked increase in use of fine-needle aspiration biopsy. Appropriate iodine intake, reduced radiation exposure and a more conservative diagnostic approach toward asymptomatic thyroid nodules may explain why this increase is less pronounced compared to other countries[4].

Slight differences were observed between provinces but lower than those observed between Belgian Regions. The nearest province from the Belgian border is the Province of Limburg. The Comprehensive Cancer Centre of Maastricht reported comparable thyroid cancer incidence rates than those reported in the Belgian Flemish Region. An increasing trend was observed both for males (from 1.3/100 000 PY in 2000 to 1.8/100 000 PY in 2010) and for females (from 2.9/100 000 PY in 2000 to 4.3/100 000 PY in 2010) (http://www.cijfersoverkanker.nl/ ; accessed on March 22nd 2012). Between 1989 and 2003, an annual increase of 10% was reported for FNAC whereas an annual decrease of 1.3% in surgical interventions was noticed. This decrease may be due to an increased application of radioactive iodine in the treatment of (toxic and nontoxic) goitre, lower prevalence of goitre due to improvements in iodine supplementation, as well as to better preoperative patient selection after the increasing use of FNAC[4].

In France, high spatial disparities in incidence rates (multiplying factor varied between 1 and 3 for women, between 1 and 2 for men) were reported between departments. Geographical variations in time trends incidence between registries reflected geographical variations in time trends incidence of small sized tumors (less than 10 mm)[56]. One specialized thyroid cancer registry in Marne Ardennes exhaustively collected the information about thyroid cancer and medical practices in these two departments since 1975. This department is really near the Walloon Region of Belgium and reported similar thyroid cancer incidence rates both for males and for females. A sharp increase was reported from 1975-1979 to 2000-2004, since rates were multiplied by 5 for males (from 0.9 to 4.7/100 000 PY) and by 3.6 for females (from 3.9 to 14.0/100 000 PY) in a 30-years period[8].

7.3.4. Explanatory hypotheses

7.3.4.1. Diagnostic strategies

It is currently unclear whether the observed increases in thyroid cancer are real or are due to increased diagnosis (common use of fine needle aspiration technology in the late 1980s in combination with thyroid ultrasound) of subclinical disease. The increased use of such techniques is reported in a lot of countries where an increasing incidence rate of thyroid cancers is observed.

However, a 120.8% increase in thyroid microcarcinomas <1 cm and a 56.2% increase of thyroid tumours >4 cm was reported from 1988–95 to 1996–2005 in the SEER 9 database arguing against advanced diagnostic techniques or increased attention to small nodules as the only explanation for the observed increasing trend of thyroid cancer[1,7,57]. Improved detection techniques may explain the higher increase in micropapillary thyroid cancer incidence compared with the average increase in neoplasm larger than 1 cm. Changes in the methods of detection cannot explain the overall increase in all sizes of papillary thyroid cancer[57].

7.3.4.2. Therapeutic strategies

An increasing use of surgery to manage benign thyroid conditions is also invoked to explain the incidental discovery of thyroid tumours. Whereas in nineties' only 26% of thyroid cancers were incidentally discovered after a thyroidectomy for a benign thyroid disease (goitre or nodular disease), this proportion increased to 38% in 2000s in France. During the same period, the proportion of very small incidental tumours (≤5 mm) increased from 50% to 64.5%[8]. Finally, 95% of incidental tumours were papillary thyroid cancers. The thyroid cancer incidence was correlated with the increasing number of total thyroidectomies. All these elements support the hypothesis that increasing the frequency of total thyroidectomies led the pathologist to examine a greater tissue thyroid mass, thereby increasing the probability of incidental small cancer finding[8].

Another study highlighted an increase of incidental findings of thyroid cancer during the pathological examination[58]. Between 1980 and 2000, the global number of surgical procedures remained stable, but the proportion of total thyroidectomies had increased at the expense of partial surgery. This evolution, which favours the chance to serendipitously discover histological lesions undetected by the clinical exam has also been demonstrated in countries that describe a "micropapillary thyroid cancer epidemic"[56]. In the Netherlands, where the ESR is relative low compared to its neighbouring countries (2.7 per 100 000 PY in 2008; http://www.cijfersoverkanker.nl/; accessed on March 15th 2011), the number of thyroid surgeries decreased on average with 73 surgeries per year between 1989 and 2003 ($p<0.0001$). Nevertheless, during the same period, the proportion of thyroid cancers among the patients who had surgery increased from 9.4% to 13.5% ($p<0.0001$)[4].

7.3.4.3. Histopathological classification and practices

The revision of the histopathological classification system for thyroid cancer in 1988 (reclassification of follicular subtypes into follicular variants of papillary cancer) could have impacted the distribution of cases by subtype without affecting the total number of cases diagnosed[3]. Moreover, the number of pathological slides derived from each surgical specimen has probably increased over time, even though such an evolution was not formally published.

7.3.4.4. Environmental factors

In countries where the potential consequences of the Chernobyl fallout were studied (France, Grand-Duchy of Luxemburg, Sweden…), epidemiological evidence does not favour any link between this ionizing radiation source and the increase of thyroid cancer incidence. The increase has begun before 1986 and the progression is continuing since 1978. The same observation is made for the US. The lowest cancer incidence rates were reported in more exposed areas (Alsace, Eastern part of France), whereas less exposed areas reported the highest rates of thyroid cancer[8]. Cardis et al.[59] have calculated the predicted number of cases of thyroid cancer in Europe up to 2065 possibly due to radiation from the Chernobyl accident and from other causes (Table 36). All European countries were grouped into 5 categories according to the level of contamination by ^{131}I received in 1986 by children younger than 5 years of age. Group 1 (<5mSv) included Belgium, Cyprus, Denmark, Estonia, Finland, France, Germany, Hungary, Iceland, Ireland, Latvia, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and the

United Kingdom. For thyroid cancer, the estimated fraction of all cancer cases attributable to radiation was 0.03% for exposure at all ages and 0.20% for exposure before age 15 up to 2005. These thyroid cancer cases attributable to radiation were respectively 0.08% and 0.16% up to 2065. The uncertainty intervals were quite large.

Table 36. Predicted number of cases of thyroid cancer in the less contaminated European countries (average thyroid dose 1mSv) possibly due to radiation from the Chernobyl accident and from other causes, 95% uncertainty intervals and estimated fraction of all thyroid cancer cases attributable to radiation (AF)

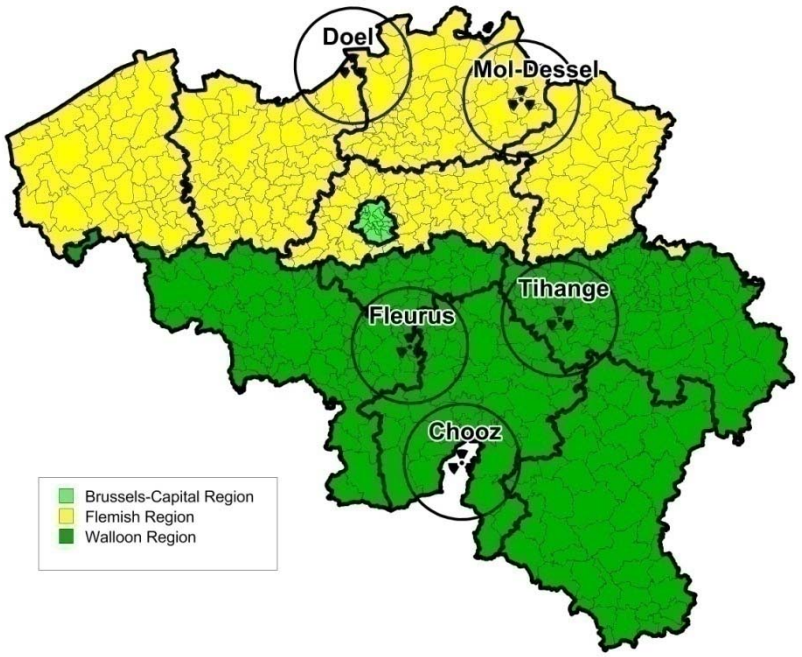
	Population in 1986	From radiation	95% UI	From other causes	AF to 2005
Exposure at all ages	311.6 10^6	60	10-270	224 000	0.03%
Exposure before age 15	60 500 000	30	5-170	15 000	0.20%
	Population in 1986	**From radiation**	**95% UI**	**From other causes**	**AF to 2065**
Exposure at all ages	311.6 10^6	800	150-4 100	950 000	0.08%
Exposure before age 15	60 500 000	700	150-3 600	440 000	0.16%

Source. Cardis et al. [59]
Note. Countries included in group 1 were Belgium, Cyprus, Denmark, Estonia, Finland, France, Germany, Hungary, Iceland, Ireland, Latvia, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and the United Kingdom

The main source of radiation exposure for the general population is background radiation. Most of the background radiation comes from radon. In Belgium, the average total exposure to ionizing radiation is estimated to be 4.5 mSv/yr[10]. This exposure is due to medical radiation for 43%, radon for 32%, terrestrial radiation for 9%, cosmic radiation for 8%, internal radiation for 7%, and industrial radiation for 1%[10]. By comparison, the average exposure from background radiation is about 3.0 mSv/yr in the USA (National Research Council 2006). Between 1980 and 2006, the average exposure to medical x-rays increased more than 5-fold[10].

The study conducted by the Scientific Institute of Public Health investigated the occurrence of new cases of thyroid cancer in a 20 km area around the Belgian power plants of Doel (Province of East Flanders, Flemish Region) and Tihange (Province of Liège, Walloon Region), the combined industrial and research sites of Fleurus (Province of Hainaut, Walloon Region) and Mol-Dessel (Province of Antwerp, Flemish Region) and on the Belgian territory around the French nuclear power plant of Chooz (covering an area of 200 hectares along the Meuse River between Charleville-Mézières (France) and Dinant (Belgium); Walloon Region) (Figure 45). On the basis of the data available up to now, no increased incidence of thyroid cancer was observed around the nuclear power plants of Doel and Tihange. For the vicinity of the French power plant of Chooz, it was impossible to draw any scientific conclusions for thyroid cancer because of instability of the results. For the nuclear sites of Mol-Dessel and Fleurus, where a combination of nuclear research and industrial activities are located, a slightly increased incidence of thyroid cancer as compared to the regional average was observed, but similar and higher increased incidences were also seen at other locations without nuclear sites[10].

Figure 45. Map of Belgium locating the five nuclear sites and their 20 km proximity area



Source: Institut Scientifique de la Santé Publique

Iodine deficiency could explain high incidence rates in areas far from the sea. In Sweden for example, residence in iodine-deficient regions was associated with a 2-fold increased risk of follicular cancer in men (RR 1.98) and a 17% increase in risk in women (RR 1.17)[60]. However, iodine deficiency, being reported in one-third of the world population before 1990, was reduced thanks to the implementation of programs of iodine supplementation in affected countries. The Netherlands achieved adequate iodine nutrition after phases of iodisation of water and salt, especially in the bakery industry. In Belgium, a mild iodine deficiency is well documented. In 1995, the median urinary iodine concentration was 55 µg/l (normal: 100-200) and the prevalence of goitre was 11% (normal: below 5%)[61]. However, Belgium and France are among the very few European countries with no official programme of salt iodisation so far, and remain affected by mild iodine deficiency[62]. In 2002, the national representatives from the West and Central European Region of the International Council for Control of Iodine Deficiency Disorders (ICCIDD) designated 15 countries iodine sufficient (≥100µg/l, among which the Finland, Netherlands, Switzerland and UK), 13 deficient (<100µg/l among which Belgium, Denmark, France, Germany, Italy and Spain), four likely sufficient (Iceland, Luxemburg, Norway and Sweden), and one likely deficient (Albania). Overall, more than 60% of the nearly 600 million people in the region live in countries that harbour iodine deficiency[63]. Nevertheless, when iodine supplementation occurs in iodine deficient regions, the proportion of papillary thyroid cancers often increases although the overall rates of thyroid cancer tend to stay the same[7].

The age-adjusted incidence rate among women in Finland is over twice that reported in Denmark in both time periods of interest (1973–1977 and 1998–2002). These differences are not easily explained as similar standards of medical care and reporting are adopted in these countries. This suggests that different levels of environmental exposure to a significant risk factor/set of risk factors could be present in these countries[7]. For example, heavy industry and associated pollution just across the Norwegian-Russian border has provoked exacerbation of allergic disease[64] as well as cancer[65]. Historic nuclear testing across the Russian border has also been incriminated in thyroid cancer[66, 67].

Environmental contamination in chemical and industrial areas can also potentially explain increase in cancer incidence rates. A descriptive epidemiological study was conducted in the Rhône Valley, where several nuclear sites are concentrated in the Tricastin area (enclosed in the border departments of Ardèche, Drôme, Gard and Vaucluse), in order to evaluate the health status of the population 10 km surrounding this area[68]. The aims were to compare incidence rates and mortality rates from cancers across this area, the 4 bordering departments and the whole country. Twenty-four cancerous localizations, including thyroid cancers were investigated. The incidence rates of cancers in the Tricastin area were 1) not statistically different from those reported in the 4 bordering departments nor in the whole country for solid tumours in children and for malignant hemopathy (leukaemia) during the period 2000-2006; 2) not statistically different from

those reported in the 4 bordering departments nor in the whole country for all cancerous localizations in adults for the period 2004-2007, except for pancreatic cancer in women (not already explained). Mortality rates from cancer in the Tricastin area were higher for prostate cancer in men, Hodgkin lymphoma and pancreatic cancer in women, but were lower for oesophageal and liver cancer than in referent areas. They were not statistically significantly different for all other cancers[68].

A large number of chemical pollutants were also incriminated in thyroid tumorigenesis (e.g. dioxins, PCBs, organochlorine pesticides, phthalates, nitrates, aluminium cadmium, solvents,…)[69]. Very few epidemiological studies have investigated the role of environmental exposure in thyroid diseases, because it is difficult to assess low- or very-low-dose exposure to chemical substances. Most studies conducted so far were occupational studies in specific environments (e.g. wood or papermaking industries, textile industry, manufactures of computers or shoes)[69].

In fact, changes in environmental factors, including population exposure to ionising radiation from fallout and residential radon, diagnostic procedures and treatment for benign and malignant conditions (radiation exposures from medical and dental X-rays, fluoroscopy, nuclear medicine, radiotherapy and computed tomography) are considered as important factors explaining the increase in thyroid cancer incidence throughout the world[48]. Whereas medical and dental X-rays constitute the most common type of diagnostic medical exposures, their contribution to the cumulative effective dose remains relatively low. By contrast, computed tomography scans only account for 7.9% of diagnostic radiology examinations but 47% of the collective effective dose from diagnostic radiation procedures in parts of the world. The radiation exposure from CT scans is substantially lower than that from radiotherapy; however, multiple computed tomography scans could result in significant cumulative doses to the thyroid[48].

7.3.5. Mortality rates

Despite the wide inter-country variation in age-adjusted incidence rates, only a small variation in sex-specific mortality rates is reported by geographic region (between 0.2 and 1.0 per 100 000 PY in women and between 0.1 and 0.7 per 100 000 PY in men)[7].

Five-year overall survival rates were 95% for papillary carcinomas, 85% for follicular subtypes, 82% for medullary subtypes and 10% for anaplastic carcinomas in France[3]. Mortality rates were somewhat similar in Grand-Duchy of Luxemburg[51]. In all countries, 5-year overall survival is lower in men (88%) than in women (96%). Survival is improving over time: considering all subtypes, the 5-year overall survival increased from 81% between 1989-1991 to 91% between 1995-1997[3]. In both sexes, survival from thyroid cancer was better if the diagnosis was made under the age of 50 years[5]. In the Nordic countries, mortality rates of thyroid cancer have been decreasing during the last 25 years, while the 5-year relative survival has been steadily increasing over the same period, leading to an overall survival of 80-90% for patients diagnosed between 1999 and 2003. However, in these countries, survival estimates are consistently lower in Denmark, particularly in patients diagnosed aged over 60[55].

Temporal and geographical differences in overall survival remain difficult to interpret without further stratification by histological subtype (excellent prognosis for papillary forms vs. poor prognosis for anaplastic carcinomas) and extent of disease. Moreover, confounding factors (e.g. smoking) can also explain survival differences between countries (the higher prevalence of smokers in Denmark in comparison with other Nordic countries can be an important prognosis factor)[55].

Key points

- **Thyroid cancer is a relatively rare cancer (4.7 in women and 1.5 in men per 100 000 in 2008), but represents more than 95% of all cancers of the endocrine system.**
- **Incidence rates vary considerably across geographical regions. Neither the highest nor the lowest rates were concentrated in only one continent for both genders. In many European countries, high spatial disparities in incidence rates are observed between regions or departments.**
- **The incidence of papillary carcinoma is the highest (85%), followed by follicular, medullar and anaplastic subtypes.**
- **An increasing trend is observed worldwide (except in Scandinavian countries and Spain without evident explanations), mainly concerning papillary cancer and to a lesser extent follicular and medullary carcinoma. Incidence rates of anaplastic tumours even decreased.**
- **An increased use of FNAC in combination with thyroid US is reported in a lot of countries where an increasing incidence rate of thyroid cancers is observed.**
- **An increasing use of surgery to manage benign thyroid conditions is also reported in many countries.**
- **In 1988, the revision of the histopathological classification system for thyroid cancer (reclassification of follicular subtypes into follicular variants of papillary cancer) could have impacted the distribution of cases by subtype.**
- **Epidemiological studies conducted in numerous European and American countries do not favour any link between Chernobyl Fallout and the increase of thyroid cancer incidence, apart from the regions in the neighbourhood of the incidents.**
- **A large number of chemical pollutants as proximity of heavy industries and nuclear sites were incriminated in thyroid tumorigenesis, without high supporting evidence.**
- **Despite the wide inter-country variation in thyroid cancer incidence rates, only a small variation in sex-specific mortality rates is reported by geographic region (between 0.2 and 1.0 per 100 000 PY in women and between 0.1 and 0.7 per 100 000 PY in men).**

7.4. Discussion

Compared to other European countries, Belgium has an intermediate thyroid cancer incidence. With an incidence of 6.7 per 100 000 PY, the Brussels-Capital and the Walloon Region were situated above the median European value of 4 per 100 000 PY, while the Flemish Region had an incidence of 3.3 per 100 000 PY. As in the majority of countries, the male/female ratio was 1:3 and papillary carcinoma was the most frequent histological type followed by follicular, medullar and anaplastic subtypes.

Worldwide, increase in thyroid cancer rates were reported between the 1970s and the 2000s. In Belgium, no records were available for such a large period, first data being available in 1999 from the Flemish Region. However, increasing rates (WSR, N/100 000 PY) were reported between 1999 and 2008 in the Flemish Region (from 1.4 to 2.0 for males; from 2.7 to 5.2 for females)[2]. Whereas the (short-term) annual increases were not significant a significant long-term effect was observed, when comparing the 2000-2001 incidence with the 2005-2008 incidence. The increasing time trend in thyroid cancer incidence was not observed in the Walloon and the Brussels-Capital Regions. This lack of increasing time trend in thyroid cancer incidence in the Walloon and the Brussels-Capital Regions could be due to the shorter period (5 years) for which thyroid cancer incidence data are available in comparison with the Flemish Region (9 years).

At an international level, such increase was potentially explained by the increasing use of sensitive diagnostic strategies (US and FNAC), the increasing use of surgery to manage benign thyroid conditions and the 1988 revision of the histopathological classification for thyroid cancer. The last explanation cannot be invoked to explain the increased rates in Belgium, since it was anterior to the observed incidence rates (between 1999 and 2008). However, other potential factors related to the pathological evaluation of surgical specimens are also evoked in the literature. Pathologists may use different thresholds to label a small

abnormality as “cancer” or can examine the surgical specimen with different degrees of scrutiny (more or less slices per thyroid gland and more or less thick sections), leading to the ‘detection’ or ‘labelling’ of more cancer cases[21, 22].

Environmental factors were not specifically analyzed in this study and no conclusion can currently be drawn about the potential association between environmental contamination by industrial or chemical pollutants and the variable incidence rates of thyroid cancer in Belgium. Mild iodine deficiency is present in all regions in Belgium. Anyway, despite the program of iodine supplementation in bread implemented since 1999, the proportion of papillary thyroid cancers continues to increase as observed at an international level[7].

Finally, mortality rates reported in Belgium between 2004 and 2008 (between 0.1 and 0.8 per 100 000 PY in women and between 0.1 and 0.4 per 100 000 PY in men)[2] are in the same ranges than those reported internationally[7]. In 2008, a lower mortality rates for females was reported in the Walloon Region than in the Flemish Region (0.1 vs. 0.4 per 100 000 PY)[2].

8. CONCLUSION

Compared to other European countries, Belgium has an intermediate thyroid cancer incidence. During the period 2004-2006, the European standardized incidence rate of thyroid cancer was 5.8 per 100 000 PY, i.e. 1 992 new thyroid cancer cases. On average, 664 new cases were diagnosed annually. However, regional variations were reported in incidence rates for all thyroid cancers but mainly for very small tumours. The Walloon Region showed the highest incidence rate of thyroid cancer and particularly the highest incidence rates of T1 (mostly T1a) thyroid papillary carcinoma as compared to the Flemish Region. The incidence rates of thyroid cancer increased in the Flemish Region from 1999 to 2008 (EAPC [Estimated Annual Percentage Change]: 5.5% [p<0.001] in males and 8.1% [p<0.001] in females)[e]. This increase seems to have no impact on mortality rates which remain very low both in males and females (<1.0 per 100 000 PY in 2008).

The aim of this study was to assess to what extent differences in thyroid cancer incidence mainly observed between the Belgian Regions could be explained by differences in diagnostic and therapeutic strategies. Different diagnostic procedures were analyzed including serum TSH testing, neck ultrasound, duplex carotid US, CT scan, MRI, ^{18}FDG-PET and fine-needle aspiration cytology. Therapeutic strategies included surgery, antithyroid drugs and radioiodine. The management of thyrotoxicosis and nodular disease was separately analyzed to enlighten the potential association between strategies used to handle these pathologies and the discovery of thyroid cancer.

Globally, in the Walloon Region, higher rates were reported for the use of a panel of diagnostic methods (neck ultrasound, duplex carotid ultrasound, CT scan, MRI, ^{18}FDG-PET) potentially leading to the discovery of a thyroid nodule. Moreover, surgical interventions were more frequently performed *per capita* in the Walloon Region for the management of nodular but also thyrotoxic thyroid disease. This combination of a higher use of sensitive

[e] In the Brussels-Capital and Walloon Regions, the incidence data were available for a 5-year period (2004-2008). This time period is not sufficient to estimate accurately trends over years.

imaging modalities and a higher use of surgery could lead to substantially more incidental discoveries of very small thyroid nodules, thereby revealing the existing disease reservoir of thyroid cancer[22], whether dormant or not. In fact, the incidence of T1 papillary carcinoma was 3-fold higher in the Walloon Region (4.6 per 100 000 PY) compared to the Flemish Region (1.4 per 100 000 PY), whereas the incidence of T2 (2cm<size≤4cm) and T3 cancers (for all histological types) is not significantly different between the regions. Moreover, this incidence difference was especially pronounced in T1a tumours (≤1 cm).

A converging array of findings points to a strong association between the use of specific diagnostic and therapeutic strategies and cancer incidence.

Unfortunately, numerous methodological limits, linked to the ecological study design, the use of retrospective data and the inference of thyroid disease on the basis of diagnostic or therapeutic procedures, preclude us from drawing definitive conclusions about a causal link between the diagnostic and therapeutic procedures studied and thyroid cancer incidence, on whatever geographical level.

The variability in diagnostic and therapeutic procedures could also be explained by the specialty of medical professionals who examined the patients and performed the diagnostic procedures and/or the treatment. In fact, medical practices can differ according to the professional background of the clinicians (endocrinologist, surgeon, specialist in nuclear medicine, …) and according to the hospital. In Belgium, endocrine care is almost exclusively hospital-based but not restricted to large referral centres. For example, in 2005, 662 surgical procedures including a thyroidectomy along with the diagnosis of a malignant neoplasm of the thyroid gland were registered in 87 hospitals[70]. In general, such a large dispersion might not guarantee the highest quality of care we can expect[71]. A large study demonstrated the impact of hospital volume of thyroidectomies on outcomes following substernal thyroidectomy. Differences reported between high-volume and low-volume hospitals were mainly explained by the experience of surgeons and their ancillary staff[72]. Such practitioners and hospitals characteristics were impossible to capture in this study but have also to be considered as potential explanations for the variability of practices.

Of course, caution is particularly needed when trying to establish a causal link between variable use of diagnostic and therapeutic techniques and thyroid cancer incidence across regions. Aggregation of events observed at one geographical level, i.e. the region or the district, could lead to observe some associations between different variables at this level of aggregation that would not be observed at the individual level or at other aggregation scales (e.g. comparison of eastern and western districts, comparison of urban and rural areas, comparison of coastal areas and remote areas). This type of study can be subject to potential bias, in particular the ecological fallacy (the failure of group level data to properly reflect individual level associations)[23, 24]. The ecological fallacy, as applied to area-based data, is closely related to the modifiable areal unit problem. Regional boundaries were chosen in this study to grasp geographical differences in medical practices. In such analysis, neighbourhood to the land borders might also be of importance. For example, highest rates of TSH dosage were observed both in Walloon districts and in some western districts in the Flemish Region, near the French border. Such observation could also reflect standard practice as learned during medical studies. The inability to control for potential confounding factors due to the design of the study implies that differences or similarities observed at the district and region level could be (or not) different at other aggregation levels, not considered in this study.

The lack of knowledge on the clinical information linked to the diagnostic and therapeutic procedures also represents one of the limitations of this study. In addition, the procedures concerning the anatomopathological examination of the resection specimens could not be analyzed.

Finally, this study suggests room for improvement in the preoperative use of FNAC, both in the North and in the South of the country. Using FNAC as proposed by international consensus and guidelines could help the clinician to delineate benign from malignant nodules that would require further treatment. A large study conducted in 797 surgical patients undergoing FNAC before their surgery reported that FNAC performed by experienced clinicians and interpreted by dedicated cytopathologists rarely resulted in false-positive and false-negative results and reached a high sensitivity (98%)[46]. With FNAC results, clinicians can better orientate the patient towards surgical treatment (definitive operation that includes total thyroidectomy for malignant tumours, at least thyroid lobectomy in patients

with follicular or Hürthle cell neoplasm) or conservative management, consisting in monitoring with serial examinations and FNAC for benign results[46]. The dissemination of recent international guidelines for patients with thyroid nodules and differentiated thyroid cancer[11] and for patients with thyrotoxicosis[25] could certainly also contribute to the reduction of the variability in diagnostic and therapeutic strategies in Belgium.

Further studies at an individual (patient) level with a stronger design (e.g. case-control or prospective studies) are therefore needed, to evaluate the association between diagnostic/therapeutic practices and thyroid cancer diagnosis and tumour size, and to draw more firm conclusions on the impact of the geographical variability of such practices and cancer incidence figures[26].

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