The Prevalence of Pituitary Adenomas

A Systematic Review

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The primary authors, as principal investigators of the study, had full access to all the data and take responsibility for the integrity of those data and the accuracy of the analysis. The study was conceived and designed by Drs. Ezzat, Asa, and Vance. Data were acquired by Drs. Ezzat, Asa, Couldwell, and McCutcheon. Dr. Ezzat was responsible for drafting the article. . Dr. Barr and Mr. Dodge provided statistical expertise. Funding was obtained by Drs. Ezzat and Asa. The study was supervised by Dr. Ezzat.

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BACKGROUND. Pituitary adenomas display an array of hormonal and proliferative activity. Once primarily classified according to size (microadenomas, < 1 cm; macroadenomas, ≥ 1 cm), these tumors are now further classified according to immunohistochemistry and functional status. With these additional classifications in mind, the goals of the current study were to determine the prevalence of pituitary adenomas and to explore the clinical relevance of the findings.

METHODS. The authors conducted a metaanalysis of all existing English-language articles in MEDLINE. They used the search string (pituitary adenoma or pituitary tumor) and prevalence and selected relevant autopsy and imaging evaluation studies for inclusion.

RESULTS. The authors found an overall estimated prevalence of pituitary adenomas of 16.7% (14.4% in autopsy studies and 22.5% in radiologic studies).

CONCLUSIONS. Given the high frequency of pituitary adenomas and their potential for causing clinical pathologies, the findings of the current study suggest that early diagnosis and treatment of pituitary adenomas should have far-reaching benefits. ***Cancer* 2004;101:613–9.** © *2004 American Cancer Society.*

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Pituitary adenomas are a diverse group of tumors arising from the pituitary gland. Historically, these tumors have been classified according to size and divided into microadenomas (dimension < 1 cm) and macroadenomas (dimension ≥ 1 cm). However, this classification has now been augmented by a more comprehensive system based on immunohistochemistry and electron microscopy.[1] Pituitary adenomas can be classified further as functional or nonfunctional, depending on their hormonal activity in vivo. Small, slow-growing, hormonally inactive lesions are typically identified as incidental findings on radiologic or postmortem examinations, whereas small, slow-growing lesions with excess hormonal activity can manifest as a clinical syndrome. Tumors that grow more rapidly, even if they are hormonally inactive, are capable of producing symptoms of an intracranial mass, such as visual field disturbances.[2]

Given the small size of many pituitary tumors and their propensity to exist without symptoms or with only insidious, nonspecific symptoms, it is a challenge to accurately measure the prevalence of pituitary adenomas in the general population. Histologic analysis of autopsy specimens and radiologic (computed tomography [CT] and magnetic resonance imaging [MRI]) data from patients being treated or studied for conditions related and unrelated to pituitary disease are the two principal methods that have been used to estimate the population prevalence of pituitary adenomas. Many studies have been

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performed using these two approaches to define the prevalence of pituitary adenomas. However, both methods have generated estimates ranging from < 1% to > 30%.[3,4] To obtain the best possible estimate of the true prevalence of pituitary adenomas in the general population, we conducted a systematic review of published studies that used either imaging or histologic methods to estimate the prevalence of pituitary tumors. To overcome interstudy variation and lack of homogeneity between studies, we used a random-effects model to estimate population prevalence.[5] This approach uses an inverse weighting algorithm in which the weights are estimated from the study variance.[5]

MATERIALS AND METHODS

Data Sources

Relevant articles were identified through a MEDLINE search conducted on November 15, 2000, with no beginning data limit imposed. The search terms used were "pituitary adenoma" or "pituitary tumor" and "prevalence." Bibliographies from articles identified in the search also were studies. Only English-language articles were selected. Using these criteria, 33 candidate articles were identified for potential inclusion in the current study.

Study Selection

Articles that assessed the prevalence of pituitary adenomas using postmortem or radiographic techniques were selected for inclusion if a detailed methodology for the determination of the presence of pituitary adenomas was provided. This included specification of the thickness of pituitary slices and of the spacing of samples in postmortem examinations, the imaging technique used in imaging studies with particular attention to the distance between slices, and the imaging aspect used (coronal, sagittal, or both). This information was considered vital so that studies performed using similar techniques could be grouped together. Twenty of the 33 studies originally identified were eliminated from evaluation because of study design (i.e., epidemiologic study) or poorly detailed methodology. Thus, 13 studies were identified for detailed data extraction and review.

Data Extraction

The published articles were reviewed for study design and for the technique used to determine the presence or absence of an adenoma, including the level of precision used. The latter was determined by capturing data regarding the thickness of slices for postmortem specimens or imaging studies and by determining whether contrast media were used (for imaging studies). Three clinicians experienced in the management of pituitary disorders reviewed selected articles using a standard form to extract specific data. The rate of adenoma development in patients was recorded. Each reviewer independently recorded parameters that could possibly influence prevalence estimates, including the number of postmortem specimens or imaging studies examined; number of tumors, or the prevalence, methodology, and immunohistochemistry results. Data concerning these three parameters were analyzed separately for each type of study. All reviewers compared their findings and any differences were resolved by consensus. There was also provision to record the results of immunocytochemical testing for prolactin (PRL), growth hormone (GH), adrenocorticotropic hormone (ACTH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), and follicle-stimulating hormone.

Statistical Methods

Our goals were to integrate the review studies and to derive the most reliable estimate of the prevalence of pituitary adenoma possible. For all studies, the mean prevalence of pituitary adenomas was extracted and the mean variance was calculated assuming a binomial distribution. Initially, the prevalence estimate and 95% confidence interval (95% CI) were plotted by study. Examination of these plots indicated that the thickness of the tissue slice was inversely correlated with the estimate of adenoma prevalence. For example, a smaller thickness of slice led to a higher prevalence estimate regardless of whether the histologic or radiologic methodologies were used in the study. The use of two methodologies was deemed important. We chose to estimate the prevalence of adenoma within these two methodologies and over all the studies regardless of methodology.

A metaanalysis approach was used to integrate the selected research studies and to estimate the prevalence of pituitary adenomas. These studies, although addressing the same research question, used different methodologies with high interstudy variation. This led us to use a random-effects model to estimate the population prevalence. The selected research study analyses were coded and analyzed using the methods defined by Laird and Mosteller.[5] This method uses an inverse weighting algorithm in which the weights are estimated from the study variance.

RESULTS

Study Inclusion

Data analysis established a high degree of correlation among the reviewers. For example, only one reviewer disagreed on one parameter of a single study. This

TABLE 1
Studies Selected for Metaanalysis

No.	Study (year)/reference	No. of patients	Method	Study objective
1	Yue et al., 1997[6]	3672	MRI, 5-mm–thick sections, no gaps, no contrast media	To describe and determine the prevalence of incidental findings in patients who underwent MRI as part of a cardiovascular health study
2	Hall et al., 1994[7]	100 volunteers	MRI (3-mm–thick sections)	To determine the prevalence of focal lesions of the pituitary gland that suggest the presence of a pituitary adenoma in asymptomatic volunteers
3	Chong et al., 1994[8]	52 (unselected)	MRI (3-mm–thick sections were imaged with a section gap of 0.5 mm)	To determine the frequency of incidental microadenomas
4	Chambers et al., 1982[4]	50	High-resolution CT	To investigate the incidence of low-density regions in the contrast-enhanced pituitary based on the supposition that these can be caused by abnormalities other than microadenomas
5	Nammour et al., 1997[3]	3550 (unselected)	CT (typically slices of 1-cm thickness having 1–14 cuts)	To determine the prevalence of incidental pituitary macroadenoma
6	Muhr et al., 1981[9]	205 (unselected)	Autopsy (5-μm–thick sections with 0.4-mm interval between sections)	To examine the extent to which minor changes or variations in the configuration and cortical layer the sella turcica correlate with microadenoma
7	Teramoto et al., 1994[10]	1000 (unselected)	Autopsy (1–1.5-mm slices)	To study the prevalence of incidental pituitary lesions, especially those $>$ 2 mm
8	Burrow et al., 1981[11]	120 (unselected)	Autopsy (1-mm–thick sections)	To study the natural history of microadenomas
9	Costello, 1936[12]	1000 (unselected)	Autopsy (1 to 1.5-mm–thick slices)	To determine the frequency of incidental microadenomas
10	Parent et al., 1981[13]	500 (unselected)	Autopsy (3-mm–thick sections in most cases)	To study the incidence of microadenoma
11	Siqueira and Guembarovski, 1984[14]	450 (unselected)	Autopsy (1 to 1.5-mm–thick slices)	To study the incidence of adenomos in supposedly normal pituitary glands
12	Tomita and Gates, 1999[15]	100 (unselected)	Autopsy (1.5-mm–thick serial sections)	To investigate the effect of sample processing on the incidence of pituitary adenoma
13	McComb et al., 1983[16]	100 (selected)	Autopsy (0.4 to 0.6-mm–thick sections)	To analyze 107 incidental adenomas by histologic and immunohistochemical techniques

CT: computed tomographic scan; MRI: magnetic resonance imaging scan; MR, magnetic resonance.

disagreement was resolved by consensus. This indicated that accurate and consistent information was being extracted from the articles.

We initially identified 13 studies for inclusion in our metaanalysis. Data from these studies (five based on radiologic data and eight based on postmortem data) are presented in Table 1.[3,4,6–16] Two of the five imaging studies using an MRI scan protocol involving coronal sections with a maximum distance of 3 mm between sellar sections were included in the meta-analysis because the methodology was sufficiently sensitive to detect microadenomas.[7,8]

Of the 13 studies, 3 were excluded from further analysis. The study by McComb et al.[16] was excluded because of an unusually high incidence of hyperplasia, which made the criteria questionable for the definition of adenoma. Two radiographic studies[3,6] were removed from the analysis because the imaging technique used was not sufficiently precise to detect microadenomas. Specifically, coronal imaging was not conducted and there was a wide (5-mm or 10-mm) distance between sections. However, these same studies[3,6] involved a large number of patients (n = 3550 and n = 3672, respectively) and were considered sufficiently sensitive to provide reliable estimates of macroadenoma ($\geq$ 1 cm) prevalence. Therefore, 10 studies (3 radiographic and 7 postmortem) were used in the final analysis.

Prevalence of Pituitary Adenomas

There was a wide range in prevalence estimates in individual studies from just $>$ 1% to nearly 40% in the imaging studies and from approximately 1% to 35% in the postmortem studies. An incidence rate of 35% was extracted from the study by Burrow et al.[11] However, this number represents the total number of adenomas (43 in 120 patients) rather than the number of pituitaries with adenomas (32 in 120 patients). The estimated prevalence of pituitary adenoma across all postmortem studies was 14.4% compared with 22.5%

TABLE 2
Restricted Maximum Likelihood Method Estimated Prevalence of Pituitary Adenomas

No.	Study (year)/reference	No. of patients	Prevalence	Variance	95% Confidence interval
Autopsy studies					
6	Muhr et al., 1981[9]	205	0.015	0.00007	−0.0018
7	Teramoto et al., 1994[10]	1000	0.031	0.00003	0.0203
8	Burrow et al., 1981[11]	120	0.350	0.00190	0.2647
9	Costello, 1936[12]	1000	0.225	0.00017	0.1991
10	Parent et al., 1981[13]	500	0.840	0.00015	0.0597
11	Siqueira and Guembarovski, 1984[14]	450	0.800	0.00016	0.0549
12	Tomita and Gates, 1999[15]	100	0.240	0.00182	0.1563
Autopsy overall			0.144	0.00192	0.0585
Imaging studies					
2	Hall et al., 1994[7]	100	0.100	0.00090	0.0412
4	Chambers et al., 1982[4]	52	0.385	0.00046	0.2524
3	Chong et al., 1994[8]	50	0.200	0.00320	0.0891
Radiographic overall			0.223	0.00456	0.0915
All studies			0.167	0.00148	0.0915

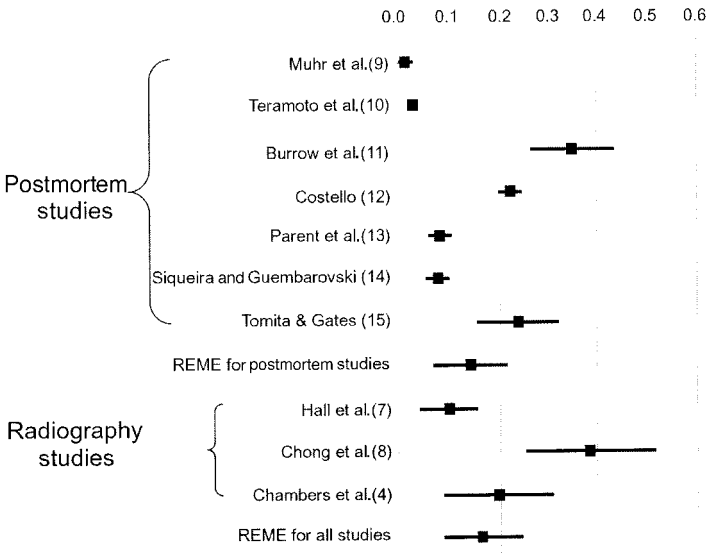

FIGURE 1. Prevalence of pituitary adenomas. The numbers in parentheses adjacent to the author names are those assigned for the purposes of meta-analysis. REME: random effects model estimate.

in radiography studies. The overall estimated prevalence of pituitary adenomas across both groups of studies was 16.7% (Table 2) (Fig. 1).[4,7–15] In addition, the 2 studies that evaluated the prevalence of macroadenomas in the population yielded a prevalence rate of 0.16–0.20%.[3,6]

Immunohistochemical staining revealed PRL-producing cells in 25–41% of tumor specimens.[9,11] Tumors producing other anterior pituitary hormones, such as GH and ACTH, also were observed but were considerably less common than PRL-producing tumors (Table 3).[9–11,15,16] In 1 study, premortem serum PRL concentrations were greater in patients in whom prolactinomas were identified postmortem (37 ng/mL vs. 19 ng/mL).[11]

DISCUSSION

The current metaanalysis estimated the prevalence rate of pituitary adenomas to be 16.7%. Separate analyses of postmortem and radiologic data produced estimated prevalence rates of 14.4% and 22.5%, respectively. These figures indicate that pituitary tumors are fairly common in the general population. With macroadenomas occurring at a rate of 1 in 600 persons, there also are likely many persons with unrecognized macroadenomas.

Epidemiologic, postmortem, and radiologic studies have been used to estimate the prevalence of pituitary adenomas. However, epidemiologic studies are limited by their dependence on population-specific

TABLE 3
Results of Immunohistochemical Testing for Pituitary Hormones in Autopsy Studies

No.	Study (year)/reference	No. of specimens available for staining	Prolactin	GH	ACTH	LH	TSH
8	Burrow et al., 1981[11]	39	16	NT	NT	NT	NT
13	McComb et al., 1983[16]	107[a]	45	2	4	1	1
6	Muhr et al., 1981[9]	4	1	0	2	NT	NT
7	Teramoto et al., 1984[10]	20	6	0	0	0	0
12	Tomita and Gates, 1999[15]	11*	10	2	1	1	0

ACTH: adrenocorticotropic hormone; FSH: follicle-stimulating hormone; GH: growth hormone; LH: luteinizing hormone; NT: not tested; TSH: thyroid-stimulating hormone.

[a] Some tumors stained positively for more than one hormone.

registries, which subject them to bias from regional influences such as diagnostic practices, reporting patterns, and case definitions. Moreover, the clinical usefulness of epidemiologic studies is limited because their dependence on clinical diagnosis to identify pituitary adenomas results in the exclusion of silent or incidental tumors from analysis. Although generally considered benign, these adenomas can have considerable compressive mass effects, endocrine manifestations with serious morbidity, or both. In contrast with epidemiologic studies, postmortem and radiologic studies are not registry dependent. Therefore, they avoid population bias by selecting subjects from across regions. To determine an accurate estimate of the prevalence of pituitary adenomas based on a broad cross-section of the population, the current analysis was based on both postmortem and radiographic studies.

Histologic examination of the pituitary gland at autopsy is acknowledged to be considerably more sensitive than contrast-enhanced MRI scans for detecting pituitary adenomas.[7] However, autopsy series generally are not reflective of the general population because young adults are generally underrepresented. Moreover, age distribution was not always provided in the postmortem studies examined in this metaanalysis. In those studies that did present these data, a clear bias existed toward patient age ($>$ 50 years) and patient gender (generally fewer women than men). Women $<$ 50 years of age tended to be underrepresented.[9,13,14]

Investigations based on postmortem data included in the current metaanalysis revealed no association between prevalence estimates and the methodology used. The study using the finest resolution (glands were serially cut in 5-μm–thick sections, with an interval between sections of 400 μm) identified not only 4 adenomas but also 18 cysts in 205 pituitary glands. There was no correlation noted between the symmetry of the gland and the presence of adenoma in this study.[9] The autopsy study that identified the highest incidence of adenoma had the specific aim of detecting microadenomas and the authors paid particular attention to the sectioning of the pituitary gland for this purpose.[11] Although both of these studies included relatively few samples, higher sampling rates observed in other studies were not associated with more consistent results. Two studies that included 1000 tissue samples, each analyzed at a similar resolution, produced widely disparate prevalence rates.[10,12] The difference noted in these prevalence rates was most likely due to the difference in the definition of adenoma, with only one study identifying small cell nests as pituitary adenoma.[10]

Immunohistochemical staining of tissue samples was performed in approximately one-half of the autopsy studies. The use of immunohistochemical characteristics rather than conventional staining procedures to classify tumors provides better information on hormone content, endocrine function, and cellular derivation.[16] Our study found prolactinomas to be the most common form of pituitary adenoma. Burrow et al.[11] also documented premortem serum prolactin concentrations and showed them to be higher in patients in whom prolactinomas were identified at postmortem examination. This is an important observation because it provides evidence that the high prevalence of small adenomas (mean size of 1 mm) observed in many studies may be clinically significant. Modest elevations of PRL concentration, in the range observed in the current study, have the potential to result in hypogonadism. This can result in symptoms of diminished libido, potency, and fertility in both men and women.

The results from McComb et al.,[16] a study that was excluded from our analysis because of differences in the definition of adenoma, echo these results with findings of PRL-containing tumors in 45 of 107 pa-

tients with tumors (42%). The relative percentages of hormonal production identified by immunohistochemistry are 43% for PRL, 2.8% for GH, 4.9% for ACTH, 1.4% for LH, and 0.7% for TSH. The results of the study by McComb et al. generally paralleled the findings in the current study, with 4 (3.7%) adenoma specimens containing ACTH, 1 specimen (0.9%) containing TSH, 1 specimen (0.9%) containing LH, and 2 specimens (1.8%) containing PRL and GH.[16]

It is common to consider small, incidentally discovered lesions in the pituitary gland to be clinically insignificant. However, multiple lines of evidence indicate that small lesions within the pituitary gland may be clinically significant. For example, sensitive MRI scan techniques do not detect demonstrable tumors in approximately 40% of patients with active Cushing disease, a well recognized condition with serious comorbidities.[17] Moreover, hypopituitarism has recently been reported to occur at an estimated frequency of 4.21 cases/100,000 (95% CI, 2.95–5.47) in the absence of large pituitary lesions,[18] which further suggests the potential for the functional relevance of small pituitary lesions.

An MRI scan is considered the imaging modality of choice for the diagnosis of pituitary disorders because of its multiplanar capability and its good soft tissue contrast. Sagittal T1-weighted images clearly display the anterior and posterior lobes and the stalk on the same plane and coronal images show the relation between the pituitary and cavernous sinuses and are optimal for identifying a pituitary adenoma. A thin slice (3 mm) generally is used to obtain optimal resolution.[19] A CT scan is also a useful diagnostic tool. Coronal scans provide the optimal view.[4] However, CT scans appear to be less sensitive than MRI scans in this application.[7] For each imaging technique, a focal hypointensity within the pituitary gland is considered abnormal and suggestive of an adenoma. Although other lesions (such as pars intermedia cysts, metastases, infarctions, epidermoid cysts, and abscesses) also appear on MRI scans as areas of low-signal intensity, surgical intervention frequently confirms the presence of an adenoma at the site of a focal hypointense area. In 1 study, blinded analysis of MRI scans from patients with surgically confirmed pituitary adenomas (manifesting as Cushing disease) predicted the presence and location of the tumor in 86% of cases.[7] Importantly, minor radiographic changes such as asymmetry in the sellar floor, previously believed to be indicative of pituitary adenoma, have been shown not to correlate with the presence of a tumor.[7,9]

Although the current metaanalysis was based on postmortem or imaging studies, it is interesting to reflect on the findings from three epidemiologic studies to reinforce the clinical relevance of the current study findings. In a descriptive epidemiologic study of primary brain and central nervous system (CNS) tumors from the Central Brain Tumor Registry of the United States (CBTRUS) from 1990–1994, Surawicz et al.[20] evaluated data concerning 20,765 tumors located in the brain, meninges, and other CNS sites, including the pituitary gland. They found that pituitary tumors accounted for 9.1% of all brain and CNS tumors, occurring at an incidence rate of 8 per 100,000 person-years.[20] In the most recent report from the CBTRUS, which provides population-based incidence rate data concerning all brain tumors, pituitary tumors accounted for 6.6% of primary brain and CNS tumors by histology (n = 37,788).[21]

In another epidemiologic study of pituitary adenomas, Nilsson et al.[22] evaluated the records of 2279 of 3321 patients with pituitary adenomas in the Swedish Cancer Registry between 1958 and 1991. They found that in the 33-year study period, the annual incidence of pituitary adenoma increased from approximately 6 per million to 11 per million, with a significant increase in overall mortality noted in patients with pituitary adenomas, primarily as a result of cardiovascular disease. The authors suggested that improperly treated or untreated GH deficiency may account for the increase in mortality due to cardiovascular disease. A third epidemiologic study specifically examined the incidence and prevalence of hypopituitarism using two cross-sectional surveys (the first from January–December 1992 and the second from January–December 1999) and a longitudinal survey (from January 1993 to December 1999).[18] The second survey demonstrated that 61% of hypopituitary cases were caused by pituitary tumors and 9% by nonpituitary tumors. The study also showed that patients with hypopituitarism secondary to tumor or its treatment were more likely to have GH deficiency than those with nontumor-related hypopituitarism. Echoing the concerns of Nilsson et al.,[22] Regal et al.[18] suggested that the mortality rate, especially from atherosclerosis, is increased among adults with hypopituitarism receiving conventional pituitary hormone replacement other than GH and that lipid abnormalities, in addition to bone and muscle strength abnormalities, may be restored by the administration of GH.

These studies demonstrate the potentially significant effects of pituitary adenomas and indicate that a substantial portion of the population may have clinically relevant pituitary adenomas. However, these studies do not reflect the entire scope of the problem because they do not include clinically silent tumors that are only detected with imaging or at postmortem examination. Many of these incidental tumors pro-

duce at least one hormone and their long-term consequences on the endocrine system are not clear. The current study found the prevalence of pituitary adenomas to be approximately 17%. This finding emphasizes the high frequency of pituitary adenoma. Given their potentially serious effects, the findings of the current study suggest that the improved diagnosis and treatment of pituitary adenomas should have far-reaching benefits.

REFERENCES

1. Asa SL. Tumors of the pituitary gland. In: Rosai J, editor. Atlas of tumor pathology. 3rd series Fascicle 22. Washington, DC: Armed Forces Institute of Pathology, 1998:1–214.
2. Asa SL, Ezzat S. The pathogenesis of pituitary tumors. *Nat Rev Cancer*. 2002;2:836–849.
3. Nammour GM, Ybarra J, Naheedy MH, Romeo JH, Aron DC. Incidental pituitary macroadenoma: a population-based study. *Am J Med Sci*. 1997;314:287–291.
4. Chambers EF, Turski PA, LaMasters D, Newton TH. Regions of low density in the contrast-enhanced pituitary gland: normal and pathologic processes. *Radiology*. 1982;144:109–113.
5. Laird NM, Mosteller F. Some statistical methods for combining experimental results. *Int J Technol Assess Health Care*. 1990;6:5–30.
6. Yue NC, Longstreth WT Jr., Elster AD, Jungreis CA, O'Leary DH, Poirier VC. Clinically serious abnormalities found incidentally at MR imaging of the brain: data from the cardiovascular health study. *Radiology*. 1997;202:41–46.
7. Hall WA, Luciano MG, Doppman JL, Patronas NJ, Oldfield EH. Pituitary magnetic resonance imaging in normal human volunteers: occult adenomas in the general population. *Ann Intern Med*. 1994;120:817–820.
8. Chong BW, Kucharczyk W, Singer W, George S. Pituitary gland MR: a comparative study of healthy volunteers and patients with microadenomas. *Am J Neuroradiol*. 1994;15:675–679.
9. Muhr C, Bergstrom K, Grimelius L, Larsson SG. A parallel study of the roentgen anatomy of the sella turcica and the histopathology of the pituitary gland in 205 autopsy specimens. *Neuroradiology*. 1981;21:55–65.
10. Teramoto A, Hirakawa K, Sanno N, Osamura Y. Incidental pituitary lesions in 1,000 unselected autopsy specimens. *Radiology*. 1994;193:161–164.
11. Burrow GN, Wortzman G, Rewcastle NB, Holgate RC, Kovacs K. Microadenomas of the pituitary and abnormal sellar tomograms in an unselected autopsy series. *N Engl J Med*. 1981;304:156–158.
12. Costello RT. Subclinical adenoma of the pituitary gland. *Am J Pathol*. 1936;12:205–214.
13. Parent AD, Bebin J, Smith RR. Incidental pituitary adenomas. *J Neurosurg*. 1981;54:228–231.
14. Siqueira MG, Guembarovski AL. Subclinical pituitary microadenomas. *Surg Neurol*. 1984;22:134–140.
15. Tomita T, Gates E. Pituitary adenomas and granular cell tumors: incidence, cell type, and location of tumor in 100 pituitary glands at autopsy. *Am J Clin Pathol*. 1999;111:817–825.
16. McComb DJ, Ryan N, Horvath E, Kovacs K. Subclinical adenomas of the human pituitary. New light on old problems. *Arch Pathol Lab Med*. 1983;107:488–491.
17. Watson JC, Shawker TH, Nieman LK, DeVroom HL, Doppman JL, Oldfield EH. Localization of pituitary adenomas by using intraoperative ultrasound in patients with Cushing's disease and no demonstrable pituitary tumor on magnetic resonance imaging. *J Neurosurg*. 1998;89:927–932.
18. Regal M, Paramo C, Sierra SM, Garcia-Mayor RV. Prevalence and incidence of hypopituitarism in an adult Caucasian population in northwestern Spain. *Clin Endocrinol (Oxf)*. 2001;55:735–740.
19. Elster AD. Modern imaging of the pituitary. *Radiology*. 1993;187:1–14.
20. Surawicz TS, McCarthy BJ, Kupelian V, Jukich PJ, Bruner JM, Davis FG. Descriptive epidemiology of primary brain and CNS tumors: results from the central brain tumor registry of the United States, 1990-1994. *Neuro-oncol*. 1999;1:14–25.
21. CBTRUS (2002–2003). Statistical Report: Primary Brain Tumors in the United States, 1995–1999. Hinsdale, IL: Central Brain Tumor Registry of the United States, 2002.
22. Nilsson B, Gustavasson-Kadaka E, Bengtsson BA, Jonsson B. Pituitary adenomas in Sweden between 1958 and 1991: incidence, survival, and mortality. *J Clin Endocrinol Metab*. 2000;85:1420–1425.