Risk of Thyroid Nodular Disease and Thyroid Cancer in Patients with Acromegaly – Meta-Analysis and Systematic Review

Kosma Wolinski, Agata Czarnywojtek, Marek Ruchala*
Department of Endocrinology, Metabolism and Internal Medicine, Poznan University of Medical Sciences, Poznan, Poland

Abstract

Introduction: Acromegaly is a quite rare chronic disease caused by the increased secretion of growth hormone (GH) and subsequently insulin-like growth factor 1. Although cardiovascular diseases remains the most common cause of mortality among acromegalic patients, increased prevalence of malignant and benign neoplasms remains a matter of debate. The aim of this study is to evaluate the risk of thyroid nodular disease (TND) and thyroid cancer in patients with acromegaly.

Materials and Methods: PubMed, Cochrane Library, Scopus, Cinahl, Academic Search Complete, Web of Knowledge, PubMed Central, PubMed Central Canada and Clinical Key databases were searched to identify studies containing. Random-effects model was used to calculate pooled odds ratios and risk ratios of TND in acromegaly. Studies which not included control groups were systematically reviewed.

Results: TND was more frequent in acromegaly than in control groups (OR = 6.9, RR = 2.1). The pooled prevalence of TND was 59.2%. Also thyroid cancer (TC) proved to be more common in acromegalic patients (OR = 7.5, RR = 7.2), prevalence was 4.3%. The pooled rate of malignancy (calculated per patient) was equal to 8.7%.

Conclusions: This study confirms that both TND and TC occur significantly more often in acromegalic patients than in general population. These results indicate that periodic thyroid ultrasound examination and careful evaluation of eventual lesions should be an important part of follow-up of patients with acromegaly.

Citation: Wolinski K, Czarnywojtek A, Ruchala M (2014) Risk of Thyroid Nodular Disease and Thyroid Cancer in Patients with Acromegaly – Meta-Analysis and Systematic Review. PLoS ONE 9(2): e88787. doi:10.1371/journal.pone.0088787

Editor: Mohammad Ebrahim Khamseh, Endocrine Research Center (Firouzgar), Institute of Endocrinology and Metabolism, Iran (Islamic Republic Of)
Received September 20, 2013; Accepted January 11, 2014; Published February 14, 2014

Copyright: © 2014 Wolinski et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: The authors have no support or funding to report.
Competing Interests: The authors have declared that no competing interests exist.

* E-mail: mruchala@ump.edu.pl

Introduction

Acromegaly is a rare chronic disease caused by the increased secretion of growth hormone (GH) and subsequently insulin-like growth factor 1 (IGF-1) [1,2]. Cardiovascular diseases are very common and remain the most common cause of mortality among acromegalic patients [2,3]. However, increased prevalence of malignant and benign neoplasms is also a matter of debate [2,4]. Most studies were focused on colorectal and thyroid tumors, however also elevated risk of other, e.g. breast, central nervous system, adrenals or urinary tract neoplasm were reported [2,4,5,6,7,8]. Meta-analysis performed by Rokkas et al. [5] proved the increased risk of colon cancer. The issue of benign and malignant thyroid tumors is not as well established as there was no meta-analysis on the topic and outcomes of particular studies were dispersed.

The aim of this study is to evaluate the risk of thyroid nodular disease (TND) and thyroid cancer (TC) in patients with acromegaly and also to combine results of the studies including control groups to assess if the risk is significantly higher than in general population.

Materials and Methods

Selection of the Studies

We have searched the PubMed/MEDLINE, Cochrane Library, Scopus, Cinahl, Academic Search Complete, Web of Knowledge, PubMed Central, PubMed Central Canada and Clinical Key databases from January 1960 up to May 2013 in order to find all relevant journal articles. We have used the search term: acromegaly and (thyroid or "thyroid cancer" or "thyroid nodules" or goitre). Only full-text journal articles written in English were taken into account. We have also searched manually the references of review articles in order to avoid eventually omitted studies. Two researchers (K.W., A.C.) searched all included databases independently and prepared list of included studies. In case of discrepancies between lists, authors were reading doubtful articles together.

Data Extraction

We have recorded data on study design, year of publication, country of origin, number of the patients, sex and age of participants, duration of the disease, methods of the thyroid examination (e.g. ultrasonography, palpation), number of patients
with and without thyroid lesions and with thyroid cancer. In case of studies including control group, same data on this group were recorded. Studies with control group matched by age and sex was included. Studies with control groups not matched by these parameters were excluded to avoid within study bias.

**Statistical Analysis**

We have meta-analyzed odds ratios (OR) and risk ratios (RR) using a random – effect model using Statistica v.10 software with medical package. Heterogeneity between studies was assessed using the Q statistics and I² statistics. Q and I² values given in “Results” are based on the odds ratio calculations. If calculation of OR was impossible due to zero cells, a constant (0.5) were added to all columns. Publication bias was assessed using Kendall’s tau. If publication bias was present we performed cumulative metaanalysis and also re-performed calculations with exclusion of the studies with highest standard error. We used also data from all included studies (with and without control groups) to calculate the

| Study | Year | Country | Patients | Mean age | Control group | Mean follow-up | Comments |
|-------|------|---------|----------|----------|---------------|---------------|----------|
| dos Santos et al. [14] | 2012 | Brasil | 124 women, 48 men | 45.1, SD = 13.4 | 199, healthy volunteers | 263, not specified | Retrospective |
| Hermann et al. [15] | 2004 | Germany | 39 women, 34 men | 55, SD = 13 | 150, non-functioning or PRL secreting adenomas | 7.3, SD = 4.1 | Retrospective |
| Gasperi et al. [16] | 2002 | Italy | 147 women, 111 men | 50, SD = 13 | 150, non-functioning or PRL secreting adenomas | 4.5, SD = 0.3 | Retrospective |
| Popovic et al. [17] | 1998 | Yugoslavia | 137 women, 83 men | 49.5, SD = 13 | 248, non-functioning or PRL secreting adenomas | 4.5, SD = 0.3 | Retrospective |
| Barzilay et al. [18] | 1991 | USA | 43 women, 44 men | Median 37 | 198, non-functioning or PRL secreting adenomas | Median - 13 | Retrospective; data on TND not included – no distinction between nodular and diffused goiter; estimated duration of acromegaly. |
| Cannavo et al. [13] | 2000 | Italy | 17 women, 11 men | Median 37 | 100, healthy volunteers | 9.9 | Retrospective; data on TND not included – no distinction between nodular and diffused goiter; estimated duration of acromegaly. |

Abbreviations: SD – standard deviation; TND – thyroid nodular disease; BMI – body mass index.
pooled prevalence of thyroid nodular disease (TND) and thyroid cancer (TC) as well as malignancy rates. These data were meta-analyzed using random – effect model according to the methodology described by Borenstein et al. [9]. Only studies assessing the thyroid by ultrasonographic (US) examination were included in calculations concerning TND. Other articles (e.g. about palpable nodules only) have been systematically reviewed.

**Results**

**Case – control Studies**

The search results and steps of selection are shown on the flowchart (figure 1). Nine studies including control group were identified. In one of them [10] only palpational examination of thyroid was performed. In one study [11] the control group was not matched by age and BMI, in another one – such details about control group were not given [12]. In study performed by Cannavo et al. [13] control group was not matched by sex. These four studies were excluded from the meta-analysis. Another five studies, two prospective and three retrospective have been included, [table 1] In case of 15 studies only data on prevalence of thyroid lesions or thyroid cancer were available (without data on the control groups). These studies were included in quantitative synthesis of pool prevalence of thyroid lesions. Two studies contained data on palpable nodules only; these studies were systematically reviewed.

For thyroid nodules the pooled OR was 3.6 with 95% confidence interval (CI) 1.8–7.4 [fig. 2, table 2], RR = 2.1, 95% CI 1.3–3.3. There were no evidences for significant heterogeneity (Q = 1.8, degrees of freedom (df) = 2, p value = 0.40; I² = 0.0%). There is no evidence for publication bias (Kendall's tau = 0.33, two – tailed p value = 0.60).

For thyroid cancers the pooled OR was 7.9 (95% CI 2.8–22.0) [fig. 3, table 3], RR = 7.6 (95% CI 2.7–20.8). There are no evidences for significant heterogeneity (Q = 2.5, degrees of freedom (df) = 4, p value = 0.65; I² = 0.0%). There is no evidence for publication bias (Kendall's tau = 0.80, two – tailed p value = 0.05). However, the calculations of publication bias was of borderline statistical significance. Exclusion of the study with the highest standard error [15] would slightly decrease the pooled result (OR 6.7) and it would eliminate this borderline publication bias (Kendall’s Tau 0.67, p = 0.17). Cumulative metaanalysis was shown on figure 4 [figure 4].

**Studies without Control Group**

Results of studies which did not include control group or included groups which were excluded from the meta-analysis according to some methodological doubts (e.g. control group not matched by age) are shown in table 4 [table 4].

Eleven studies were included. Using also the data about prevalence from case – control studies, there were 13 papers containing data on TND frequency in ultrasound (US) examination and also 13 bringing data on thyroid cancer occurrence. Two further studies contained information about palpable thyroid nodules.

Prevalence of thyroid lesions fluctuated from 43.2% to 75.6% in US examination. In total there were 668 patients with and 457 without TND included. The pooled prevalence meta-analyzed using random – effect model is equal to 59.2% with 95% CI 52.7%–66.5%.

In two studies about the prevalence of palpable thyroid nodules was given in two papers and it was 38.8 and 10.5%.

Prevalence of TC fluctuated from 0.8% to 11.8%. In total there were 55 patients with and 1317 without TC included. The pooled prevalence meta-analyzed using random – effect model is equal to 4.3% with 95% CI 3.0%–6.2%.

**Register – based Studies**

Four studies based on registers of acromegalic patients and cancer patients were identified [table 4].

### Table 2. Results of case – control studies containing data on frequency of thyroid nodular disease in patients with acromegaly.

| Study                  | Patients with TND | Patients without TND | Control group – TND | Control group without TND | OR     |
|------------------------|-------------------|----------------------|---------------------|--------------------------|--------|
| dos Santos et al. [14] | 67                | 57                   | 96                  | 167                      | 2.0 (1.3–3.2) |
| Hermann et al. [15]    | 46                | 27                   | 66                  | 133                      | 3.4 (2.0–6.0) |
| Gasperi et al. [16]    | 143 (including 37 toxic nodular goiter) | 115                  | 23                  | 127                      | 6.9 (4.1–11.4) |
| Total (random effect model) |                   |                      |                     |                          | **3.6 (1.8–7.4)** |

Abbreviations: SD – standard deviation; TND – thyroid nodular disease; OR – odds ratio.

doi:10.1371/journal.pone.0088787.t002
Malignancy Rate in Thyroid Nodules

Ten studies included data both on thyroid nodules and thyroid cancer frequency what allows to calculate the risk of malignancy in acromegalic patients with TND. There were 620 patients with TND including 48 malignancies. The pooled rate of malignancy (calculated per patient) meta-analyzed using random – effect model is equal to 8.7% with 95% CI 6.1% –12.3%. Comparing the risk of malignancy in the studies containing control group, the RR of malignancy in patients with TND and acromegaly was insignificantly higher than in patients with TND and without acromegaly – RR = 3.2, 95% CI 0.5–20.1.

Discussion

Thyroid nodular disease turned out to be significantly more frequent in patients with acromegaly than in control groups (OR = 3.6, RR = 2.1) and it seems to be a very common disorder in these patients (prevalence slightly below 60%). According to Wüster et al. [10] also palpable thyroid nodules occurs significantly more often in acromegalic patients TC also proved to be more common in acromegaly (OR = 7.9, RR = 7.6), however the calculations of publication bias was of borderline significance (p = 0.05), what can suggest slight overestimation of the result. Prevalence of TC was quite high - about 4%. The risk of malignancy in acromegalic patients with TND was insignificantly higher than in control groups. There was also visible tendency that in newer studies thyroid disorders are reported more frequently – e.g. in studies published from 2008 TND occurred in about 65% of patients whereas in older studies – in about 54%; similar tendency can be observe in case of TCs – they were present in almost 6% of patients in papers published from 2008 and about 3% in older studies. This result is in line with suggestions, that the improving diagnostic and treatment of acromegaly extends the life duration what increases the prevalence of benign and malignant neoplasms. In the past, more patients died before neoplasms appeared or became clinically relevant [4]. The fact that our meta-analysis includes study performed in the period of over 50 years could be consider as limitation of this research. On the second,
**Table 4. Studies without control group or with control group excluded from meta-analysis.**

| Author | Year | Country | Patients | Age | Patients with TND | Patients with TC | % of malignant nodules | Duration of the follow-up |
|--------|------|---------|----------|-----|-------------------|-----------------|-----------------------|--------------------------|
| Rogozinski et al. [19] | 2012 | Argentina | 22 women, 12 men | Median -55 | 23 (67.6%) | 4 (11.8%) | 17.4% |
| Gullu et al. [20] | 2010 | Turkey | 60 women, 45 men (thyroid US performed in 100 patients) | 47.9, SD = 11.5 | 62 (62.0%) | 5 (5.0%) | 8.1% | 13.02, SD = 7.1 |
| Cheung et al. [11] | 1997 | Australia | 16 women, 21 men | 49.5, SD = 14.5 | 16 (43.2%) | 23 (67.6%) | 17.4% |
| Junik et al. [12] | 1997 | Poland | 18 women, 21 men | 42, SD = 8 | 18 (46.2%) | 18 (46.2%) | 18 (46.2%) |
| Anagnostis et al. [21] | 2011 | Greece | 70 women, 45 men | 47, SD = 14 | 85 (74.1%) | 3 (2.9%) | 13.02, SD = 7.1 |
| Baldys-Waligórska et al. [22] | 2010 | Poland | 71 women, 30 men | 51.8, SD = 15.4 | 64 (63.0%) | 3 (2.9%) | 4.7% | 9.4, SD = 6.5 |
| Ruchala et al. [23] | 2009 | Poland | 52 women, 34 men | 49.9, SD = 11.1 | 65 (75.6%) | 5 (5.8%) | 7.7% |
| Kurimoto et al. [24] | 2008 | Japan | 86 women, 54 men, thyroid US in 83 patients | 55, SD = 25 | 62 (74.7%) | 4 (4.8%) | 6.5% |
| Bolanowski et al. [25] | 2006 | Poland | 75 women, 55 men | women – 52.6, men – 51.6 | 1 (0.8%) | Women – 10.5, men – 12.0 |
| Tita et al. [26] | 2005 | Italy | 70 women, 55 men | 49.9 | 72 (57.6%) | 9 (7.2%) | 12.5% | Median 8.2 |
| Cannavo et al. [13] | 2000 | Italy | 17 women, 11 men | 51.1, SD = 11.2 | 14 (50.0%) | 14 (50.0%) | 14.2, SD = 7.5 |
| Higuchi et al. [27] | 2000 | Japan | 19 women, 25 men | women: 50.9, men: 53.3 | 2 | Women: 7.5 men: 5.3, |
| Kasagi et al. [28] | 1999 | Japan | 26 women, 22 men | 46.7, SD = 12.2 | 16 (43.2%) | 2 (5.4%) | 12.5% |
| Nabarro et al. [29] | 1987 | UK | 123 women, 133 men | 123 women, 133 men | 27 | 27 | 6.8 |
| Register - based | | | | | | | | |
| Mestron et al. [30] | 2004 | Spain | 741 women, 478 men | 45 | 2 | 2 |
| Baris et al. [31] | 2001 | Sweden, Denmark | 888 women, 746 men | 60.7 | 3 (SIR = 4.3) | Sweden – 10.3, Denmark – 9.0 |
| Orme et al. [32] | 1998 | UK | 1239 | 1 (SIR = 2.5) | 1 (SIR = 2.5) |
| Ron et al. [33] | 1991 | USA | 1041 men | 1 (SIR = 4.3) |

1 data were included only when it was clearly reported if given time was the time since diagnosis or since estimated onset of the disease;
2 at the time of diagnosis;
3 estimated time of duration of the disease;
4 palpable nodules only.

11 patients examined only by palpation were excluded; descriptive statistics refer to the whole group.

**Abbreviations:** SD – standard deviation; SIR – standardized incidence ratio; TC – thyroid cancer; TND – thyroid nodular disease.
however there were numerous studies on the topic, amount of most reliable papers – prospective, including sex and age matched control groups and data both on the prevalence of TC and TND is unsatisfactory. This fact is another limitation of this meta-analysis and it causes that confidence intervals of ORs and RRs are very wide, it also precludes detailed analysis of case – control studies in subgroups (e.g. newer vs. older studies).

It also calls attention that studies based on matching data from registers of acromegalic patients with data from cancer registers showed much lower frequency of TC than other, especially prospective studies, however in most cases insignificantly higher than expected [31, 32]. This discrepancy can be partially caused by inaccuracies in registers. On the other hand, these results may suggest, that TCs remained undiagnosed in great proportion.

In included studies the risk of malignancy for patients with TND was about 8%, what is in the range considered for general population [34]. Case – control studies also did not show significantly increased risk. However, the amount of studies is unsatisfactory; further researches are necessary to determine, if the risk of malignancy in acromegalic patients with TND is higher than in general population or if the frequency of TC is elevated proportionally to increased prevalence of TND.

However, many studies was published on the topic of increased risk of benign and malignant neoplasms in acromegaly, it remains controversial as results were often divergent. Among neoplasms, the increased prevalence of colon polyps and cancer seems to be most widely agreed, in large part thanks to meta-analysis performed by Rokkas et al. [5]. Comparing results of that meta-analysis with our outcomes, the risk of TC is elevated even more strongly than the risk of colon cancer (OR 7.9 vs. 4.4). Prevalence of these two malignancies seems to be similar in acromegalic patients, about 4.5%.

In conclusion, our meta-analysis proved that patients with acromegaly are at an increased risk of thyroid nodular disease and thyroid cancer. These results indicate, that periodic thyroid US examination and careful evaluation of eventual lesions should be important part of follow-up of acromegalic patients.

This study was performed with concorance with the PRISMA statement [35].

### Supporting Information

#### Checklist S1 PRISMA checklist. (DOC)

#### Author Contributions

Conceived and designed the experiments: KW AC MR. Performed the experiments: KW AC. Analyzed the data: KW. Wrote the paper: KW AC MR.

### References

1. Ruchala M, Szczepanek-Parulka E, Komorska-Piotrowski E. (2011) Diagnosi,ka i leczenie akromegalii. Oncoreview 4: 240–247.

2. Colao A, Ferone D, Marzullo P, Lombardi P. (2004) Systemic Complications of Acromegaly: Epidemiology, Pathogenesis, and Management. Endocr Rev 25: 102–152.

3. Golkowski F, Krzentowska-Korek A, Baldys-Waligorska A, Hubalewska-Dydeyczka A. (2011) Goiter, cardiovascular and metabolic disorders in patients with acromegaly. Endor Regul 45: 191–197.

4. Ruchala M, Szczepanek-Parulka E, Fularz M, Welinski K. (2012) Risk of neoplasms in acromegaly. Contemp Oncol (Pozn) 16: 111–117.

5. Rokkas T, Psiotas D, Sechopoulos P, Margaritini G, Koulouxa G. (2008) Risk of colorectal neoplasm in patients with acromegaly: A meta-analysis. World J Gastroenterol 14: 3480–3489.

6. Jenkins PJ, Beser M. (2001) Acromegaly and Cancer: A Problem. J Clin Endocrinol Metab 86: 2935–2941.

7. Terzolo M, Reimondo G, Gasperi M, Cozzi E, Picone S, et al. (2005) Colonoscopic screening and follow-up in patients with acromegaly: a multicenter study in Italy. J Endocrinol Metab 90: 84–90.

8. Scaroni C, Selce R, Benedini S, De Menis E, Arsoio M, et al. (2008) Adrenal morpho-functional alterations in patients with acromegaly. J Endocrinol Invest 31: 602–606.

9. Borenius M, Hedges LV, Higgins JPT, Rothstein HR. (2009) Introduction to Meta-analysis. John Wiley & Sons, Ltd, Chichester, UK.

10. Wüster C, Steger G, Schmelzle A, Gottswinter J, Minne HW, et al. (1991) Increased incidence of euthyroid and hyperthyroid goiters independently of thyrotropin in patients with acromegaly. Horm Metab Res 23: 131–134.

11. Cheung NW, Bovages SC. (1997) The thyroid gland in acromegaly: an ultrasonographic study. Clin Endocrinol (Oxf) 46: 545–549.

12. Junik R, Savicka J, Kozak W, Gembicka M. (1997) Thyroid volume and function in patients with acromegaly living in iodine deficient areas. J Endocrinol Invest 20, 134–137.

13. Cannavò S, Squadrito S, Finocchiaro MD, Curto L, Almanto B, et al. (2000) Goiter and impairment of thyroid function in acromegalic patients: basal evaluation and follow-up. Horm Metab Res 32: 190–195.

14. dos Santos MC, Nascimento GC, Nascimento AG, Carvalho VC, Lopes MH, et al. (2013) Thyroid cancer in patients with acromegaly: a case-control study. Piniary 16: 109–114.

15. Herrmann BL, Baumann H, Jansen OE, Goesch R, Schmid KW, et al. (2004) Impact of disease activity on thyroid diseases in patients with acromegaly: basal evaluation and follow-up. Exp Clin Endocrinol Diabetes 112: 225–230.

16. Gasperi M, Martino E, Manetti L, Arosio M, Porrett S, et al. (2002) Acromegaly Study Group of the Italian Society of Endocrinology. Prevalence of thyroid diseases in patients with acromegaly: results of an Italian multi-center study. J Endocrinol Invest 25: 240–245.

17. Popovic V, Damjanovic S, Micu D, Nesovic M, Djonovic M, et al. (1998) Increased incidence of neoplasia in patients with pituitary adenomas. The Pituitary Study Group. Clin Endocrinol (Oxf) 49: 441–445.

18. Barzilay J, Healey GJ, Cushing GW. (1991) Benign and malignant tumors in patients with acromegaly. Arch Intern Med 151: 1629–1632.

19. Rucchinif A, Furioso A, Glikman P, Junco M, Laudi R, et al. (2012) Thyroid nodules in acromegaly. Ann Bras Endocrinol Metabol 56: 300–304.

20. Gulhi BE, Celik O, Gazioglu N, Kadioglu P. (2010) Thyroid cancer is the most common cancer associated with acromegaly. Piniary 13: 242–248.

21. Anagnostis P, Efthathiadou ZA, Polyzos SA, Adamidou F, Slavakis A, et al. (2011) Acromegaly: presentation, morbidity and treatment outcomes at a single centre. Int J Clin Pract 65: 896–902.

22. Baldys-Waligorska A, Krzentowska A, Golkowski F, Sokolowski G, Hubalewska-Dydeyczka A. (2010) The prevalence of benign and malignant neoplasms in acromegalic patients. Endokrynol Pol 61: 29–34.

23. Ruchala M, Skiba A, Jurgilas E, Uruski P, Wasko R, et al. (2009) The occurrence of thyroidal nodules in patients with acromegaly. Pol J Endocrinol 59: 77–80.

24. Kurimoto M, Fukuda I, Hisoka N, Takano K. (2008) The prevalence of benign and malignant tumors in patients with acromegaly at a single institute. Endocr J 55: 67–71.

---

**Figure 4. Cumulative forest plot for studies comparing the prevalence of thyroid cancer in acromegalic patients and control groups.**

doi:10.1371/journal.pone.0088787.g004
25. Bolanowski M, Zarezka K, Kaluzny M, Zielinski G, Bednarek-Tupikowska G, et al. (2006) A follow-up of 130 patients with acromegaly in a single centre. Neuro Endocrinol Lett 27: 828–832.
26. Tita P, Ambrosio MR, Scollio C, Carta A, Gangemi P, et al. (2005) High prevalence of differentiated thyroid carcinoma in acromegaly. Clin Endocrinol (Oxf) 63: 161–167.
27. Higuchi Y, Saei N, Iuchi T, Uchino Y, Tatsuno I, et al. (2000) Incidence of malignant tumors in patients with acromegaly. Endocr J 47 Suppl: 57–60.
28. Kasagi K, Shimatsu A, Miyamoto S, Misaki T, Sakahara H, et al. (1999) Goiter associated with acromegaly: sonographic and scintigraphic findings of the thyroid gland. Thyroid 9: 791–796.
29. Nabarro JDN. (1987) Acromegaly. Clin Endocrinol (Oxf) 26: 481–512.
30. Mestron A, Webb SM, Astorga R, Benito P, Catala M, et al. (2004) Epidemiology, clinical characteristics, outcome, morbidity and mortality in acromegaly based on the Spanish Acromegaly Registry (Registro Espanol de Acromegalia, REA). Eur J Endocrinol 151: 439–446.
31. Baris D, Gridley G, Ron E, Weiderpass E, Mellemkjaer L, et al. (2002) Acromegaly and cancer risk: a cohort study in Sweden and Denmark. Cancer Causes Control 13: 395–400.
32. Orme SM, McNally RJ, Cartwright RA, Belchetz PE. (1998) Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. J Clin Endocrinol Metab 83: 2730–2734.
33. Ron E, Gridley G, Hrubec Z, Page W, Arora S, et al. (1991) Acromegaly and gastrointestinal cancer. Cancer 68: 1673–1677.
34. Tan GH, Gharib H. (1997) Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. Ann Intern Med 126: 226–231.
35. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, et al. (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 339: b2700.