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# High Prevalence of Pituitary Adenomas: A Cross-Sectional Study in the Province of Liège, Belgium

Adrian F. Daly, Martine Rixhon, Christelle Adam, Anastasia Dempegioti, Maria A. Tichomirowa, and Albert Beckers

*Department of Endocrinology, Centre Hospitalier Universitaire de Liège, University of Liège, 4000 Liège, Belgium*

**Context:** Prevalence data are important for assessing the burden of disease on the health care system; data on pituitary adenoma prevalence are very scarce.

**Objective:** The objective of the study was to measure the prevalence of clinically relevant pituitary adenomas in a well-defined population.

**Design:** This was a cross-sectional, intensive, case-finding study performed in three regions of the province of Liège, Belgium, to measure pituitary adenoma prevalence as of September 30, 2005.

**Setting:** The study was conducted in specialist and general medical practitioner patient populations, referral hospitals, and investigational centers.

**Methods:** Three demographically and geographically distinct districts of the province of Liège were delineated precisely using postal codes. Medical practitioners in these districts were recruited, and patients with pituitary adenomas under their care were identified. Diagnoses were confirmed after retrieval of clinical, hormonal, radiological, and pathological data; full demographic and therapeutic follow-up data were collected in all cases.

**Results:** Sixty-eight patients with clinically relevant pituitary adenomas were identified in a population of 71,972 individuals; the mean (± SD) prevalence was 94 ± 19.3 cases per 100,000 population (95% confidence interval, 72.2 to 115.8). The group was 67.6% female and had a mean age at diagnosis of 40.3 yr; 42.6% had macroadenomas and 55.9% underwent surgery. Prolactinomas comprised 66% of the group, with the rest having nonsecreting tumors (14.7%), somatotropinomas (13.2%), or Cushing's disease (5.9%); 20.6% had hypopituitarism.

**Conclusion:** The prevalence of pituitary adenomas in the study population (one case in 1064 individuals) was more than 3.5–5 times that previously reported. This increased prevalence may have important implications when prioritizing funding for research and treatment of pituitary adenomas. **(*J Clin Endocrinol Metab* 91: 4769–4775, 2006)**



TUMOR PREVALENCE DATA are important for the estimation of disease burden in populations and are often used to calculate health care resource distribution within and among clinical specialties. Existing data on the prevalence of pituitary adenomas are discordant. Estimates from cancer registries suggest that pituitary adenomas are uncommon, particularly as compared with solid tumors such as breast, lung, and colon cancers (1). In contrast, a comprehensive metaanalysis of data from autopsy and radiological studies indicates that pituitary tumors may be present in as many as one in every six people (2). The inclusion of a sizable number of small nonclinically relevant adenomas (incidentalomas) in autopsy/radiological series probably accounts for a proportion of the reported high prevalence, but as noted by Ezzat *et al.* (2), many tumors from autopsy series are immunohistochemically positive for pituitary hormones. Existing epidemiological data suggest that the incidence of pituitary adenomas is rising, although it is difficult to determine whether this is due to widespread access to magnetic resonance imaging (MRI) and accurate biochemical testing, leading to improved recognition of clinically relevant pituitary tumors (3). The uncertainty regarding the true prevalence of clinically active pituitary adenomas led us to undertake an intensive, cross-sectional epidemiological study of the current prevalence of pituitary adenomas in a tightly defined geographical area in Liège, Belgium.

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Abbreviations: CT, Computerized tomography; FIPA, familial isolated pituitary adenoma; MEN1, multiple endocrine neoplasia type 1; MRI, magnetic resonance imaging.

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## Patients and Methods

### *Study setting*

Three separate geographic areas within the province of Liège were chosen for the study. The definition of *prevalence* for this study was that generally used in cancer epidemiology: "prevalence is the number and/or proportion of people with a past or present diagnosis of a pituitary adenoma within a well-defined population at a fixed point in time" (4). To reflect the diverse characteristics of the Belgian population densities, the individual areas had specific demographic profiles: rural (Soiron), suburban (Oupeye), and urban (Ans-Alleur), and all had a similar number of inhabitants. To define the geographical boundaries of each study region precisely, Belgian post office code designations were used. Study district I, Soiron (postal codes 4860, 4861, 4870, 4877), consisted of a population of 21,024 inhabitants; study district II, Oupeye (postal codes 4680, 4681, 4682, 4683, 4684), had 23,598 inhabitants; and study district III, Ans-Alleur (postal codes 4430, 4431, 4432), had 27,350 inhabitants (Fig. 1). The total population for the study was 71,972. Only living individuals residing within the predetermined geographic boundaries on a specific day were deemed eligible for inclusion in the study. The defined date for validating whether patients were alive and were residing in one of the postal code-defined areas was September 30, 2005. The study protocol was approved by the Ethics Committee of the University of Liège (Liège, Belgium) and was performed under the tenets of the Declaration of Helsinki and its subsequent amendments.

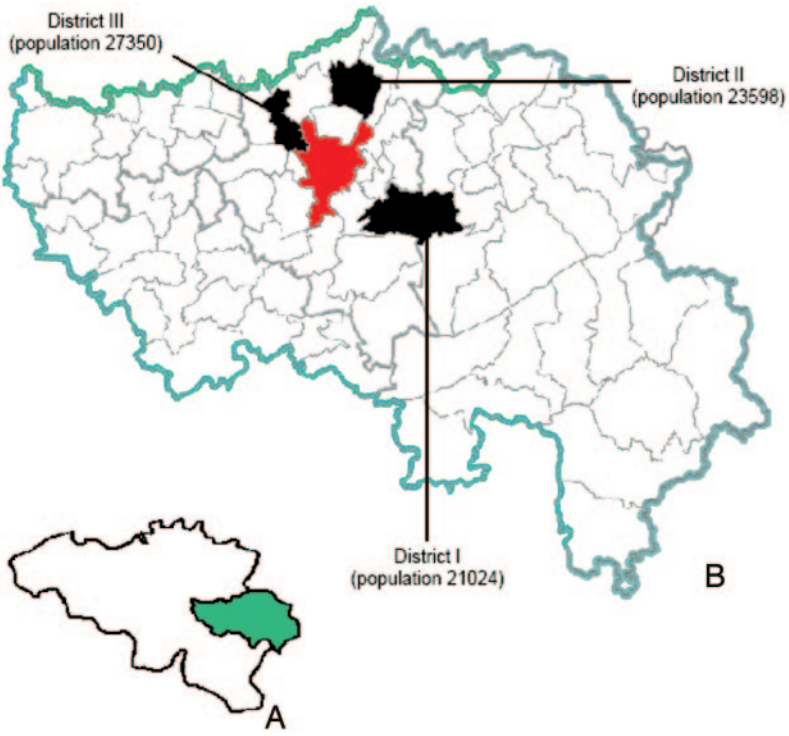


FIG. 1. Map of Belgium (A) with province of Liège outlined (*green*). Detailed view of districts in the province of Liège, including the three study districts (*black*) and the city of Liège (*red*). [Adapted with permission from the Institut Géographique National-Belgique (www.ign.be).]

### *Data gathering*

Within the three defined study areas, all general practitioners and relevant specialists (endocrinologists, gynecologists, neurosurgeons) working in public/private practice were identified. Subsequently, the identified medical practitioners were contacted directly to recruit them to the study, and each received a simple case report form containing headings for demographic and disease characteristic criteria. Educational meetings on the topic of the clinical recognition, investigation, and management of patients with pituitary tumors were organized for medical practitioners within each study area; attendees received information regarding the design and purpose of the present epidemiological study. The proportion of medical practitioners within the study sample sites that participated in the study was 70–80%. Participating medical practitioners analyzed their patient records to identify individuals with an established (past or current) diagnosis of a pituitary adenoma.

Patients were contacted to inform them of the study and the anonymous nature of data gathering and to confirm their eligibility (living and residing in one of the three study areas). Individual patient characteristics including data on demographics, residence, diagnosis, date of diagnosis, therapy, and site of hospital treatment were recorded on the case report form. Thereafter in each case further definitive information establishing the diagnosis of a pituitary adenoma was sought from hospital case files or other relevant clinical records. Patients with other pituitary conditions like craniopharyngioma or inflammatory lesions were excluded. In all cases, the primary clinical signs/symptoms at presentation (maximum of three), radiological imaging studies of the pituitary region, and hormonal profiles demonstrating relevant disordered secretion had to be available. In cases in which surgery was performed, operative findings and pathological reports were sought. Patient follow-up data (treatment and disease control) also had to be available in all cases; for the purpose of this study, patients were defined as having biochemically stable disease if their hormonal levels were controlled to a level at which hormonal hypersecretion symptoms were not evident. In the case of patients with acromegaly, IGF-I had to be controlled to within the normal ranges for age and sex. Furthermore, patients with hypopituitarism were required to have evidence of adequate dosing with hormonal replacement therapy before being assessed as biochemically stable. Tumor stability was assessed in all cases, either in terms of whole tumor size changes in nonoperated cases or tumor remnant behavior in cases with incomplete primary resection of the pituitary adenoma. Before being included in the final cohort, each patient's symptom and hormonal, radiological, pathological, and follow-up data were reviewed and verified separately by two of the authors (A.F.D. and A.B.).

### *Familial screening*

The study had its genesis in the investigation of a series of patients with pituitary adenomas in a valley area in one of the postal code regions of study district I (Soiron) involving less than 5000 people. During this initial work, the issue of family clustering was suggested; however, investigation of patients' family histories and genealogies revealed no familial cases. Given the relatively close geographic distance between the study sampling sites, in the current study, identified patients also underwent screening for familial links to assess for clustering due to pituitary tumor-associated syndromes such as multiple endocrine neoplasia-1 (MEN1) and familial isolated pituitary adenomas (FIPA) (5, 6). Medical practitioners and patients were questioned about their knowledge of other family members with diseases suggestive of MEN1 and for the presence of other family members with pituitary adenomas (Carney's complex, FIPA). Further assessments of patients' medical records were undertaken to rule out the presence of biochemical abnormalities typical of MEN1.

### *Data analysis*

Means and ranges were calculated for the following criteria for each tumor type and the total pituitary adenoma population: age, symptom duration before diagnosis, number of MRI/computerized tomography (CT) scans, and maximum tumor diameter. Data on sex, the main three symptoms at presentation, tumor characteristics (macro-/microadenoma, suprasellar extension, invasion), requirement for surgery, postoperative medical therapy, and disease control (biochemical, tumor) were collected, summarized, and tabulated for each tumor type and for the group as a whole. The prevalence of pituitary adenomas at each of the three sampling sites was calculated individually, and the overall prevalence in the study was expressed as the mean (± SD; 95% confidence interval) of the three individual values.

## Results

### *Prevalence of pituitary adenomas*

A total of 68 living patients with clinically confirmed pituitary adenomas were resident in the study areas as of September 30, 2005. The mean (± SD) prevalence across the three study areas was 94 cases per 100,000 population (95% confidence interval, 72.2 to 115.8 cases). This translates into a mean of one case per 1064 individuals (95% confidence interval, 1:864 to 1:1385). A further 30 patients who were highlighted by the participating medical practitioners were excluded for the following reasons: deceased before cutoff date of September 30, 2005 (n = 10); mild hormonal abnormalities (predominantly hyperprolactinemia) without verifiable evidence of a tumor on MRI (n = 9); resident outside the geographical limits of the study sites (n = 7); craniopharyngioma (n = 2) and arachnoid cyst (n = 2).

### *Demographics*

The summary details of the individual patients are shown in Table 1. The group of patients with verified pituitary adenomas consisted of 22 males and 46 females. Two patients were of North African origin; the rest were Caucasian. The mean age at diagnosis was 40.3 yr (range 12–86 yr), and patients on average had suffered symptoms attributable to their diagnosis for 45.3 months (range 1–300 months) before a diagnosis was made. Patients were not uniformly distributed by age at diagnosis: 0–9 yr (n = 0), 10–19 yr (n = 5), 20–29 yr (n = 13), 30–39 yr (n = 18), 40–49 yr (n = 13), 50–59 yr (n = 9), 60–69 yr (n = 7), 70–79 yr (n = 2), 80–89 yr (n = 1), older than 90 yr (n = 0).

### *Disease characteristics*

Overall, prolactinomas were the most frequent tumor found (45 of 68; 66.2%), followed by nonsecreting tumors (10 of 68; 14.7%), somatotropinomas (nine of 68; 13.2%), and Cushing's disease (four of 68; 5.9%). No patient in the cohort had a tumor that secreted TSH alone, although one patient with acromegaly had a tumor that cosecreted GH, prolactin, and TSH, and the patient exhibited signs/symptoms of hyperthyroidism in addition to acromegaly. Familial links among patients were not found in this cohort, and only one patient (a female with a macroprolactinoma) had sporadic MEN1 that had been confirmed by genetic screening.

Radiological diagnosis and follow-up were performed using MRI of the pituitary (3-mm cuts) in 56 patients. The remaining 12 patients had tomography or CT at diagnosis, and nine of these 12 patients subsequently had their tumor characteristics confirmed during surgery. MRI was used for long-term follow-up in all patients originally diagnosed using tomograms and CT. The mean number of MRI and CT scans per patient during their diagnosis and follow-up was 4.9 (range 1 to 16 scans). All 68 patients had valid radiological results to determine the presence of a macroadenoma (n = 29) or a microadenoma (n = 39); the mean maximal tumor diameter was 12.9 mm (range: 2–50 mm) for the group overall. Suprasellar extension was noted in eight patients with prolactinomas (17.8%), seven patients with nonsecreting adenomas (70%), and four patients with acromegaly (44.4%). Tumor invasion was noted in eight (17.8%), four (40%), four (44.4%), and one patient (25%) in the prolactinoma, nonsecreting adenoma, acromegaly, and Cushing's disease groups, respectively (Table 1).

### *Treatment and follow-up*

A total of 38 patients (55.9%) underwent surgery, and the approach was transsphenoidal in all but one patient (transnasal), whereas two patients underwent repeat surgery. Pathological results were available in 34 of 38 operated cases (89.5%), and in all cases tumors were benign adenomas. Only two patients received radiotherapy: the patient with MEN1 whose macroprolactinoma was resistant to surgery and dopamine agonists and a second patient with Cushing's disease and residual tumor postoperatively. Hypopituitarism was present at diagnosis in eight patients, all of whom had nonsecreting adenomas. Postoperatively, seven of these patients still had hypopituitarism, along with six patients with prolactinoma and one with acromegaly.

As noted above, prolactinomas were the most frequent tumors encountered in the current study (66.2%), and approximately 80% were microprolactinomas that occurred in females. The most frequent presenting symptoms in these cases were oligo or amenorrhea in two thirds of cases, followed by galactorrhea and headache in about 50% of cases each. As shown in Table 1, dopamine agonists were used in 39 of 45 patients with prolactinomas, 26 of whom did not have surgery. Of the 19 patients (12 female) who underwent surgery, nine patients had macroadenomas. Among prolactinomas, biochemical control was achieved in all but four cases, and tumor size remained stable during subsequent dopamine agonist therapy. Three of these patients had macroadenomas, two of whom were males with invasive tumors. Eight of the nine patients with acromegaly underwent surgery (one twice); long-term medical therapy with somatostatin analogs was used in four cases. Only one patient with acromegaly failed to achieve adequate long-term biochemical control; this patient was intolerant to both somatostatin analogs and pegvisomant postoperatively. Seven patients with nonsecreting adenomas underwent surgery. As noted above, one patient with Cushing's disease had persistent biochemically active disease despite surgery and therefore required radiotherapy; the patient remains hormonally controlled and without hypopituitarism at this time.

## Discussion

In this cross-sectional study, we found that verified, clinically relevant pituitary adenomas occurred with a prevalence of 1:1064 of the population, which is notably higher than previous data would suggest. This is the first cross-sectional study of pituitary adenomas to involve an intensive case-finding approach at a community level involving not only endocrinologists but also general practitioners and other medical specialists. This approach was intended to maximize the identification of relevant cases within the study districts irrespective of the site or manner in which they were followed up clinically.

Specific epidemiological studies regarding clinically active pituitary adenomas are relatively scarce. Most available in-

**TABLE 1.** Characteristics of patients with clinically active pituitary tumors in the study population

| Patient no. | District | Sex | Age at diagnosis (yr) | Duration prediagnosis (months) | Biochemical diagnosis | Max. tumor diameter (mm) |
|---|---|---|---|---|---|---|
| Prolactinomas | | | | | | |
| 1 | I | M | 19 | 12 | Increased PRL, +TRH test | 20 |
| 2 | I | F | 33 | 5 | Increased PRL, +TRH test | 3.5 |
| 3 | I | M | 61 | 36 | Increased PRL, +TRH test | 20 |
| 4 | I | F | 42 | 36 | Increased PRL, +TRH test | 15 |
| 5 | I | M | 48 | N/A | Increased PRL | 27 |
| 6 | I | F | 47 | 24 | Increased PRL, +TRH test | 6 |
| 7 | I | F | 21 | 24 | Increased PRL, ± TRH test | 6 |
| 8 | I | F | 50 | N/A | Increased PRL | 4 |
| 9 | II | M | 38 | 90 | Increased PRL, +TRH test | 7 |
| 10 | II | F | 33 | 18 | Increased PRL | N/A |
| 11 | II | F | 23 | 60 | Increased PRL, +TRH test | 8 |
| 12 | II | F | 24 | 54 | Increased PRL, +TRH test | 7.5 |
| 13 | II | F | 36 | 24 | Increased PRL, +TRH test | 5 |
| 14 | II | F | 28 | 42 | Increased PRL, +TRH test | 6 |
| 15 | II | F | 51 | 18 | Increased PRL, +TRH test | 9 |
| 16 | II | F | 24 | 36 | Increased PRL, +TRH test | 6 |
| 17 | II | M | 12 | 12 | Increased PRL, +TRH test | 8 |
| 18 | II | F | 32 | 6 | Increased PRL, +TRH test | 9 |
| 19 | II | F | 53 | N/A | Increased PRL, +TRH test | N/A |
| 20 | II | M | 31 | N/A | Increased PRL, +TRH test | 5 |
| 21 | II | F | 35 | 144 | Increased PRL, +TRH test | 10 |
| 22 | II | F | 28 | 12 | Increased PRL, +TRH test | 4 |
| 23 | II | M | 39 | 1 | Increased PRL, +TRH test | 20 |
| 24 | II | F | 54 | N/A | Increased PRL | 35 |
| 25 | II | F | 52 | 6 | Increased PRL, +TRH test | 25 |
| 26 | II | M | 54 | | Increased PRL | 5 |
| 27 | II | F | 42 | N/A | Increased PRL | N/A |
| 28 | II | F | 42 | N/A | Increased PRL | 4 |
| 29 | II | F | 21 | 12 | Increased PRL | 5 |
| 30 | II | F | 45 | N/A | Increased PRL | 4 |
| 31 | II | F | 40 | 12 | Increased PRL, +TRH test | 7 |
| 32 | III | F | 23 | 72 | Increased PRL, +TRH test | 20 |
| 33 | III | F | 26 | 12 | Increased PRL, +TRH test | 5 |
| 34 | III | F | 32 | 180 | Increased PRL, +TRH test | N/A |
| 35 | III | F | 27 | 6 | Increased PRL, +TRH test | 9 |
| 36 | III | F | 40 | 216 | Increased PRL, +TRH test | N/A |
| 37 | III | F | 26 | 1 | Increased PRL, +TRH test | 20 |
| 38 | III | F | 28 | 36 | Increased PRL, +TRH test | 5 |
| 39 | III | F | 45 | 120 | Increased PRL, +TRH test | 3 |
| 40 | III | F | 15 | N/A | Increased PRL, +TRH test | 5 |
| 41 | III | M | 30 | 12 | Increased PRL, +TRH test | 5 |
| 42 | III | F | 30 | 6 | Increased PRL, +TRH test | 4 |
| 43 | III | F | 37 | 18 | Increased PRL, +TRH test | 5 |
| 44 | III | F | 35 | N/A | Increased PRL | 3 |
| 45 | III | F | 25 | 12 | Increased PRL, +TRH test | 2 |
| Somatotropinomas | | | | | | |
| 46 | I | M | 35 | 12 | Increased IGF-I, GH, +OGTT | 11 |
| 47 | I | M | 47 | 180 | Increased GH, IGF-I, +OGTT | 13 |
| 48 | I | M | 60 | 300 | Increased GH, IGF-I | 36 |
| 49 | II | M | 19 | 60 | Increased GH, PRL, TSH, +OGTT | 15 |
| 50 | II | M | 32 | 72 | Increased GH, IGF-I, +OGTT | 30 |
| 51 | III | F | 63 | 20 | Increased GH, +OGTT | 14 |
| 52 | III | F | 17 | 36 | Increased GH, +OGTT | N/A |
| 53 | III | F | 56 | 60 | Increased GH, IGF-I, +OGTT | 28 |
| 54 | III | M | 65 | 48 | Increased GH, IGF-I, +OGTT | 15 |
| Nonsecreting adenomas | | | | | | |
| 55 | I | M | 50 | 12 | Low LH/FSH/GH, +ITT | 15 |
| 56 | I | F | 77 | 24 | Low LH/FSH, +TRH/LHRH test | 35 |
| 57 | I | M | 76 | 4 | Low LH, low Tes | 20 |
| 58 | II | F | 42 | 24 | No pituitary hormone abnormality | 5 |
| 59 | III | M | 49 | 4 | Panhypopituitarism, +TRH/LHRH test | 19 |
| 60 | III | M | 69 | 36 | High LH/FSH | 23 |
| 61 | III | M | 86 | 1 | Low LH, low IGF-I | 50 |
| 62 | III | M | 61 | 12 | Low Tes/IGF-I, +ITT | 35 |
| 63 | III | M | 62 | 24 | Low Tes | 14 |
| 64 | III | F | 41 | 120 | Low LH/FSH, low Est | 10 |
| Cushing's disease | | | | | | |
| 65 | I | F | 55 | 120 | Increased ACTH, + including 24-h dexamethasone suppression test | 5 |
| 66 | I | F | 30 | N/A | Increased ACTH, + 24 h urinary cortisol | 5 |
| 67 | II | F | 37 | 24 | Increased ACTH, + 24 h urinary cortisol | N/A |
| 68 | III | F | 36 | 24 | Increased cortisol, + 24 h urinary cortisol, + dexamethasone suppression test | 12 |

**TABLE 1.** *Continued*

| Micro/macro | Suprasellar extension | Invasion | Surgery | Radiotherapy medical therapy | Hormonal control | Tumor stable |
|---|---|---|---|---|---|---|
| Macro | Yes | Yes | TS | CAB, Tes, GH | No | Yes |
| Micro | No | No | No | CAB | Yes | Yes |
| Macro | Yes | Yes | TS | CAB, HC, Tes, GH | Yes | Yes |
| Macro | Yes | No | TS | CAB | Yes | Yes |
| Macro | No | Yes | TS | CAB | No | Yes |
| Micro | No | No | No | BR | Yes | Yes |
| Micro | No | No | TS | CAB | Yes | Yes |
| Micro | No | No | No | CAB | Yes | Yes |
| Micro | No | Yes | TS | CAB | Yes | Yes |
| Micro | No | No | No | CAB | Yes | Yes |
| Micro | No | No | TS | | Yes | Yes |
| Micro | No | No | TS | | Yes | Yes |
| Micro | No | No | TS | CAB | Yes | Yes |
| Micro | No | No | No | CAB | Yes | Yes |
| Micro | No | No | No | CAB | Yes | Yes |
| Micro | No | No | TS | | Yes | Yes |
| Micro | No | No | TS | | Yes | Yes |
| Micro | No | No | TS | CAB, Thy, HC | Yes | Yes |
| Micro | No | Yes | No | CAB | Yes | Yes |
| Micro | No | No | No | CAB | Yes | Yes |
| Macro | No | Yes | No | CAB | No | Yes |
| Micro | No | No | TS | | Yes | Yes |
| Macro | Yes | Yes | TS | CAB, Tes, GH | Yes | Yes |
| Macro | Yes | Yes | TS | Radiotherapy CAB, Thy, HC | Yes | Yes |
| Macro | Yes | No | TS | CAB | Yes | Yes |
| Micro | No | No | No | CAB | Yes | Yes |
| Micro | No | No | No | CAB | Yes | Yes |
| Micro | No | No | No | CAB | Yes | Yes |
| Micro | No | No | No | BR | Yes | Yes |
| Micro | No | No | No | CAB | Yes | Yes |
| Micro | No | No | No | CAB | Yes | Yes |
| Macro | Yes | No | No | CAB | Yes | Yes |
| Micro | No | No | TS | | Yes | Yes |
| Macro | No | No | TS | BR | Yes | Yes |
| Micro | No | No | No | CAB | Yes | Yes |
| Micro | No | No | No | BR | Yes | Yes |
| Macro | Yes | No | TS | CAB, Thy, HC, Est | Yes | Yes |
| Micro | No | No | No | CAB | Yes | Yes |
| Micro | No | No | No | CAB | Yes | Yes |
| Micro | No | No | No | CAB | Yes | Yes |
| Micro | No | No | No | CAB | Yes | Yes |
| Micro | No | No | No | BR | No | Yes |
| Micro | No | No | No | CAB | Yes | Yes |
| Micro | No | No | No | CAB | Yes | Yes |
| Micro | No | No | No | CAB | Yes | Yes |
| Macro | No | No | TS | | Yes | Yes |
| Macro | No | No | TS | LAN | Yes | Yes |
| Macro | No | Yes | TS | LAN | Yes | Yes |
| Macro | Yes | Yes | TS (× 2) | | Yes | Yes |
| Macro | Yes | Yes | No | LAN | Yes | Yes |
| Macro | No | No | TS | | No | |
| Micro | No | No | TS | Thy, Est, GH | Yes | Yes |
| Macro | Yes | Yes | TS | OCT | Yes | Yes |
| Macro | Yes | No | TS | | Yes | Yes |
| Macro | No | No | No | Thy, HC | Yes | Yes |
| Macro | Yes | Yes | TS | CAB, Thy, HC, | Yes | Yes |
| Macro | Yes | Yes | TS | | Yes | Yes |
| Micro | No | No | No | | Yes | Yes |
| Macro | Yes | No | TS | Thy, HC, Tes, GH | Yes | Yes |
| Macro | Yes | No | TS | | Yes | Yes |
| Macro | Yes | No | TS | Thy, HC | Yes | Yes |
| Macro | Yes | Yes | TS | Thy, HC, Tes, GH | Yes | Yes |
| Macro | No | Yes | No | Tes | Yes | Yes |
| Macro | Yes | No | TN | HC | Yes | Yes |
| Micro | No | No | TS | | Yes | Yes |
| Micro | No | No | TS | Radiotherapy | Yes | Yes |
| Micro | No | No | TS | | Yes | Yes |
| Macro | No | Yes | TS (× 2) | | Yes | Yes |

Data are divided as per tumor phenotype and then listed in order of study district. Biochemical control was defined as a hormonal level at which patients' symptoms were kept at bay; whereas in the case of acromegaly, patients had to have an IGF-I level in the normal range for age and sex to be considered controlled. N/A, Not available; BR, bromocriptine; CAB, cabergoline, Est, estrogen, HC, hydrocortisone, ITT, insulin tolerance test, LAN, lanreotide, OCT, octreotide, OGTT, oral glucose tolerance test, PRL, prolactin, Tes, testosterone; Thy, thyroxine; TN, transnasal; TS, transsphenoidal.

formation comes from larger cancer registries, in which data on pituitary adenomas are reported as a subgroup of all brain or central nervous system tumors. Such registry data reveal that pituitary adenomas comprise approximately 5–20% of primary central nervous system tumors, which would translate into a relatively low prevalence of pituitary adenomas (7). In contrast, data from autopsy series or MRI studies of unselected populations indicate that the presence of a pituitary tumor, irrespective of clinical correlates, is relatively common. In their recent metaanalysis, Ezzat *et al.* (2) reported that pituitary adenomas occurred with a frequency of 14.4% (range: 1–35%) and 22.5% (range: 1–40%) in pooled autopsy and radiological series, respectively. Of autopsy specimens that underwent immunohistochemical analysis, 25–41% of cells were prolactin positive, with much more infrequent staining for other pituitary hormones (0.7–4.9%).

These interesting data suggest that a proportion of cases found at autopsy may represent undiagnosed clinically relevant pituitary tumors. The metaanalytic data need to be balanced against the small size of the database from which prevalence data were derived; the autopsy population included 3375 patients, and the radiology series comprised 202 individuals. Autopsy/radiology estimates do not include clinical correlates, such as symptoms and hormonal data, whereas the current study included clinically relevant pituitary adenomas that had already been diagnosed. The study was not designed to screen for either occult pituitary adenomas with relevant, albeit undiagnosed, clinical effects or pituitary incidentalomas that lacked clinical correlates. Therefore, the current study may underestimate the true prevalence of pituitary adenomas in the general population. It remains practically difficult to estimate what proportion of incidentally discovered autopsy cases, particularly microadenomas, have objective hormonal abnormalities or significant symptomatology. We would suggest, however, that the inclusion of true incidentalomas into prevalence estimates does not aid the assessment of the clinical burden attributable to pituitary adenomas in the general population.

Current estimates of brain cancer epidemiology from the Central Brain Tumor Registry of the United States suggests a prevalence of 130.8 cases per 100,000 population (1, 8). Data from 2005 in Finland reported an even higher prevalence of primary brain tumors, with a prevalence rate of 228 cases per 100,000 (9). With respect to the Central Brain Tumor Registry of the United States data, Davis *et al.* (1) estimated that benign tumor cases constitute 97.5 cases per 100,000, a large majority of the total prevalence. These benign cases are comprised of meningiomas and other histological types in addition to pituitary adenomas, so a precise estimate of the prevalence of the latter alone is not readily feasible. The proportional incidence rates of pituitary tumors, 7.2% of primary brain tumors by site and 6.3% by histology, is not particularly helpful in estimating prevalence (8). The low associated mortality in pituitary adenomas would lead to a higher elevated prevalence rate during long-term follow-up as compared with other brain tumors that have a higher annual incidence rate but a concomitantly high 1- to 5-yr mortality rate.

As noted by Monson (10), the indolent nature of many endocrine tumors, the patterns of clinical care among various specialties, and the lack of a relationship between incidence and mortality may mitigate against obtaining accurate epidemiological data on endocrine tumors. These factors are particularly true in the case of pituitary adenomas. Historically, benign brain tumors, such as pituitary adenomas, have been underreported in cancer registries due to a lack of legally obligated reporting (1, 11). This will change in the future with greater emphasis being placed on nonmalignant tumors; in the United States, the passage of the Benign Brain Tumor Cancer Registries Amendment Act means that new cases of pituitary adenomas have been reportable since January 1, 2004 (12). It will therefore be some years before comprehensive data on pituitary adenoma incidence and prevalence are available from major cancer registries.

Few studies specifically examining the epidemiology of pituitary adenomas have been undertaken. In a study of the Stoke-on-Trent region in the United Kingdom between 1988 and 1998, Davis *et al.* (13) reported that pituitary adenomas occurred with a prevalence of 190–280 cases/million (1:3571 to 1:5263). In that study, patients investigated by an endocrinologist were included whether or not they had surgery. It is not clear, however, whether the study captured all patients with pituitary adenomas resident in the region that may have received treatment outside the geographical boundaries. Our study reported a prevalence rate of 3.4–5 times that of Davis *et al.*, and this may have been due, in part, to our being able to identify and verify patients with pituitary adenomas more completely in a more tightly controlled population. Nilsson *et al.* (3) studied incidence and mortality data in a Swedish Cancer Registry study. This study, which excluded patients with acromegaly and Cushing's disease, reported an incidence of 11 cases/million population per year during a period up to 1991. This constituted nearly a doubling in annual incidence in comparison with previous data from 1958. It is unknown whether this apparent rise in incidence was due to the advent of better diagnostic techniques or a true increase in incidence. Widespread access to both MRI and laboratory techniques may have had an important impact on the ability to diagnose pituitary adenomas that are associated with subtle signs and symptoms. Also, patients may be more likely than before to seek medical attention earlier for more insidious symptoms associated with pituitary adenomas, such as disorders of libido, sexual dysfunction, and infertility. Importantly, as therapies have improved, the life span of patients with pituitary tumors has also undoubtedly lengthened, which would tend to increase the prevalence of pituitary tumors in the population. We would suggest that the high prevalence of pituitary adenomas seen in the current study may be due to such a combination of these factors.

As compared with large cancer registries that assess data on millions of patients, the current study population may appear limited in size. However, the aim of the study was to identify pituitary tumors in alliance with community medical practitioners and report on only those with verifiable hormonal, radiological, and clinical profiles. We undertook an intensive process of identifying, recruiting, and informing the entirety of the medical population of the chosen study sites, followed by a similar process of identifying, validating, and recruiting potential patients. Given these requirements and the parallel process of data validation in all cases, a

population of approximately 72,000 approached the maximum feasible for an academic cross-sectional study. Further confirmation of these results will require international cooperative efforts using new or existing data-gathering and epidemiological tools.

We considered the question of clustering of cases within the study regions and the effect that might have on our estimates. Few or no data exist on the potential impact of race, socioeconomic status, age, and environmental factors on the development of pituitary adenomas. We did, however, verify that known inherited factors did not influence the data, using a combination of family history data and genetic studies (14). Only one patient, a female with a relatively treatment-resistant macroprolactinoma, had MEN1, and this was a sporadic case with no other relatives forming part of the study population. Carney's complex is very rare and was not a feature of the patients with somatotropinomas. Of potentially greater relevance is the syndrome of FIPA, which may be linked to mutations in the aryl hydrocarbon receptor interacting protein (6, 15). The patients included in the current study did not have known relatives with a diagnosis of pituitary tumors, making the influence of FIPA in this population unlikely. The role of specific environmental factors such as carcinogen exposure in the etiology of pituitary adenomas requires further assessment, particularly because the aryl hydrocarbon receptor, for which aryl hydrocarbon receptor interacting protein is a ligand, mediates cell responses to toxins such as dioxin (16).

In the current study, prolactinomas comprised 66% of the entire series, of which the majority were microadenomas in female patients (80%) that presented classically with either oligo/amenorrhea, galactorrhea, or headache. This is in keeping with previous data from surgical series and immunohistochemical studies of autopsy data (13, 17, 18). Despite the fact that the majority of prolactinomas were small, the attendant use of health care resources appears sizable, given the performance of multiple MRI/CT scans, dynamic pituitary function tests, and the frequent requirement for medical or surgical therapy. The management of other tumor types requires even greater resource use than for prolactinomas. High health care resource use in the setting of a much increased prevalence of pituitary adenomas represents an important issue for calculating medical and research budgets, although confirmation in formal pharmacoeconomic studies is required.

In conclusion, the current cross-sectional study indicates that clinically active pituitary adenomas occur relatively frequently in the general population. In contrast to autopsy and radiological studies, the current study included only patients that had a previous definitive diagnosis of a pituitary adenoma. The historical lack of mandatory reporting of benign brain tumors may have led to an underestimation of the prevalence of pituitary adenomas in large cancer registries. In the absence of registry data, larger cooperative studies using a similar intensive case finding approach to ours and involving diverse population samples from multiple centers could help to provide further information on the true prevalence of pituitary adenomas internationally.

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Address all correspondence and requests for reprints to: Professor Albert Beckers, M.D., Ph.D., Department of Endocrinology, Centre Hospitalier Universitaire de Liège, Domaine Universitaire du Sart Tilman, 4000 Liège, Belgium. E-mail: albert.beckers@chu.ulg.ac.be.

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