Published by v|b|z

REVIEW

# Acromegaly and cancer

**Maja Radman[1], Tanja Miličević[1]**

1Department of Endocrinology, Diabetes and Metabolic Diseases, University Hospital Center Split, University of Split Medical School, Spinčićeva 1, 21000, Split, Croatia

**Corresponding author:** Maja Radman, Department of Endocrinology, Diabetes and Metabolic Diseases, University Hospital Center Split, University of Split Medical School, Spinčićeva 1, 21000, Split, Croatia; E-mail: maja.radman1@st.t-com.hr

**DOI:** 10.21040/eom/2016.2.4

Received: January 14th 2016
Accepted: February 20th 2016
Published: March 14th 2016



**Funding:** None.
**Conflict of interest statement:** The authors declare that they have no conflict of interest.
**Data Availability Statement:** All relevant data are within the paper.

**Abstract**

Acromegaly is a chronic disease characterized by sustained elevation of circulating growth hormone (GH) and insulin-like growth factor-I (IGF-I). It is clearly associated with increased morbidity and overall mortality, primarily due to cardiovascular, metabolic, and respiratory diseases. Although the influence of acromegaly on carcinogenesis remains controversial, numerous studies have confirmed that acromegalic patients are at an increased risk of developing different types of neoplasms. Endangered patients are especially those who have been untreated for a long period and show increased serum concentrations of GH and IGF-I. Prevention and early detection of potential neoplasms remain a crucial part of treatment. This review will focus on the occurrence and mortality of benign and malignant tumors in acromegalic patients.

**Key words:** acromegaly, growth hormone, insulin-like growth factor-I, cancer risk, morbidity, mortality

## 1. Introduction

Acromegaly is a rare chronic disease caused by excessive secretion of growth hormone (GH) and consequently of insulin-like growth factor-I (IGF-I). The excess of GH induces insulin-like growth factor-binding protein 3 (IGFBP-3) and IGF-I levels and promotes dysregulated cell growth balance. It results in peripheral tissue exposure to both excessive growth-promoting and growth-arresting influences. Classic clinical features of acromegaly include acral overgrowth, sweating, glucose intolerance, hypertension, menstrual disturbances, impotence, and headaches. Long-term tissue exposure to GH hypersecretion leads to cardiovascular, respiratory, metabolic, or malignant diseases. Acromegaly reduces the patients' life expectancy and leads to many complications. Acromegalic patients have a four-fold higher mortality rate compared to the general population [1]. The cancer risk of these patients is still controversial. In 1950, Moon et al. first suggested the correlation between GH and cancer [2]. They observed a high incidence of lung, adrenal, and mammary tumors in female rats treated with high doses of pituitary hormones. Large cohort studies of acromegalic patients exploring the most common types of tumors, indicate higher rates of both benign and malignant neoplasms [3]. Results of some studies are shown in Table 1. However, earlier retrospective studies did not demonstrate increased risk of carcinogenesis, probably because many of these patients died prematurely due to unregulated disease [4]. According to some authors, in cases of concomitantly present neoplasms, acromegaly should be aggressively treated, because elevated IGF-I levels could stimulate tumor growth; however, there is no clear evidence that tumor initiation is triggered by IGF-I [5]. On the other hand, some authors presume that acromegaly and concomitantly present neoplasms might share a common non-endocrine etiology [6]. Hence, it is of essence to clarify whether or not elevated GH and IGF-I levels are an initiating or permissive factor in carcinogenesis.

## 2. Cancer incidence and acromegaly

### 2.1. Colorectal neoplasms

Studies analyzing cancer incidence and mortality in acromegalic patients seem to report the most reliable data exactly for this group of neoplasms [7].

Previous studies examining the incidence of colorectal neoplasms in acromegaly varied significantly depending on the study population and design. However, a recent meta-analysis has proved a statistically significant higher incidence of premalignant lesions such as tubulo-villous adenomas and hyperplastic polyps (OR 3.3 and 3.6 respectively), as well as colorectal cancer (OR 4.4) [8]. Furthermore, there is some evidence that colorectal neoplasms tend to have different characteristics compared to the general population. Neoplastic lesions are more likely to be right-sided (35-68% of adenomas, 50% of carcinomas), situated in the ascending and transverse colon [9,10,11], tend to be multiple, larger, more dysplastic, and often have malignant alteration [12]. Moreover, there is also a 25% chance of their recurrence within 3 years. According to these findings, patients with acromegaly should be regarded as a high-risk group and offered regular colonoscopy screening visits [11]. This requirement is difficult to fulfill due to several practical issues that affect the success of colonoscopy in acromegalic patients. These are the increased length and volume of the colon, which can be overcome by rigorous bowel preparation [8, 11]. The question arises as to when the screening should begin and how often it should be repeated. Approximately 19.3% of acromegalic patients younger than 40 years have been shown to have colonic neoplasia when compared to 4.4% of controls [12]. Therefore, initial screening is suggested at the time of diagnosis with subsequent reevaluation intervals dependent on the colonoscopic findings and disease activity. Jenkins et al. found that all patients with a new tubular adenoma detected on follow up colonoscopy had significantly higher IGF-I concentrations when compared to controls [13]. Therefore, in patients with polyps or persistently elevated IGF-I concentrations screening should be done every 5 years, while in those without polyps and normal IGF-I concentrations screening should be repeated every 10 years [14].

The mechanism for developing colorectal neoplasia is likely to be multifactorial. The most frequently discussed factor is the role of IGF-I. In-vitro models have found IGF-I receptors on the surfaces of colon cancer cells and of normal gastrointestinal cells. IGF-I is a known mitogen that stimulates proliferation of intestinal cells and their migration, but the exact contribution to colon carcinogenesis still remains unclear [15]. In the normal intestinal cell, deactivation of the tumor suppressor adenomatous polyposis coli (APC) gene may lead to the

cell transformation, proliferation and further polyps appearance. In vivo, GH and IGF-I have been shown to activate c-myc transcription, which is believed to play a central role in sporadic colorectal tumorigenesis [16,17]. It is found that not only the absolute concentration of IGF-I, but also the ratio of IGF-I to IGFBP-3 concentration play an important role in carcinogenesis [7]. In acromegaly, GH excess increases IGF-I concentration and, to a lesser extent, IGFBP-3 concentration resulting in greater IGF-I to IGFBP-3 ratio [8]. The GH/IGF-I axis is most likely involved in the pathogenesis of colorectal neoplasia as a permissive factor [5].

In the case of colorectal cancer, other mechanisms should also be taken into consideration. Alterations in the intracolonic environment might play a role, for instance the unconjugated secondary bile acid and deoxycholic acid (DCA). Serum concentration of DCA reflects intracolonic concentration and appears to be elevated in patients with neoplasia. Similar difference also exists in acromegalic patients [18,19]. In vivo, somatostatin analogues increase DCA concentration, while in vitro they seem to inhibit the growth of colonic cancer cell lines [20,21].

### 2.2. Thyroid neoplasms

Series of studies have shown that acromegaly is clearly associated with thyroid patology.

Thyroid nodular disease is more frequent in acromegalic patients (OR = 3.6, RR = 2.1), with a prevalence rate of 60% [22]. Disease duration correlates with the number of nodules on palpation. However, the majority of patients have normal thyroid function [7]. The increase in the incidence can partially be explained by the diagnostic improvement and better treatment of acromegalic patients who now live long enough to develop both benign and malignant lesions. Wolinski et al. found that the risk of malignant alteration to thyroid cancer is about 8%, which is insignificantly higher than in control group [22].

However, the most recent meta-analysis confirmed that thyroid cancer is more common in patients with acromegaly (OR = 7.5, RR = 7.2) with the prevalence of 4.3% [22]. When comparing these results with results of meta-analysis focusing on other neoplasms, they support the fact that thyroid cancer is one of the most commonly detected cancers in acromegaly [23]. A large retrospective study evaluated 442 acromegalic patients during the period of 6 years and reported that 4.7% of patients were diagnosed with cancer. Thyroid cancer was the most common type of cancer in the latter cohort [24]. This indicates that periodic thyroid ultrasound examination should be important part of follow-up of these patients, especially in a case of palpable thyroid nodules [14,23]. Special emphasis should be placed on the fine-needle aspiration of all non-functioning nodules 1 cm or greater in size [25].

The reason why this malignancy appears more often in acromegaly, may be explained by the effect of IGF-I on thyrocytes. Not only does IGF-I induce proliferation and inhibit apoptosis itself, but also potentiates TSH-mediated thyroid cell proliferation [26]. Other potential causes include pituitary irradiation and hereditary syndromes accompanied by acromegaly (i.e. Carney syndrome, MEN-1) [27].

### 2.3. Breast cancer

The incidence of breast cancer is even more difficult to ascertain due to the restriction to female patients [6,28]. A study by Nabarro et al. showed a 4-fold increase in the risk of developing breast carcinoma [29], while the study by Ruchała et al. found similar association but only for a subgroup of premenopausal acromegalic patients [7]. Moreover, Orme et al. noted a 1.6-fold increase in breast carcinoma mortality in acromegaly, but without increase in the incidence. This suggests that patients with acromegaly may have more aggressive forms of breast cancer [4].

In contrast to colorectal neoplasms, there is some evidence that GH/IGF-I axis is engaged in the pathogenesis of breast cancer in general population. Growth hormone receptor (GH-R) is found in normal tissue as well as in human breast cell lines, which suggests a possible autocrine/paracrine role for GH on tumor development and growth [30,31]. Similarly, IGF-I receptor (IGF-I-R) is expressed on cultures of malignant breast epithelial cells, as well as in estrogen-dependent and, at lower levels, in estrogen-independent cell lines [32]. Furthermore, non-acromegalic patients with breast cancer have significantly higher serum GH and IGF-I levels compared to those without cancer. High IGF-I levels along with low IGFBP-3 level, are associated with increased risk of breast cancer in premenopausal, but not in postmenopausal women [33]. Therefore, it is advisable to offer female acromegalic patients a regular mammography screening, even before the age of 50 [7].

### 2.4. Prostate cancer

Acromegaly is associated with benign prostate hyperplasia as well as micro- and macro-calcifications [34]. Even though elevated serum IGF-I levels are often found in patients with prostate cancer, there is no evidence for higher incidence of prostate cancer in patients with acromegaly [4,35]. As observed in breast cancer studies, both in vitro studies and studies on general population have confirmed the involvement of GH/IGF-I axis in prostate cancer [5]. The meta-analysis estimated an odds ratio of 1.83 for developing prostate cancer comparing the uppermost levels of serum IGF-I to the lowermost levels [36]. Furthermore, increased expression of IGF-I-R is associated with progression of androgen-sensitive to androgen-independent prostate cancer cell lines [37]. Studies have also demonstrated synergistic effect of high testosterone level and high IGF-I levels in increase of risk for prostate cancer [38]. Moreover, patients with prostate cancer have decreased serum IGFBP-3 levels and decreased expression of IGFBP-3 in prostatic tissue [39]. Since the IGFBP-3 is a prostate specific antigen (PSA) substrate, elevated PSA levels in the prostate cancer facilitates disease progression by proteolytically cleaving IGFBP-3, and thereby increasing IGF-I at the cellular level [40]. Since IGFBP-3 proteolysis is not increased in acromegaly, it might have protective effect against developing prostate cancer [41]. Nevertheless, men with acromegaly should be screened for prostate cancer and provided regular serum PSA measurement, rectal examination, and/or prostatic ultrasound annualy. Those with persistently high IGF-I levels, receiving replacement testosterone, should be monitored with special attention [6].

### 2.5. Haematopoietic system neoplasms

The data regarding the association between acromegaly and the incidence of hematopoietic neoplasms are scarce. There are few reports of three cases of leukemia in a group of 106 acromegalic patients and three cases of hematopoietic malignancies (one case of Hodgkin's lymphoma and two cases of leukemia) in a different cohort of 220 patients [42,43]. The rest of the studies found either no increase or a small increase (OR = 1.2-2.0) in the incidence of hematopoietic malignancies in acromegalic patients [44,45].

### 2.6. Lung cancer

In a meta-analysis by Renehan et al. IGF-I was not associated with the risk for lung cancer [46]. Experimental studies have shown that normal and tumoral lung tissue does express the IGF-I-R and produces IGF-I in an autocrine fashion. Stimulation with IGF-I or increase of expression of the IGF-I-R induces cell proliferation and increases the metastatic activity of lung cancer cells [47].

### 2.7. Neoplasms of the urinary tract

While some authors have found 3 times higher incidence of renal cancer in acromegalic patients, others estimated that the prevalence of these neoplasms is approximately the same as in the general population [35,48]. According to some of them, the increased risk of developing malignant tumors of urinary system is only confirmed within the period of five years from the diagnosis of acromegaly [49].

### 2.8. Neoplasms of the central nervous system

The most common type of CNS tumor in acromegalic patients is meningeoma [35,50]. The higher incidence of CNS neoplasms can be explained by the use of pituitary irradiation as a modality of treatment of acromegaly [35].

### 2.9. Other neoplasms

Numerous case reports describe various benign and malignant tumors including bone tumors [51], skin epidermoid tumors, dermatosis and melanomas, parathyroid and adrenal tumors [1,52,53]. Baris et al. observed higher morbidity in small intestine carcinoid tumors; however, this was limited to patients with the MEN-1 syndrome [35]. According to Ron et al. the incidence of oesophageal and gastric cancer was higher in a group of 1041 male acromegalic patients [48]. Finally, Cohen et al. detected uterine myomas in 81% of female acromegalic patients [54].

## 3. Overall and cancer mortality

Retrospective studies focusing on mortality in acromegaly have shown that approximately 60% of patients succumb to cardiovascular disease, 25% from respiratory disease and 15% due to malignancy [5]. Some older studies demonstrated 2-3 fold increase in overall mortality in acromegaly, while cancer related mortality rates were either not increased or increased only in females or in males [6]. Such studies evaluated cancer mortality

rates in comparison to post-treatment GH levels. If the post-treatment GH level was within normal range, both overall and cancer mortality was similar to the general population. Thus, cancer mortality was increased only in patients with poorly controlled disease [5]. Orme et al. found a 1.8 fold increase in mortality risk for all cancers, a 4.6 fold increase in colon cancer mortality risk and 2.9 fold increase in breast cancer mortality risk if random serum GH levels were higher than 10 ng/ml. On contrary, there was no significant relationship between the duration of acromegaly and cancer related mortality [4].

A recent meta-analysis clearly showed 72% increase in overall mortality in acromegaly compared with the general population [55]. Even transsphenoidal surgery, which is in 60-80% of patients effective in controlling GH levels, is associated with a 32% increased overall mortality. This excess of mortality may be related to a high proportion of patients with poorly controlled disease. However, even a biochemical cure rate of 100% will not result in complete normalization of mortality rates [55]. For patients with acromegaly, it seems that balancing GH levels, controlling hypertension and heart disease are the most important for improving overall mortality [5].

## 4. Conclusions

Studies reporting higher incidence of neoplasms in acromegalic patients should be interpreted carefully. Epidemiological studies with sufficient power are still lacking due to low incidence of acromegaly. In summary, few meta-analyses have found increased incidence of colorectal and thyroid neoplasms [8,22]. Colonoscopy should be performed at diagnosis in all patients and repeated in 5-year intervals in patients with polyps and 10-year intervals in patients with normal findings. Acromegaly is associated with an increased thyroid volume and nodularity. Thus, thyroid ultrasound is suggested in all patients with palpable thyroid nodules. Some evidence exists that patients with active acromegaly have increased incidence of breast and prostate cancer, but further epidemiological studies on this matter are required. Therefore, we can not recommend routine mammography or PSA measurement in all patients. Since cancer is strongly associated with age, adequate treatment of acromegaly and long-term follow up, may reveal some new insights in the future. Individualized approach in patients with acromegaly is mandatory, taking into consideration age, disease activity and genetic susceptibility.

## Author contributions

MR gave an idea for the article, participated in drafting the article and gave the final approval. TM reviewed the previously published literature, participated in drafting the article and gave the final approval.

## References

1. Bolfi F, Miot HA, Resende M, Mazeto GMSF, Romeiro FG, da Silva Yamashiro, et al. Frequency of various types of neoplasia in a group of acromegalic patients. Arq Bras Endocrinol Metab 2013;57:612-6. http://dx.doi.org/10.1590/S0004-27302013000800005

2. Moon HD, Simpson ME, Li CH, Evans HM. Neoplasms in rats treated with pituitary growth hormone v. absence of neoplasms in hypophysectomized rats. Cancer Res 1951;11:535-9.

3. Kurimoto M, Fukuda I, Hizuka N, Takano K. The prevalence of benign and malignant tumors in patients with acromegaly at a single institute. Endocr J 2008; 55:67-71. http://dx.doi.org/10.1507/endocrj.K07E-010

4. Orme SM, McNally RJQ, Cartwright RA, Belchetz PE. Mortality and cancer incidence in acromegaly: a retrospective cohort study. J Clin Endocrinol Metab 1998;83:2730-4. http://dx.doi.org/10.1210/jc.83.8.2730

5. Melmed S. Acromegaly and cancer: not a problem? J Clin Endocrinol Metab 2001;86:2929-34. http://dx.doi.org/10.1210/jcem.86.7.7635

6. Loeper S, Ezzat S. Acromegaly: re-thinking the cancer risk. Rev Endocr Metab Disord 2008;9:41-58. http://dx.doi.org/10.1007/s11154-007-9063-z

7. Ruchała M, Szczepanek-Parulska E, Fularz M, Woliński K. Risk of neoplasms in acromegaly. Contemp Oncol (Pozn) 2012;16: 111-17. http://dx.doi.org/10.5114/wo.2012.28790

8. Rokkas T, Pistiolas D, Sechopoulos P, Margantinis G, Koukoulis G. Risk of colorectal neoplasm in patients with acromegaly: a meta-analysis. World J Gastroenterol 2008;14:3484-9. http://dx.doi.org/10.3748/wjg.14.3484

9. Renehan AG, Bhaskar P, Painter JE, O´Dwyer ST, Haboubi N, Ball SG, et al. The pravalence and characteristics of colorectal neoplasia in acromegaly. J Clin Endocrinol Metab 2000;85:3417-24. http://dx.doi.org/10.1210/jcem.85.9.6775

10. Vasen HF, van Erpecum KJ, Roelfsema F, Raue F, Koppeschaar H, Griffioen G, et al. Increased prevalence of colonic adenomas in patients with acromegaly. Eur J Endocinol 1994;131:235-7. http://dx.doi.org/10.1530/eje.0.1310235

11. Jenkins PJ, Besser GM, Fairclough PD. Colorectal neoplasia in acromegaly. Gut 1999;44:585-7. http://dx.doi.org/10.1136/gut.44.5.585

12. Terzolo M, Reimondo G, Gasperi M, Cozzi R, Pivonello R, Vitale G, et al. Colonoscopic screening and follow-up in patients with acromegaly: a multicenter study in Italy. J Clin Endocrinol Metab 2005;90:84-90.
http://dx.doi.org/10.1210/jc.2004-0240

13. Jenkins PJ, Crockett LS, Lowe DG, Grossman AB, Monson J, Besser GM, et al. Insulin-like growth factor-I as a risk factor for colonic adenomas in patients with acromegaly (abstract). Gut 1998;42(suppl 1):A14.

14. Katznelson L, Laws Jr ER, Melmed S, Molitch ME, Murad MH, Utz A, et al. Acromegaly: an Endocrine society clinical practice guideline. J Clin Endocrinol Metab 2014;99:3933-51.
http://dx.doi.org/10.1210/jc.2014-2700

15. Simmons JG, Pucilowska JB, Lund PK. Autocrine and paracrine actions of intestinal fibroplast-derived-insulin-like growth factors. Am J Physil 1999;276:G817-G827.

16. Murphy LJ, Bell GI, Friesen HG. Growth hormone stimulates sequential induction of c-myc and insulin-like growth factor I expression in vivo. Endocrinology 1987;120:1806-12.
http://dx.doi.org/10.1210/endo-120-5-1806

17. Sumantran VN, Feldman EL. Insulin-like growth factor I regulates c-myc and GAP-43 messenger ribonucleic acid expression in SH-SY5Y human neuroblastoma cells. Endocrinology 1993;132:2017-23.

18. Bayerdorffer E, Mannes GA, Richter WO, Ochenkuehn T, Wiebecke B, Koepcke W, et al. Increased serum deoxycholic acid levels in men with colorectal adenomas. Gastroenterology 1993;104:145-51.

19. Bayerdorffer E, Mannes GA, Ochsenkuhn T, Dirschedl P, Wiebecke B, Paumgartner G. Unconjugated secondary bile acids in the serum of patients with colorectal adenomas. Gut 1995;36:268-73.
http://dx.doi.org/10.1136/gut.36.2.268

20. Veysey MJ, Mallet A, Jenkins P, Besser GM, Murphy GM, Dowling RH. Deoxycholic (DCA) and cholic acid kinetics in acromegalic patients treated with octreotide (OT) [abstract]. Gut 1998;42(suppl 1):A11.

21. Hussaini SH, Pereira SP, Veysey MJ, Kennedy C, Jenkins P, Murphy GM, et al. Roles of gall bladder emptying and intestinal transit in the pathogenesis of octreotide induced gall bladder stones. Gut 1996;38:775-83.
http://dx.doi.org/10.1136/gut.38.5.775

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

23. Gullu BE, Celik O, Gazioglu N, Kadioglu P. Thyroid cancer is the most common cancer associated with acromegaly. Pituitary 2010;13:242-48.
http://dx.doi.org/10.1007/s11102-010-0224-9

24. Mercado M, Gonzalez B, Vargas G, Ramirez C, de los Monteros ALE, Sosa E, et al. Successful mortality reduction and control of comorbidities in patients with acromegaly followed at a highly specialized multidisciplinary clinic. J Clin Endocrinol Metab 2014;99:4438-46.
http://dx.doi.org/10.1210/jc.2014-2670

25. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2006;16:109-42.
http://dx.doi.org/10.1089/thy.2006.16.109

26. Tramontano D, Cushing GW, Moses AC, Ingbar SH. Insulin-like growth factor-I stimulates the growth of rat thyroid cells in culture and synergizes the stimulation of DNA synthesis induced by TSH and Graves'-IgG. Endocrinology 1986;119:940-2.
http://dx.doi.org/10.1210/endo-119-2-940

27. Klein I, Parveen G, Gavaler JS, Vanthiel DH. Colonic polyps in patients with acromegaly. Ann Intern Med 1982;97:27-30.
http://dx.doi.org/10.7326/0003-4819-97-1-27

28. Jenkins PJ, Besser M. Clinical perspective: acromegaly and cancer: a problem. J Clin Endocrinol Metab 2001;86:2935-41.
http://dx.doi.org/10.1210/jcem.86.7.7634

29. Nabarro JD. Acromegaly. Clin Endocrinol (Oxf) 1987;26:481-512.
http://dx.doi.org/10.1111/j.1365-2265.1987.tb00805.x

30. Mertani HC, Garcia-Caballero T, Lambert A, Gerard F, Palayer C, Boutin JM, et al. Cellular expression of growth hormone and prolactin receptors in human breast disorders. Int J Cancer 1998;79:202-11.
http://dx.doi.org/10.1002/(SICI)1097-0215(19980417)79:2<202::AID-IJC17>3.0.CO;2-B

31. Wennbo H, Tornell J. The role of prolactin and growth hormone in breast cancer. Oncogene 2000;19:1072-6.
http://dx.doi.org/10.1038/sj.onc.1203349

32. Pollak MN, Perdue JF, Margolese RG, Baer K, Richard M. Presence of somatomedin receptors on primary human breast and colon carcinomas. Cancer Lett 1987;38:223-30.
http://dx.doi.org/10.1016/0304-3835(87)90218-7

33. Hankinson SE, Willett WC, Colditz GA, Hunter DJ, Michaud DS, Deroo B, et al. Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. Lancet 1998;351:1393-6.
http://dx.doi.org/10.1016/S0140-6736(97)10384-1

34. Colao A, Marzullo P, Spiezia S, Ferone D, Giaccio A, Cerbone G, et al. Effect of growth hormone (GH) and insulin-like growth factor I on prostate diseases: an ultrasonographic and endocrine study in acromegaly, GH deficiency, and healthy subjects. J Clin Endocrinol Metab 1999;84:1986-91.
http://dx.doi.org/10.1210/jcem.84.6.5776

35. Baris D, Gridley G, Ron E, Weiderpass E, Mellemkjaer L, Ekbom A, et al. Acromegaly and cancer risk: a cohort study in Sweden and Denmark. Cancer Causes Control 2002;13:395-400.
http://dx.doi.org/10.1023/A:1015713732717

36. Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis.

Lancet 2004;363:1346-53.
http://dx.doi.org/10.1016/S0140-6736(04)16044-3

37. Nickerson T, Chang F, Lorimer D, Smeekens SP, Sawyers CL, Pollak M. In vivo progression of LAPC-9 and LNCaP prostate cancer models to androgen independence is associated with increased expression of insulin-like growth factor I (IGF-I) and IGF-I receptor (IGF-IR). Cancer Res 2001;61:6276-80.

38. Mantzoros CS, Tzonou A, Signorello LB, Stampfer M, Trichopoulos D, Adami HO. Insulin-like growth factor 1 in relation to prostate cancer and benign prostatic hyperplasia. Br J Cancer 1997;76:1115-8.
http://dx.doi.org/10.1038/bjc.1997.520

39. Kanety H, Madjar Y, Dagan Y, Levi J, Papa MZ, Pariente C, et al. Serum insulin-like growth factor-binding protein-2 (IGFBP-2) is increased and IGFBP-3 is decreased in patients with prostate cancer: correlation with serum prostate-specific antigen. J Clin Endocrinol Metab 1993;77:229-33.

40. Cohen P, Peehl DM, Graves HC, Rosenfeld RG. Biological effects of prostate specific antigen as an insulin-like growth factor binding protein-3 protease. J Endocrinol 1994;142(3):407-15.
http://dx.doi.org/10.1677/joe.0.1420407

41. Colao A, Ferone D, Marzullo P, Lombardi G. Systemic complications of acromegaly: epidemiology, pathogenesis, and management. Endocr Rev 2004;25(1):102-52.
http://dx.doi.org/10.1210/er.2002-0022

42. Au WY, Chows WS, Lam KS, Ko GT, Cockram CS, Kwong YL. Acute leukaemia in acromegaly patients. Br J Haematol 2000;110:871-3.
http://dx.doi.org/10.1046/j.1365-2141.2000.02262.x

43. Popovic V, Damjanovic S, Micic D, Nesovic M, Djurovic M, Petakov M, et al. Increased incidence of neoplasia in patients with pituitary adenomas. The Pituitary Study Group. Clin Endocrinol (Oxf) 1998;49.441-5.

44. Higuchi Y, Saeki N, Iuchi T, Uchino Y, Tatsuno I, Uchida D, et al. Incidence of malignant tumors in patients with acromegaly. Endocr J 2000; 47 Suppl: S57-60.
http://dx.doi.org/10.1507/endocrj.47.SupplMarch_S57

45. Kurimoto M, Fukuda I, Hizuka N, Takano K. The prevalence of benign and malignant tumors in patients with acromegaly at a single institute. Endocr J 2008; 55:67-71.
http://dx.doi.org/10.1507/endocrj.K07E-010

46. Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet 2004;363:1346-53.
http://dx.doi.org/10.1016/S0140-6736(04)16044-3

47. Nakanishi Y, Mulshine JL, Kasprzyk PG, Natale RB, Maneckjee R, Avis I, et al. Insulin-like growth factor-I can mediate autocrine proliferation of human small cell lung cancer cell lines in vitro. J Clin Invest 1988;82:354-9.
http://dx.doi.org/10.1172/JCI113594

48. Ron E, Gridley G, Hrubec Z, Page W, Arora S, Fraumeni Jr JF. Acromegaly and gastrointestinal cancer. Cancer 1991; 68: 1673-7.
http://dx.doi.org/10.1002/1097-0142(19911015)68:8<1673::AID-CNCR2820680802>3.0.CO;2-0

49. Kauppinen-Makelin R, Sane T, Valimaki MJ, Markkanen H, Niskanen L, Ebeling T, et al. Increased cancer incidence in acromegaly – a nationwide survey. Clin Endocrinol 2009;72:278-9.
http://dx.doi.org/10.1111/j.1365-2265.2009.03619.x

50. Bałdys-Waligórska A, Krzentowska A, Gołkowski F, Sokołowski G, Hubalewska-Dydejczyk A. The prevalence of benign and malignant neoplasms in acromegalic patients. Endokrynol Pol 2010;61:29-34.

51. Lima GA, Gomes EM, Nunes RC, Vieira NL, Sieiro AP, Brabo EP, et al. Osteosarcoma and acromegaly: a case report and review of the literature. J Endocrinol Invest 2006;29:1006-11.
http://dx.doi.org/10.1007/BF03349215

52. Corcuff JB, Ogor C, Kerlan V, Rougier MB, Bercovichi M, Roger P. Ocular naevus and melanoma in acromegaly. Clin Endocrinol (Oxf) 1997;47:119-21.
http://dx.doi.org/10.1046/j.1365-2265.1997.2001010.x

53. Boguszewski CL, Fighera TM, Bornschein A, Marques FM, Dénes J, Rattenbery E, et al. Genetic studies in a coexistence of acromegaly, pheochromocytoma, gastrointestinal stromal tumor (GIST) and thyroid follicular adenoma. Arq Bras Endocrinol Metabol 2012;56:507-12.
http://dx.doi.org/10.1590/S0004-27302012000800008

54. Cohen O, Schindel B, Homburg R. Uterine leiomyomata a feature of acromegaly. Hum Reprod 1998;13:1945-6.
http://dx.doi.org/10.1093/humrep/13.7.1945

55. Dekkers OM, Biermasz NR, Pereira AM, Romijn JA, Vandenbroucke JP. Mortality in acromegaly: a metaanalysis. J Clin Endocrinol Metab 2008; 93:61-7.
http://dx.doi.org/10.1210/jc.2007-1191