# Natural History of Nonfunctioning Pituitary Adenomas and Incidentalomas: A Systematic Review and Metaanalysis

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**Context:** The natural history of pituitary incidentalomas (PIs) and nonfunctioning pituitary adenomas (NFPAs) remains poorly understood.

**Objective:** The objective of the study was to synthesize the literature on the prognostic factors involved in the progression of PIs and NFPAs in patients followed up conservatively.

**Data Sources:** We searched MEDLINE, EMBASE, and Cochrane CENTRAL. We sought to identify further studies by reviewing the reference lists from selected studies and reviews and by querying experts.

**Study Selection:** Eligible studies were longitudinal observational cohort studies that enrolled patients with PIs/NFPAs and followed them up without any treatment from the time of detection and reported on mortality, lesion progression, and development of pituitary hormonal deficiency, apoplexy, or visual field defects.

**Data Extraction:** Reviewers working independently and in duplicate determined studies' eligibility and collected descriptive, methodological quality, and outcome data. Event rates per 100 person-years (PYs) and associated 95% confidence intervals (CIs) were estimated from each study and pooled using the random-effects model.

**Data Synthesis:** The 11 included studies had noncomparative single-cohort design. Follow-up duration ranged from 3 to 15 yr. There was a greater tendency for tumor growth in macroadenomas (12.5 per 100 PYs; 95% CI 7.9, 17.2) and in solid lesions (5.7 per 100 PYs; 95% CI 2.3, 9.2) in comparison with microadenomas (3.3 per 100 PYs; 95% CI 2.1, 4.5) and cystic lesions (0.05 per 100 PYs; 95% CI 0.0, 0.2). The development of pituitary apoplexy and worsening of visual field defects were rare. The overall incidence of new endocrine dysfunction was 2.4 per 100 PYs; 95% CI 0.0, 6.4. The majority of these analyses were associated with significant heterogeneity. There was a trend that did not reach statistical significance for greater incidence of pituitary apoplexy and new endocrine dysfunction worsening in macroadenomas compared with microadenomas. The quality of the evidence (risk of bias) was very low due to heterogeneity, methodological limitations, and imprecision caused by the small number of events.

**Conclusions:** Despite the relatively high prevalence of PIs/NFPAs, the evidence on the natural history of these entities is scarce and of low quality. PIs/NFPAs seem to have fairly rare complications that may be more common when lesions are large (>10 mm) and solid. **(*J Clin Endocrinol Metab* 96: 905–912, 2011)**

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Abbreviations: CI, Confidence interval; CT, computerized tomography; MRI, magnetic resonance imaging; NFPA, nonfunctioning pituitary adenoma; PI, pituitary incidentaloma; PY, person-year.

The wide use of diagnostic imaging techniques in the last 30 yr such as magnetic resonance imaging (MRI) and computerized tomography (CT) has led to a substantial increase in the frequency of incidental findings, including masses in the pituitary gland. Pituitary adenomas are usually benign monoclonal neoplasms caused by a mixture of pituicyte alterations in combination with an altered endocrine and paracrine regulatory milieu (1). Pituitary incidentalomas (PIs) are defined as asymptomatic and incidentally discovered pituitary adenomas or sellar lesions. On the other hand, nonfunctioning pituitary adenomas (NFPAs) are pituitary tumors that do not demonstrate hormonal hyperproduction but can exert a mass effect that leads to visual field defects and may progress to hypopituitarism.

Pituitary adenomas are likely quite common, although an accurate estimate of their prevalence is not available. The prevalence of clinically significant adenomas that present to medical attention as determined in cross-sectional community-based studies ranges from 78 to 94 cases per 100, 000 inhabitants (2, 3). The proportion of these cases that are true incidentalomas or NFPAs is unclear. Case series have documented that 68% of adenomas are macroadenomas in contrast with the exceptionality of this finding in autopsy or MRI studies (4–8). These studies also suggest that up to 10% of microadenomas and 20% of macroadenomas grow significantly during follow-up.

Thus, PIs constitute an increasingly common clinical problem with unclear natural history. To our knowledge, despite the high prevalence of this finding, there is no systematic review summarizing the evidence regarding the prognosis of these lesions. Knowledge of the natural history and prognostic factors associated with poor outcomes of PIs would help formulate clinical practice guidelines. The Endocrine Society Task Force on the management of PIs commissioned the conduct of this review. The focus of this report is on PIs, although in some studies patients were described as having a combination of PIs and NFPAs, and differentiation between the two was not feasible. Therefore, throughout this report we will use the term PIs/NFPAs.

## Patients and Methods

We developed a systematic review protocol with the input from the expert members of the commissioning task force from The Endocrine Society. This report adheres to the reporting guidelines of systematic reviews (Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Metaanalysis Of Observational Studies in Epidemiology) (9, 10).

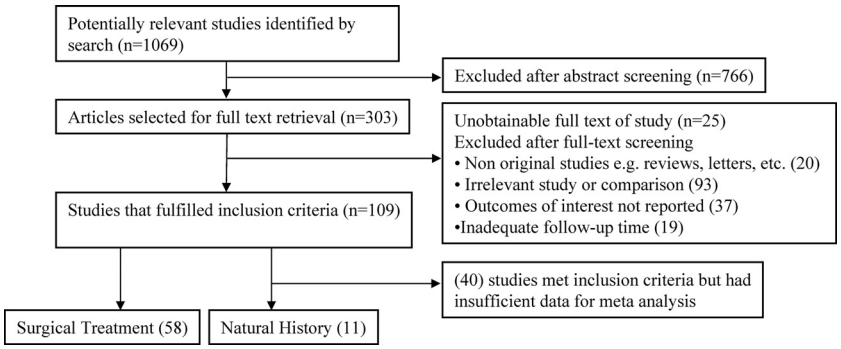


**FIG. 1.** Study selection process.

### Eligibility criteria

Eligible studies were longitudinal observational cohort studies that enrolled patients with PIs/NFPAs and followed them up without any treatment from the time of detection. The outcomes of interest in this systematic review are change in size; development of visual field defects, neurological deficits, alteration of pituitary function, pituitary apoplexy, and mortality. We excluded case reports or cross-sectional studies with no longitudinal follow-up and those with follow-up less than 1 yr.

### Study identification

An expert reference librarian (P.J.E.) conducted the electronic search with input from study investigators with expertise in systematic reviews (V.M.M. and M.H.M.). We searched MEDLINE, EMBASE, and Cochrane CENTRAL electronic databases from 1966 through February 2009. The detailed strategy is available in the Supplemental Appendix, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org. To identify additional candidate studies, we reviewed the reference lists of the eligible primary studies, narrative reviews, and systematic reviews; and we queried the expert members of the commissioning task force.

### Study selection

Working independently and in duplicate, reviewers screened all abstracts and titles. After obtaining all potentially eligible studies in full text, these reviewers, again working independently and in duplicate, determined eligibility with acceptable chance-adjusted agreement (mean $\kappa = 0.80$). Disagreements were resolved by consensus or arbitration.

### Data collection

Using a standardized, piloted, and web-based data extraction form and working in duplicate, we abstracted the following descriptive data from each study: description of study characteristics and participants (age, sex, hormonal and visual function at baseline, percentage of macroadenomas, geographical origin,

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**TABLE 1.** Description of the included studies

| Author, year | Patients | Age | Sex (% male) | At baseline | | |
|---|---|---|---|---|---|---|
| | | | | Patients with hormonal function (%) | Patients with visual field defects (%) | Other complaints |
| Arita *et al.*, 2006 (21) | 42 patients with incidentally found NFPAs | 61.0 ± 10.4 yr | 43% | None | None | 31% headache |
| Baker *et al.*, 2003 (24) | 27 patients with incidentally found pituitary tumors | Mean 45.6 ± 27.2 (5 months to 84 yr) | 44% | None | None | 55.6% headache |
| Dekkers *et al.*, 2007 (19) | 28 patients with nonfunctioning macroadenomas, not treated after initial diagnosis | 55 ± 3 yr | NR | 44% pituitary deficiency; 14% panhypopituitarism | 14% | 14% apoplexy; 7% chronic headache |
| Donovan and Corenblum, 1995 (4) | 31 adult patients with PI followed up conservatively | Median 33 yr; range 6–58 yr | 35% | N cortisol response to ITT | NR | NR |
| Fainstein Day *et al.*, 2004 (22) | 46 patients with incidentally found pituitary tumors | Range 16–77 yr | 48% | 41.4 partial hypopituitarism; 30% hypogonadism; 13% hypothyroidism; 8.7% hypoadrenalism; seven patients had prolactinomas | 22% with VFD | 28% headache |
| Feldkamp *et al.*, 1999 (5) | 50 patients with PIs followed up conservatively | Mean 47.0 ± 18.0 yr (17–84 yr) | 34% | 10% of patients with NFPA had hypogonadism | None (the ones with VFDs were surgically treated) | 4% pituitary apoplexy |
| Karavitaki *et al.*, 2007 (15) | 40 patients with imaging suggestive of pituitary adenoma without clinical or biochemical evidence of hormonal hypersecretion (NFPA) and conservative follow-up | Median 52 yr (range 18–89 yr) | 45% | 46% hypogonadism; 25% hypocortisolism; 21% hypothyroidism; all deficiencies only in macroadenomas | 21%, all in macroadenomas | NR |
| Igarashi *et al.*, 1999 (6) | 23 patients with sellar lesions followed up without initial therapy to evaluate natural history. Only four patients were really asymptomatic at baseline. Most of them complained of VFD and headache, suggestive of pituitary apoplexy. Lesions are classified as cystic or solid and follow-up is analyzed accordingly | Mean 47.3 yr; range 17–78 yr | 44% | 13% hypopituitarism | 35% | 30% headache; 4% vertigo;17% incidental |
| Nishizawa *et al.*, 1998 (7) | 28 patients with PIs greater than 1 cm | Mean 62.5 yr; range 45–72 yr | 46 | NR | NR | NR |
| Sanno *et al.*, 2003 (17), Oyama *et al.*, 2005 (16)[a] | 550 patients with incidentally found pituitary tumors, excluded if visual symptoms or hormone excess symptoms; of them: 289 followed up conservatively | Mean 48.6 yr; range 8–86 yr | 39 | NR | If VFD, then excluded | 37.5% headache |

ITT, insulin tolerance test; NR, not reported; UC, unclear; VFD, visual field defect.

[a] For Sanno *et al.*, 2003(17) and Oyama *et al.*, 2005 (16), study populations overlap; however, different outcomes are reported in both studies; hence, data were extracted from both studies but patients did not overlap in analyses.

period of inclusion, and length of follow-up). We extracted the outcomes of interest at the longest point of complete follow-up. We contacted authors for missing data when needed.

## Quality assessment

We used the GRADE approach to rate the quality of evidence (11), *i.e.* the extent to which we can be confident in the estimates with the purpose of making recommendations. To assess the methodological quality of the studies, we determined how the cohorts were selected, whether there was a follow-up protocol and the extent of loss to follow-up, and how outcomes were ascertained. We also noted how each study defined the increase in tumor size.

## Metaanalyses

We estimated from each study the event rate per 100 person-years (PYs) and associated 95% confidence interval (CI) and pooled using the DerSimonian and Laird random-effects model (12). We quantified inconsistency using the $I^2$ statistic, which describes the proportion of heterogeneity across studies that is not due to chance, thus describing the extent of true inconsis-

**TABLE 1.** Continued

| Macroadenomas (%) | Population | Period of inclusion of the patients | Length of follow-up |
|---|---|---|---|
| 88 | Japan | 1990–2002 | 61.9 ± 38.2 months (10.8–168.2 months) |
| 26 | United States | 1995–1999 | 18.9 ± 19.4 months (0–69.4 months) |
| 100 | The Netherlands | 1981–2005 | 85 ± 13 months |
| 56.1 | Canada | After 1983 | Macroincidentalomas 6.1 ± 2.2 yr; microincidentalomas 6.7 ± 1.1 yr |
| 59 | Argentina | 1994–2000 | Mean 3.2 yr; range 0.75–6 yr |
| 37.3 | Germany | 1992–1996 | 2.7 yr |
| 60 | United Kingdom | 1989–2005 | Mean 42 months; range 8–128 months |
| NC | Japan | NR/UC | Mean 5.1 yr; range 1.5–11.6 yr |
| 100%; 82% grade A, 18% grade B | Japan | NR/UC | Mean 5.6 yr; range 6 months to 10 yr |
| 16.8 | Japan | 1996–2000, 1999–2002 | Mean 27.3 months, range 6–173 months |

tency in results across trials (13). $I^2$ less than 25% and $I^2$ greater than 50% reflect small and large inconsistency, respectively.

### Subgroup and sensitivity analyses

To explore causes of inconsistency and subgroup-treatment interactions, subgroup analyses were specified *a priori* according to the following factors: tumor size at presentation (microadenoma *vs.* macroadenoma with cutoff defined at 10 mm), tumor characteristics on imaging (solid *vs.* cystic), patient's sex and age (younger than 65 yr *vs.* older). A test of interaction (14) was used to explore subgroup effects. Sensitivity analysis was planned to determine whether the exclusion of borderline eligible studies or unpublished studies would affect study conclusions.

## Results

### Search results

The search identified 1069 candidate references, of which 13 studies described in 14 publications deemed el-

igible (4–8, 15–23). We found one additional unpublished study (24) by contacting experts in the field. We excluded three studies (8, 18, 20) because the case identification was done using older CT scan techniques that were not comparable with current MRI studies and due to the lack of sufficient data for metaanalysis (23), making the total number of included studies 11 (Fig. 1). The two studies by Sanno *et al.* (17) and Oyama *et al.* (16) had overlapping populations; hence, data were extracted from both papers but avoiding overlap in analysis. The characteristics of included studies are summarized in Table 1. The median follow-up was 3.9 yr (range 1–15). All the included studies in this report were of single-cohort design. Studies were single-center studies, except for a few (16, 22). Loss to follow-up was not reported in five studies and higher than 30% in four. The quality of the included studies is described in Table 2 and was in general suboptimal with several methodological limitations.

## Baseline characteristics

The frequency of PIs/NFPAs was higher in females. Age range was very wide, from 5 months to 89 yr. The inclusion criteria of the included studies were heterogeneous in terms of the presence of mass-related symptoms or underlying endocrine dysfunction, and subsequently outcome data were reported in aggregate. Hence, the differentiation between PIs and NFPAs was not feasible. Mixed series reported macroadenomas in 17–98% of cases. This wide range of frequencies reflects differences in the definition of incidentaloma and clinical processes at each center. Centers with more stringent criteria for the inclusion of a pituitary tumor as incidentaloma, *e.g.* a NFPA without any clinical, visual, or hormonal dysfunction attributable to the tumor, had the lowest prevalence of macroadenomas and visual field defects attributed to the mass. Among symptomatic patients, the most common complaint at baseline was headache, and the most common pituitary

**TABLE 2.** Study quality

| | Cohort selection | Loss to follow-up (%) | Ascertainment of outcomes | Follow-up protocol | Definition of increase in size |
|---|---|---|---|---|---|
| Arita *et al.*, 2006 (21) | Consecutive cases followed up prospectively | 0 | Prospective registry of clinical assessment | MRI at baseline, 6 months and yearly; frequency of endocrinological and ophthalmological assessment other than at baseline not clearly stated | NR |
| Baker *et al.*, 2003 (24) | Population-based survey of incidentally found pituitary masses among patients undergoing conventional MRI for reasons nonattributable to pituitary pathology | 40 | Medical records | UC | NR |
| Dekkers *et al.*, 2007 (19) | Consecutive patients presenting at the university medical center | NR | Medical records | Repeat MRI was performed within 1 yr after the initial diagnosis. If no growth was observed, subsequent MRI scanning was performed every second year | >1 mm |
| Donovan and Corenblum, 1995 (4) | Consecutive cases followed up prospectively | 0 | Prospective registry of clinical assessment | CT or MRI and Goldman perimetry at baseline, 6 months, and yearly | >1 mm |
| Fainstein Day *et al.*, 2004 (22) | Retrospective analyses of 46 cases of PIs recruited at different hospitals | NC | Medical records | Hormonal levels, MRI, and perimetry at baseline and yearly thereafter | NR |
| Feldkamp *et al.*, 1999 (5) | Consecutive cases followed up prospectively | 0 | Prospective registry of clinical assessment | CT or MRI and Goldman perimetry at baseline, 6 months, and yearly | NR |
| Igarashi *et al.*, 1999 (6) | UC | NR | NR/UC | MRI | NR |
| Karavitaki *et al.*, 2007 (15) | All consecutive patients presenting to endocrinology clinic | 2 | Medical records | CT only when MRI was contraindicated; Goldmann perimetry | >1 mm |
| Nishizawa *et al.*, 1998 (7) | All consecutive patients who received head imaging in a university hospital | NR | Prospective registry of medical records; ophthalmology and endocrinology studies once per year | MRI once per year | NR |
| Sanno *et al.*, 2003 (17), Oyama *et al.*, 2005 (16) | UC | NR | Medical records | MRI and Goldman perimetry | NR |

NR, Not reported; UC, unclear; CT, computerized tomography; VF, visual fields.

**TABLE 3.** Incidence of adverse events in untreated patients with PIs per 100 PYs[a]

| | Incidence (100 PYs) and 95% CI | $I^{2b}$ | $P_{interaction}$ |
|---|---|---|---|
| Increase in size (growth) | | | |
| Macroadenoma | 12.53 (7.86–17.20) | 99% | 0.01 |
| Microadenoma | 3.32 (2.13–4.50) | 97% | |
| Solid | 5.72 (2.28–9.16) | 99% | 0.01 |
| Cystic | 0.05 (0.0–0.18) | NA | |
| Overall | 5.75 (4.99–6.51) | 99% | |
| Apoplexy | | | |
| Macroadenoma | 1.1 (0.0–2.5) | 58% | 0.41 |
| Microadenoma | 0.4 (0.0–1.4) | NA | |
| Average growth <1 mm | 0.5 (0.4–0.6) | NA | 0.01 |
| Average growth 1–3.5 mm | 0.2 (0.1–0.2) | NA | |
| Average growth >3.5 mm | 14.3 (12.9–15.7) | NA | |
| Overall | 0.2 (0.0–0.5) | 32% | |
| New endocrine dysfunction | | | |
| Macroadenoma | 11.9 (0.0–30.8) | 66% | 0.22 |
| Microadenoma | 4.0 (0.0–31.5) | NA | |
| Overall | 2.4 (0.0–6.4) | 43% | |
| Worsening of visual field | | | |
| Average growth <1 mm | 0.5 (0.4–0.6) | NA | 0.01 |
| Average growth 1–3.5 mm | 0.2 (0.1–0.2) | NA | |
| Average growth >3.5 mm | 64.3 (60.1–68.5) | NA | |
| Overall | 0.65 (0.47–0.82) | 99% | |

[a] Median follow-up 3.9 yr (range 1–15 yr).

[b] $I^2$ represents the proportion of heterogeneity that is not due to chance.

dysfunction was hypogonadism. Pituitary apoplexy and diabetes insipidus at baseline were quite uncommon.

### Metaanalysis

The results are presented in Table 3. Data on mortality were not reported. The overall event rate per 100 PYs for tumor growth was 5.8 (95% CI 5.0, 6.5). Pituitary apoplexy was rare (0.2 per 100 PYs; 95% CI 0.0, 0.5) and so was the outcome of worsening of visual field defects (0.7 per 100 PYs; 95% CI 0.5, 0.8). The overall incidence of new endocrine dysfunction was 2.4 per 100 PYs (95% CI 0.0, 6.4). The majority of these analyses were associated with significant heterogeneity.

Subgroup analysis showed a greater event rate of growth in size in macroadenomas (12.5; 95% CI 7.9, 17.2) and solid lesions (5.7; 95% CI 2.3, 9.2) in comparison with microadenomas (3.3; 95% CI 2.1, 4.5) and cystic lesions (0.1; 95% CI 0.0, 0.2). There was a trend that did not reach statistical significance for greater incidence of pituitary apoplexy and new endocrine dysfunction worsening in macroadenomas compared with microadenomas. Despite the sparse data with only three studies contributing to this analysis (4, 17, 19), there is a statistical interaction, suggesting that in studies with larger average tumor growth (>3.5 mm), there was higher incidence of apoplexy and worsening of visual field deficits.

We conducted sensitivity analysis by excluding the unpublished study by Baker *et al.* (24). The event rate per 100 PYs without data from this study are: tumor growth (5.7; 95% CI 4.9, 6.5); pituitary apoplexy (0.6; 95% CI 0.5, 0.8); worsening of visual field defects (0.6; 95% CI 0.5, 0.8); and new endocrine dysfunction (0.8; 95% CI 0.3, 1.3).

## Discussion

### Principal findings

Despite the high prevalence of incidental pituitary adenomas, the literature reporting on the natural history of this entity is scarce, restricted to noncomparative cohort studies, and includes mainly small series of patients. The largest series (16, 17) followed up conservatively 289 patients with PIs/NFPAs, whereas other series ranged from seven to 50 patients.

This systematic review and metaanalyses shows that the incidence of tumor growth in PIs/NFPAs is higher in macroadenomas and solid lesions in comparison with microadenomas and cystic lesions. Similar inferences regarding the other outcomes of interest can be drawn. In general, the development of patient-important outcomes, *i.e.* outcomes that affect how patients live, feel, or survive (25), occurred rarely and seemed to be higher in patients harboring tumors with higher average growth, particularly for the outcomes of apoplexy and worsening of visual field defects, an intuitive finding.

### Limitations and strengths

The strengths of this study include the comprehensive literature search and the application of bias protection measures (*i.e.* duplicate independent judgment with adequate interobserver agreement) in the selection of studies, the assessment of study quality, and data extraction. Our rigorous review uncovers that the summarized evidence was very low quality, particularly because of the methodological limitations of the included studies and their inconsistent methods and results. Such inconsistency may be in part due to the inability to provide clear separate incidence estimates for PIs and NFPAs. Although the two entities have clear different definitions, it is difficult to separate them in the realm of study design, not to mention challenges in the way the literature is reported and indexed. Precision was hampered by the size of the series and the small number of adverse events. Publication bias is common in reviews of small observational studies. Reporting bias is quite likely, considering that not all the outcomes were reported in all papers (2) despite the fact that these outcomes are well known and of great importance to patients and clinicians.

### Implications for practice and research

To our knowledge this is the first systematic review on the prognosis of PIs/NFPAs. The clinical implications of the findings of this report will be presented in the accompanying clinical practice guidelines by The Endocrine Society Task Force. Despite the high prevalence of PIs, the published literature is not very helpful in predicting the natural history of these tumors. Future studies that will increase the sample size of the present body of literature are needed to increase our confidence in the estimates presented here. These studies should be prospective and use clear and explicit criteria for inclusion, objective outcome definitions and assessment, and uniform follow-up. At present, in light of very low-quality evidence and the resulting uncertainty, clinical action will need to carefully match the values and preferences of informed patients and rely on an adequate patient-clinician relationship to manage the anxiety that patients with these common incidental findings may experience.

### Conclusions

Very low-quality evidence suggests that the clinical and etiologically heterogeneous entities grouped as PIs/NFPAs have fairly rare complications that may be more common when lesions are large (>10 mm) and solid. More investigation is needed to fully inform the decision to conservatively follow up these lesions and monitor selected patients at evidence-based intervals to prevent and treat adverse patient important outcomes such as visual field defects, pituitary dysfunction, or emergencies such as pituitary apoplexy.

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