

CLINICAL PERSPECTIVE

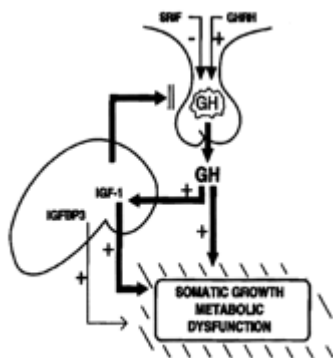
Acromegaly and Cancer: Not a Problem?

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Acromegaly is usually caused by a GH-secreting pituitary adenoma. Somatic growth and metabolic dysfunction occur subsequent to unrestrained GH secretion and elevated insulin-like growth factor (IGF)-I and IGF-binding protein (IGFBP)-3 levels (1) (Fig 1*). Classic clinical features of acromegaly include acral overgrowth, sweating, headaches, menstrual disturbances, and glucose intolerance (Table 1*) (2). Well-documented clinical risks of long-term tissue exposure to uncontrolled GH hypersecretion include cardiac disease and hypertension, diabetes, respiratory disorders, joint disease, and neuropathy (Table 2*) (3). The degree of risk for malignancy in these patients is unresolved; and acromegaly, representing an experiment of nature, could answer the question of whether or not elevated GH and IGF levels provide a permissive growth advantage for neoplasms, resulting in more aggressive malignant disease and/or increased cancer-associated mortality (4).



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Figure 1. Pathogenesis of acromegaly. Unrestrained GH secretion, elaborated by a pituitary tumor, results in elevated IGF-I and IGFBP-3 levels, somatic growth, and metabolic dysfunction. Paracrine IGF-I and IGFBP-3 may also influence tissue growth. Adapted from 1 .

Table 1. Review of clinical features in 639 patients reported with acromegaly

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Clinical features in acromegaly		
Features	n	Incidence (%)
Acral enlargement	626	98
Hyperhidrosis	526	70
Menstrual disturbances	318	69
Headaches	809	59
Paresthasias	469	49
Glucose intolerance	726	40
Skin tags	157	38
Impotence	400	34
Visual field abnormalities	751	28
Goiter	554	25
Hypertension	643	23

Reproduced from Ref. 2.

Table 2. Documented determinants of mortality outcome in retrospective studies of acromegaly

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Acromegaly: outcome determinants			
Causes of death	%	Survival determinants	<i>P</i>

Cardiovascular	60	Last GH	<0.0001
Respiratory	25	Hypertension	<0.02
Malignancy	15	Cardiac disease	<0.03
		Diabetes	<0.03
		Symptom duration	<0.04

Control of GH levels (see text for definition) is associated with reversal of adverse mortality. Adapted from Refs. 5–14.

Analysis of the determinants for mortality outcome in acromegaly indicates that approximately 60% of patients succumb to cardiovascular disease; 25% from respiratory disease; and in 15% of patients, the cause of death is attributed to malignancy (Table 2⁺). Nevertheless, absolute circulating GH values seem to constitute the most significant single determinant of survival, regardless of the cause of death ([5](#), [6](#), [7](#), [8](#), [9](#), [10](#), [11](#), [12](#), [13](#), [14](#)). Several recent compelling studies support the critical role of GH, suggesting that GH control is associated with reversal of adverse mortality rates, regardless of the nature of associated comorbidity ([13](#)). Thus, suppression of GH to less than 1 ng/mL, during an oral glucose tolerance test, and normalization of IGF-I levels portend a favorable mortality outcome ([15](#)).

Pathogenesis of somatic dysfunction in acromegaly

Peripheral tissue somatic growth and metabolic dysfunction are caused by direct effects of GH on peripheral receptors, impact of hepatic-derived circulating and paracrine IGF-I, and also the impact of elevated circulating IGFBP-3 levels. Elevated IGF-I bioactivity and activation of the IGF-I receptor are associated with cell proliferation and growth advantage, whereas IGFBP3 bioactivity promotes an apoptotic advantage ([16](#), [17](#), [18](#), [19](#)). Thus, excess GH, by inducing both IGFBP3 and IGF-I levels, promotes dysregulated cell growth balance characterized by dynamic signals for cell apoptosis vs. cell growth advantage (Fig 2⁺).

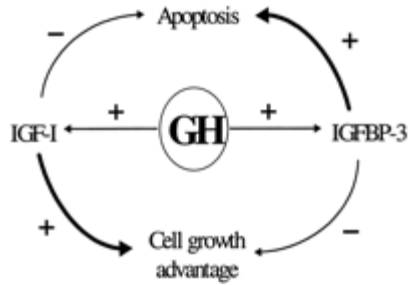


Figure 2. Balance of GH influences on cell growth regulation. GH stimulates both IGF-I and IGFBP-3, which mediate cell proliferation and cell removal, respectively. Adapted from [21](#) [22](#) [23](#) .

Because IGFBP-3 levels are high in acromegaly ([20](#)) (Fig 3*) and correlate with IGF-I levels, an imbalance of circulating IGFBP-3 level vs. IGF-I action is manifested by the broad spectrum of clinical somatic features of the disease and is reflective of a broad range of respective circulating values for these two factors in patients with acromegaly. This is especially noteworthy because, *in vitro*, IGFBP-3 inhibits IGF-I-induced prostate cancer cell growth ([21](#)) (Fig 4*), and breast cancer cells are diverted into an apoptotic phase by IGFBP-3 ([22](#)). In acromegaly, the activated IGF-I receptor accounts for increased kidney, heart, or acral bony tissue functional cell mass. These patients, therefore, potentially harbor a tumor growth advantage mediated by IGF-I-activated cell renewal and increased functional mass; whereas concomitantly, elevated IGFBP-3 accounts for an enhanced cell removal process and apoptosis ([23](#)). Thus, pathologically elevated GH results in peripheral tissue exposure to both excessive growth-promoting and growth-arresting influences.

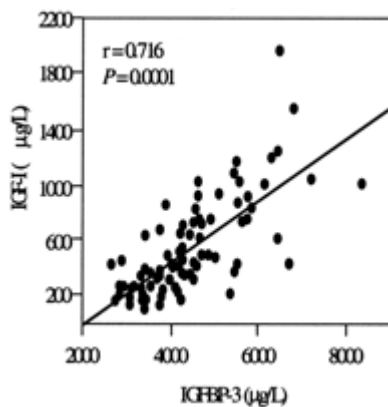


Figure 3. IGFBP-3 levels are elevated in acromegaly and correlate with IGF-I levels. Adapted from [20](#) .

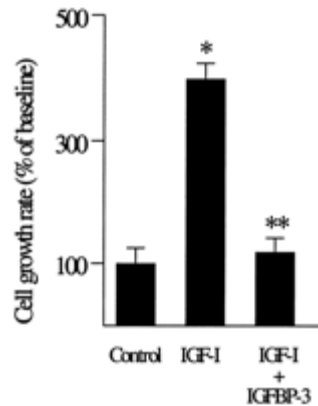


Figure 4. IGFBP-3 inhibits prostate cancer cell growth. From [21](#) .

The role of the GH-IGF-I axis in tumorigenesis has been extensively studied. *In vitro* evidence supporting the role of these growth factors in development of neoplasia includes reports that GH and IGF-I readily transform lymphocytes, and also induce cell proliferation. IGF-I receptor mass is increased in neoplastic tissues, and the activated IGF-I receptor also mediates cell transformation ([16](#), [17](#), [24](#), [25](#), [26](#)). Several growth factors and inactivated tumor-suppressing genes also stimulate IGF-I receptor synthesis ([18](#)). However, there are no reports of enhanced spontaneous tumor formation in IGF-I-expressing transgenic mice ([27](#)). Targeted expression of IGF-I by a human keratin promoter was shown to result in epidermal hyperplasia and hyperkeratosis, with enhanced sensitivity to tumor induction by administered TPA ([28](#)). These latter observations suggest a permissive, rather than an initiating, role for IGF-I in tumorigenesis. In classic earlier papers by Moon and colleagues ([29](#)), impure extracted GH was injected into rats at very high doses (up to 3 mg/day) for up to 16 months, and these animals developed primarily lymphoid hyperplasia and lung lymphosarcomas. *In vivo*, GH induces neoplasm formation and also *c-myc* expression in experimental models, and mice overexpressing GH transgenes develop tumors over the long term ([30](#), [31](#)). Several decades of earlier experience with hypophysectomy showed the procedure to be protective or palliative for patients with neoplasia ([32](#)). Somatostatin administration lowers IGF-I levels and also retards transplanted tumor growth in some animal models. Thus, several lines of *in vitro* and *in vivo* evidence indicate a role for the GH-IGF-I axis in mediating both physiologic and pathologic cell growth and tissue hypertrophy ([19](#)). The impact of this cumulative experimental evidence on risk for tumorigenesis in patients with acromegaly remains unclear.

Epidemiology of IGF-cancer link

Recently, several retrospective epidemiologic studies have suggested that elevated IGF-I levels may be concordant with a higher risk of cancer in the general population, and that high IGFBP-3 levels are concordant with a lower risk for cancer ([33](#), [34](#), [35](#)).

Breast cancer specifically has been epidemiologically linked to IGF-I levels in premenopausal women ([36](#)). As levels of IGF-I increase, there also seems to be an

enhanced relative risk for colon cancer development, whereas higher levels of IGFBP-3 are associated with decreased relative risk for colon cancer. Extrapolation of these findings to acromegaly should take into account the protective effect of IGFBP-3, especially because both IGF-I and IGFBP-3 are elevated in the disorder. Patients harboring GH-secreting tumors would thus fall into the low-risk quartile of IGF-I and IGFBP3 levels, because they usually exhibit elevations of both these factors (33). Several caveats are important to consider in extrapolating these epidemiologic retrospective studies to acromegaly. First, preexisting cancer should be critically excluded in the test population at the time of retrospective serum sampling, for subsequent IGF-I measurement. Other potentially important cancer risk factors, including family and genetic history, should also be considered. Nevertheless, extrapolation of the epidemiological results, derived from the general population, to acromegaly would, in fact, categorize an acromegaly cohort as low risk (Fig 5*). Clinical prudence indicates that if, in fact, a neoplasm is concomitantly present, acromegaly should be aggressively treated, because elevated IGF-I levels could be growth stimulators for that neoplasm; there is, however, no clear evidence that tumor initiation is triggered by IGF-I. Although GH treatment induces mammary hyperplasia in primates (19), observations from pharmacovigilant studies of patients receiving GH as replacement for pituitary damage have not reported significant increased risks for colon, breast, or prostate cancer thus far. In fact, GH-deficient adults receiving GH replacement, aimed to achieve high-normal IGF-I levels, exhibited unaltered markers of colon epithelial cell proliferation (37).

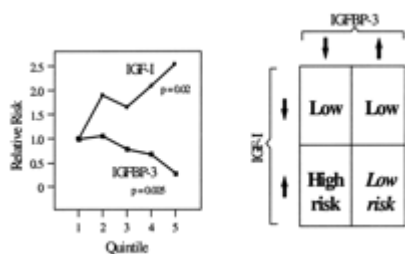


Figure 5. Relative risk for development of colon cancer. IGF-I and IGFBP-3 levels were measured retrospectively in the general population. Because patients with acromegaly exhibit both elevated IGF-I and IGFBP-3 levels, their relative risk for cancer development seems to be low. Adapted from 33 .

Colon polyps in acromegaly

Over the years, numerous retrospective and a few prospective studies have suggested an increased incidence of benign and precancerous colon polyps in patients with acromegaly (38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51) (Table 3*). In an attempt to understand the role of the GH-IGF-I axis in colon cell growth, two transgenic animal models are particularly illuminating (52, 53). These models of respective GH or IGF-I overexpression distinguish two different murine phenotypes of hypersomatotropism. The selectively overexpressed GH transgene is associated with both high GH and high IGF-I levels, whereas the IGF-I transgenic mouse has high IGF-I and low GH levels (52, 53). Although both models exhibit biochemical and clinical features characteristic of

acromegaly, no renal or hepatic changes are apparent in the IGF-I transgenic mouse (53). These animals do, however, exhibit increased bowel length, with highly proliferative colonic crypt cells and decreased apoptosis, whereas no cellular bowel changes are apparent in the GH transgenic model (52, 53, 54, 55, 56). Thus, IGF-I is a powerful mediator of enterotrophic effects, even in the absence of GH (55). This latter observation would suggest that a factor other than IGFBP-3 may, in fact, protect colon cells from proliferative signals when GH is elevated. Another variable in these models is the bowel cell type expressing IGF-I colonic epithelial; or mesenchymal paracrine expression may determine differing phenotypes of cell proliferation. These suboptimal animal models of acromegaly, differing in colonic phenotype, may elucidate the very discrepant clinical literature describing the pathogenesis of benign colon polyps in acromegaly.

Table 3. Colon polyps in acromegaly

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n	Polyps					Carcinoma	Reference
	M/F	Mean age	Adenoma	Hyperplastic	Total		
17	10/7	49	5	3	8	2	(38)
12	11/11	56	2	1	3	2	(39)
29	na	na	4	0	4	2	(40)
23	12/11	47	8	1	9	0	(41)
54	26/28	47	5	11	19	0	(42)
50	25/25	25–70	11	12	23	1	(46)
49	30/19	54	11	5	16	0	(44)
31	11/20	52	11	8	16	0	(43)

103	49 /54	51	23	25	48	0	(45)
129	68 /60	57	33	42	75	6	(47)
115	63 /69	54.8 ¹	27	18	45	3	(50)
66 ²	na	32.7	25	18	43	1	(51)
678			165	144	309	17	
			(24%)	(21%)	(45%)	(2.5%)	

Incidence of colonic lesions in 524 patients prospectively studied in 12 studies. Of note, approximately 20–40% asymptomatic males, age >50 yr, harbor colon adenomas. Refs. 57–59. na, Not ascertainable.

¹ Median age.

² Repeat colonoscopy.

In summarizing 12 prospective colonoscopy studies from the literature reporting 678 patients with acromegaly, colon adenomas were detected in 24%, 21% had hyperplastic polyps, and 2.5% harbored colon carcinoma (Table 3★). Thus, although approximately 47% of selected patients with diagnosed acromegaly prospectively seem to harbor a colonic lesion ([38](#), [39](#), [40](#), [41](#), [42](#), [43](#), [44](#), [45](#), [46](#), [47](#), [50](#), [51](#)), up to 40% of asymptomatic unselected males over the age of 50 yr in the general population harbor colonic lesions ([57](#), [58](#), [59](#)). Therefore, extrapolation of this literature for assessing risk in patients with acromegaly should be cautious without appropriate age-, sex-, and environmentally-matched control population groups. A recent prospective study with rigorous autopsy and population-derived controls demonstrated no increased prevalence of colorectal neoplasia in 115 patients with acromegaly ([50](#)).

Total colon length and sigmoid loop length are increased, and mucosal hypertrophy with documented prolonged colon transit times are reported ([49](#), [50](#)). If, in fact, colon polyps are detected in patients with acromegaly, about 50% are right-sided lesions, justifying full colonoscopy for these patients. If a colon polyp is detected and resected in a patient with acromegaly, there is also a 25% chance that it will recur within 3 yr. Regarding age-related risk for polyps in acromegaly, the literature is diverse, and the risk of colonic lesions is paradoxically reported as being either higher in patients under 55 or in those over 60 yr ([43](#), [45](#), [49](#), [60](#)). There is certainly a higher risk for patients with a positive family history of colon tumors, multiple skin ([61](#)) tags, and history of previous polyps, and increased vigilance is recommended for these subjects. Although repeat colon polyp

growth in acromegaly seems to occur in patients with higher IGF-I levels (51), there is, as yet, little compelling evidence supporting a strong correlation of circulating GH or IGF-I levels and the presence of colon polyps (50, 62), perhaps reflecting the wide spectrum of colon cell dysfunction observed in transgenic animal models of acromegaly. Although eight patients with newly discovered colonic adenomas exhibited higher IGF-I levels than patients with normal or hyperplastic polyps (51), larger studies are required to resolve this important question.

Cancer incidence in acromegaly

Although the role of GH-IGF-I axis in mediating normal cell and tissue growth is well documented, the question of whether patients with acromegaly harbor an enhanced risk for developing cancer is unresolved. Cancer does not appear in descriptions of acromegaly clinical features; and in a comprehensive symptom and sign review of more than 800 patients reported in the literature, cancer is not listed (2). Multiple uncontrolled reports have associated neoplasms of the skin, gastrointestinal system, breast, thyroid, thymus, parathyroid, brain, bone, and hematologic system with acromegaly. In largely selective retrospective and uncontrolled case reports or small series (3, 63, 64, 65), benign tumors have been especially highlighted, including skin tags, colon polyps, adenomas, thymic tumors, parathyroid adenomas, meningiomas, and neurinomas. No enhanced association with breast or prostate cancer has been reported (66).

Several retrospective reports have documented the incidence of malignant disease in acromegaly (Table 4*). Mustacchi (67) reported a 12-center analysis of the incidence of cancer in patients with acromegaly. In patients ranging in age from 1–79 yr, and a total of 2,981 persons at risk, no observed overexpected increased cancer prevalence was found. This very-well-documented study, concluded that the material analyzed does not disclose the presence of a definite influence of the pituitary on the initiation of cancer. If this stimulus exists, it does not seem to be a very potent one (67). Evans examined 100 consecutive death certificates of patients with acromegaly and found no recorded increase in cancer incidence (68). In a retrospective review of 4 million patient charts, 1,200 patients with acromegaly were identified; 22 female subjects, and 149 patients with cancer diagnosed before the diagnosis of acromegaly, were excluded from analysis. In the study cohort of 1,041 males, modestly enhanced (~1.6-fold) incidence of colon, esophageal, and stomach cancer and melanoma was detected (69). From this large retrospective chart review, many have concluded that, in fact, acromegaly is associated with cancer. Careful analysis of this report, however, implies an acromegaly prevalence of 1 in 4,000 in this highly selected hospitalized population. This is clearly far higher than the expected prevalence of approximately 4–6 per million in the general population (6). Therefore, the ascertainment bias inherent in this study makes it difficult to extrapolate to the nonhospitalized overall population of patients with acromegaly (69). The Orme study was an important contribution to the literature reporting 16,000 person years at risk in the UK (70). Cancer incidence in patients with acromegaly was, in fact, low (0.76 Standardized Incidence Ratio, $P < 0.05$), with a sharply lower incidence of bronchial cancer (0.33 Standardized Incidence Ratio, $P < 0.05$) in this group. Female breast cancer

and colon cancers were not significantly increased, and overall cancer incidence rates were significantly lower than observed in the general population.

Table 4. Acromegaly and cancer incidence: multicenter analysis

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	n	Person-years at risk	Cancers		<i>P</i>
			Observed	O/E	
Females	95	1,351	8	1.33	ns
Males	128	1,630	5	1.30	ns
Total ¹	223	2,981	13	1.3	
²	4,822	21,740	178	0.76–3.4	na

¹ Multicenter analysis of cancer incidence in patients with acromegaly, ranging in age from 1–79 yr. Adapted from Ref. 67.

² Analysis of retrospective published reports (1956–1998) of cancer incidence in patients with acromegaly. Included are data from Refs. 5–8, 60, 63, 65, 67, 69 and 70). O/E, Observed/expected ratio; ns, not significant.

With the aforementioned caveats inherent in interpreting selected reports, reviewing retrospective published reports from 1957 through 1999, summarizing over 20,000 reported exposure years, the incidence of cancer ranges from 0.76- up to 3.4-fold the observed overexpected ratio (Table 4*). Prospective controlled longitudinal studies are clearly required to resolve the significance of these observations.

Cancer mortality in acromegaly

Overall mortality in patients with acromegaly correlates with the degree of GH control, and mortality rates from cancer also stratify according to posttreatment GH levels (70) (Table 5*). Overall, if posttreatment GH is controlled, both overall mortality and cancer mortality are unchanged from the control general population (9, 70). Enhanced mortality from cancer is thus only significant if GH levels are uncontrolled. There are no published

studies of long-term prospective evaluation of cancer prevalence or its relationship to biochemical or clinical disease activity in acromegaly. Other unrelated risk factors seem far more important for cancer incidence and mortality, including genetic predisposition, enhanced family risk, and the impact of tight GH control on malignancy-associated mortality. Quite clearly, patients with acromegaly now live longer, and the impact of improved overall general mortality and reduced cardiovascular morbidity may unmask unrelated, age-related cancer incidence previously not clinically apparent. These unknown factors further confound our understanding of cancer risk in acromegaly.

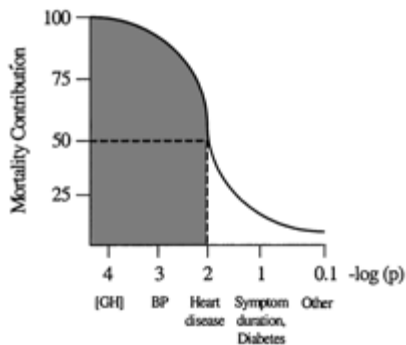
Table 5. Posttreatment GH levels and mortality in acromegaly

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Mortality	Posttreatment GH (ng/mL)			<i>P</i>
	<2.5 n = 541	2.5–9.9 n = 493	>10 n = 207	
Overall	1.10 (0.89–1.15)	1.41 (1.16–1.69)	2.12 (1.70–2.62)	<0.0001
Cancer-related	0.96 (0.63–1.41)	0.81 (0.50–1.24)	1.81 (1.13–2.74)	<0.05

Posttreatment GH levels correlate with mortality in acromegaly. Standardized mortality ratios are depicted for overall mortality and for cancer-related mortality. Adapted from Ref. 70.

Nevertheless, the murky risk perspectives of cancer in acromegaly should be compared with the striking well-documented risk of cardiac disease and diabetes. Mortality, in patients with acromegaly and cardiac disease at the time of diagnosis, occurs within 15 yr in almost 100% of the cases, and only 20% of patients with diabetes and acromegaly survive 20 yr (12). These survival curves differ strikingly from the marginal impact of malignancy on overall mortality derived from metaanalysis of papers published over the last 50 yr. The relative contributions to mortality in acromegaly, as measured by elevated GH levels, hypertension, and heart disease, clearly account for the major negative survival determinants in these patients. Symptom duration and other factors (including cancer) account for relatively low mortality impact (Fig 6★).



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Figure 6. Depiction of mortality determinants in patients with acromegaly. The x-axis reflects the P value (log) as calculated from published retrospective reports ([8](#) [9](#) [10](#) [11](#) [12](#) [13](#) [14](#)).

For patients with acromegaly, it seems that controlling GH levels, hypertension, and heart disease are important for improving ultimate mortality. Fifteen percent of deaths in acromegaly are attributable to malignancies, which is lower than would be expected from the general population, and confirmed by Orme (Table 2 \clubsuit). Uncontrolled acromegaly may provide a growth advantage to concurrently occurring neoplasms in these patients; and based upon experimental information, cancer in a patient with acromegaly and uncontrolled GH levels will likely be more aggressive, with potentially increased cancer-associated morbidity and mortality. However, there is no clear evidence for enhanced *de novo* cancer initiation in acromegaly and, as yet, no direct proven causal relationship of acromegaly with malignant disease.

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References

1. **Melmed S.** 1990 Acromegaly. *N Engl J Med.* 322:966–977. [\[Medline\]](#)
2. **Molitch ME.** 1992 Clinical manifestations of acromegaly. *Endocrinol Metab Clin North Am.* 21:597–614. [\[Medline\]](#)
3. **Melmed S.** 1996 Unwanted effects of growth hormone excess in the adult. *J Pediatr Endocrinol Metab.* 9(Suppl 3):369–374.

4. **Ezzat S, Melmed S.** 1991 Clinical Review 18. Are patients with acromegaly at increased risk for neoplasia? *J Clin Endocrinol Metab.* 72:245–249.[\[Medline\]](#)
5. **Wright AD, Hill DM, Lowy C, Fraser TR.** 1970 Mortality in acromegaly. *Q J Med.* 39:1–16.[\[Medline\]](#)
6. **Alexander L, Appleton D, Hall R, Ross WM, Wilkinson R.** 1980 Epidemiology of acromegaly in the Newcastle region. *Clin Endocrinol (Oxf).* 12:71–79.[\[Medline\]](#)
7. **Nabarro JD.** 1987 Acromegaly. *Clin Endocrinol (Oxf).* 26:481–512.[\[Medline\]](#)
8. **Bengtsson BA, Eden S, Ernest I, Oden A, Sjogren B.** 1988 Epidemiology and long-term survival in acromegaly. A study of 166 cases diagnosed between 1955 and 1984. *Acta Med Scand.* 223:327–335.[\[Medline\]](#)
9. **Bates AS, Van't Hoff W, Jones JM, Clayton RN.** 1993 An audit of outcome of treatment in acromegaly. *Q J Med.* 86:293–299.[\[Medline\]](#)
10. **Etxabe J, Gaztambide S, Latorre P, Vazquez JA.** 1993 Acromegaly: an epidemiological study. *J Endocrinol Invest.* 16:181–187.[\[Medline\]](#)
11. **Rajasoorya C, Holdaway IM, Wrightson P, Scott DJ, Ibbertson HK.** 1994 Determinants of clinical outcome and survival in acromegaly. *Clin Endocrinol (Oxf).* 41:95–102.[\[Medline\]](#)
12. **Abosch A, Tyrrell JB, Lamborn KR, Hannegan LT, Applebury CB, Wilson CB.** 1998 Transsphenoidal microsurgery for growth hormone-secreting pituitary adenomas: initial outcome and long-term results. *J Clin Endocrinol Metab.* 83:3411–3418.[\[Abstract/Free Full Text\]](#)
13. **Swearingen B, Barker FG, Katznelson L, et al.** 1998 Long-term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. *J Clin Endocrinol Metab.* 83:3419–3426.[\[Abstract/Free Full Text\]](#)
14. **Freda PU, Wardlaw SL, Post KD.** 1998 Long-term endocrinological follow-up evaluation in 115 patients who underwent transsphenoidal surgery for acromegaly. *J Neurosurg.* 89:353–358.[\[CrossRef\]](#)[\[Medline\]](#)
15. **Giustina A, Barkan A, Casanueva FF, et al.** 2000 Criteria for cure of acromegaly: a consensus statement. *J Clin Endocrinol Metab.* 85:526–529.[\[Abstract/Free Full Text\]](#)
16. **Baserga R, Prisco M, Hongo A.** 1999 IGFs and cell growth. In: Roberts CT, Rosenfeld RG, eds. *The IGF system. Molecular biology, physiology, and clinical applications.* Totowa, NJ: Humana Press; 329–353.

17. **LeRoith D, Werner H, Beitner-Johnson D, Roberts Jr CT.** 1995 Molecular and cellular aspects of the insulin-like growth factor I receptor. *Endocr Rev.* 16:143–163. [\[Medline\]](#)
18. **LeRoith D.** 2000 Regulation of proliferation and apoptosis by the insulin-like growth factor I receptor. *Growth Horm IGF Res.* 1:12–13.
19. **Ng ST, Zhou J, Adesanya OO, Wang J, LeRoith D, Bondy CA.** 1997 Growth hormone treatment induces mammary gland hyperplasia in aging primates. *Nat Med.* 3:1141–1144. [\[Medline\]](#)
20. **Grinspoon S, Clemmons D, Swearingen B, Klibanski A.** 1995 Serum insulin-like growth factor-binding protein-3 levels in the diagnosis of acromegaly. *J Clin Endocrinol Metab.* 80:927–932. [\[Abstract\]](#)
21. **Cohen P, Peehl DM, Graves HC, Rosenfeld RG.** 1994 Biological effects of prostate specific antigen as an insulin-like growth factor binding protein-3 protease. *J Endocrinol.* 142:407–415. [\[Medline\]](#)
22. **Gill ZP, Perks CM, Newcomb PV, Holly JM.** 1997 Insulin-like growth factor-binding protein (IGFBP-3) predisposes breast cancer cells to programmed cell death in a non-IGF-dependent manner. *J Biol Chem.* 272:25602–25607. [\[Abstract/Free Full Text\]](#)
23. **Rajah R, Valentinis B, Cohen P.** 1997 Insulin-like growth factor (IGF)-binding protein-3 induces apoptosis and mediates the effects of transforming growth factor-beta1 on programmed cell death through a p53- and IGF-independent mechanism. *J Biol Chem.* 272:12181–12188. [\[Abstract/Free Full Text\]](#)
24. **Cullen KJ, Yee D, Sly WS, et al.** 1990 Insulin-like growth factor receptor expression and function in human breast cancer. *Cancer Res.* 50:48–53. [\[Abstract\]](#)
25. **Prager D, Li HL, Asa S, Melmed S.** 1994 Dominant negative inhibition of tumorigenesis *in vivo* by human insulin-like growth factor I receptor mutant. *Proc Natl Acad Sci USA.* 91:2181–2185. [\[Abstract\]](#)
26. **Daughaday WH.** 1990 The possible autocrine/paracrine and endocrine roles of insulin-like growth factors of human tumors. *Endocrinology.* 127:1–4. [\[Medline\]](#)
27. **D’Ercole JA.** 1999 Actions of IGF system proteins from studies of transgenic and gene knockout models. In: Roberts CT, Rosenfeld RG, eds. *The IGF system: molecular biology, physiology, and clinical applications.* Totowa, NJ: Humana Press; 545–574.
28. **Bol DK, Kiguchi K, Gimenez-Conti I, Rupp T, DiGiovanni J.** 1997 Overexpression of insulin-like growth factor-1 induces hyperplasia, dermal

- abnormalities, and spontaneous tumor formation in transgenic mice. *Oncogene*. 14:1725–1734. [\[CrossRef\]](#)[\[Medline\]](#)
29. **Moon HD, Simpson ME, Li CH, Evans HM.** 1950 Neoplasms in rats treated with pituitary growth hormone I. pulmonary and lymphatic tissues. *Cancer Res*. 14:297–308.
 30. **Murphy LJ, Bell GI, Friesen HG.** 1987 Growth hormone stimulates sequential induction of c-myc and insulin-like growth factor I expression *in vivo*. *Endocrinology*. 120:1806–1812. [\[Abstract\]](#)
 31. **Snibson KJ, Bhathal PS, Hardy CL, Brandon MR, Adams TE.** 1999 High, persistent hepatocellular proliferation and apoptosis precede hepatocarcinogenesis in growth hormone transgenic mice. *Liver*. 19:242–252. [\[Medline\]](#)
 32. **Luft R.** 1957 Surgical hypophysectomy in patients with cancer. In: Pearson OH, ed. *Hypophysectomy*. Springfield, IL: Charles Thomas; 3–67.
 33. **Ma J, Pollak MN, Giovannucci E, et al.** 1999 Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I and IGF-binding protein-3. *J Natl Cancer Inst*. 91:620–625. [\[Abstract/Free Full Text\]](#)
 34. **Chan JM, Stampfer MJ, Giovannucci E, et al.** 1998 Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. *Science*. 279:563–566. [\[Abstract/Free Full Text\]](#)
 35. **Wolk A, Mantzoros CS, Andersson SO, et al.** 1998 Insulin-like growth factor 1 and prostate cancer risk: a population-based, case-control study [see Comments]. *J Natl Cancer Inst*. 90:911–915. [\[Abstract/Free Full Text\]](#)
 36. **Hankinson SE, Willett WC, Colditz GA, et al.** 1998 Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. *Lancet*. 351:1393–1396. [\[CrossRef\]](#)[\[Medline\]](#)
 37. **Beentjes JA, van Gorkom BA, Sluiter WJ, de Vries EG, Kleibeuker JH, Dullaart RP.** 2000 One year growth hormone replacement therapy does not alter colonic epithelial cell proliferation in growth hormone deficient adults. *Clin Endocrinol (Oxf)*. 52:457–462. [\[CrossRef\]](#)[\[Medline\]](#)
 38. **Klein I, Parveen G, Gavalier JS, VanThiel DH.** 1982 Colonic polyps in patients with acromegaly. *Ann Intern Med*. 97:27–30. [\[Medline\]](#)
 39. **Ituarte EA, Petrini J, Hershman JM.** 1984 Acromegaly and colon cancer. *Ann Intern Med*. 101:627–628. [\[Medline\]](#)

40. **Brunner JE, Johnson CC, Zafar S, Peterson EL, Brunnes JF, Mellinger RC.** 1990 Colon cancer and polyps in acromegaly: increased risk associated with family history of colon cancer. *Clin Endocrinol (Oxf)*. 32:65–71. [\[Medline\]](#)
41. **Ezzat S, Strom C, Melmed S.** 1991 Colon polyps in acromegaly. *Ann Intern Med*. 114:754–755. [\[Medline\]](#)
42. **Ladas SD, Thalassinos NC, Ioannides G, Raptis SA.** 1994 Does acromegaly really predispose to an increased prevalence of gastrointestinal tumours? *Clin Endocrinol (Oxf)*. 41:597–601. [\[Medline\]](#)
43. **Terzolo M, Tappero G, Borretta G, et al.** 1994 High prevalence of colonic polyps in patients with acromegaly. Influence of sex and age. *Arch Intern Med*. 154:1272–1276. [\[Abstract\]](#)
44. **Vasen HFA, Erpecum KJ, Roelfsema F, et al.** 1994 Increased prevalence of colonic adenomas in patients with acromegaly. *Eur J Endocrinol*. 31:1–3.
45. **Delhougne B, Deneux C, Abs R, et al.** 1995 The prevalence of colonic polyps in acromegaly: a colonoscopic and pathological study in 103 patients. *J Clin Endocrinol Metab*. 80:3223–3226. [\[Abstract\]](#)
46. **Colao A, Balzano A, Ferone D, et al.** 1997 Increased prevalence of colonic polyps and altered lymphocyte subset pattern in the colonic lamina propria in acromegaly. *Clin Endocrinol (Oxf)*. 47:23–28. [\[Medline\]](#)
47. **Jenkins PJ, Fairclough PD, Richards T, et al.** 1997 Acromegaly, colonic polyps and carcinoma. *Clin Endocrinol (Oxf)*. 47:17–22. [\[Medline\]](#)
48. **Jenkins PJ, Besser GM, Fairclough PD.** 1999 Colorectal neoplasia in acromegaly. *Gut*. 44:585–587. [\[Free Full Text\]](#)
49. **Jenkins PJ.** 2000 Acromegaly and colon cancer. *Growth Horm IGF Res*. 35–36.
50. **Renehan AG, Bhaskar P, Painter JE, et al.** 2000 The prevalence and characteristics of colorectal neoplasia in acromegaly. *J Clin Endocrinol Metab*. 85:3417–3424. [\[Abstract/Free Full Text\]](#)
51. **Jenkins PJ, Frajese V, Jones AM, et al.** 2000 Insulin-like growth factor I and the development of colorectal neoplasia in acromegaly. *J Clin Endocrinol Metab*. 85:3218–3221. [\[Abstract/Free Full Text\]](#)
52. **Mathews LS, Hammer RE, Behringer RR, et al.** 1988 Growth enhancement of transgenic mice expressing human insulin-like growth factor I. *Endocrinology*. 123:2827–2833. [\[Abstract\]](#)

53. **Quaife CJ, Mathews LS, Pinkert CA, Hammer RE, Brinster RL, Palmiter RD.** 1989 Histopathology associated with elevated levels of growth hormone and insulin-like growth factor I in transgenic mice. *Endocrinology*. 124:40–48. [\[Abstract\]](#)
54. **Lund PK.** 1999 IGFs and the digestive tract. In: Roberts CT, Rosenfeld RG, eds. *The IGF system molecular biology, physiology, and clinical applications*. Totowa, NJ: Humana Press; 517–544.
55. **Ohneda K, Ulshen MH, Fuller CR, D’Ercole AJ, Lund PK.** 1997 Enhanced growth of small bowel in transgenic mice expressing human insulin-like growth factor I. *Gastroenterology*. 112:444–454. [\[Medline\]](#)
56. **Ulshen MH, Dowling RH, Fuller CR, Zimmermann EM, Lund PK.** 1993 Enhanced growth of small bowel in transgenic mice overexpressing bovine growth hormone. *Gastroenterology*. 104:973–980. [\[Medline\]](#)
57. **DiSario JA, Foutch PG, Mai HD, Pardy K, Manne RK.** 1991 Prevalence and malignant potential of colorectal polyps in asymptomatic, average-risk men. *Am J Gastroenterol*. 86:941–945. [\[Medline\]](#)
58. **Lieberman MD, Weiss DG, Bond JN, et al.** 2000 Use of colonoscopy to screen asymptomatic adults for colorectal cancer. *N Engl J Med*. 343:162–168.
59. **Rex DK, Lehman GA, Ulbright TM, et al.** 1993 Colonic neoplasia in asymptomatic persons with negative fecal occult blood tests: influence of age, gender, and family history. *Am J Gastroenterol*. 88:825–831. [\[Medline\]](#)
60. **Cheung NW, Boyages SC.** 1997 Increased incidence of neoplasia in females with acromegaly. *Clin Endocrinol (Oxf)*. 47:323–327. [\[CrossRef\]](#)[\[Medline\]](#)
61. **Chobanian SJ, Van Ness MM, Winters C, Cattau EL.** 1985 Skin tags as a marker for adenomatous polyps of the colon. *Ann Intern Med*. 103:892–893. [\[Medline\]](#)
62. **Sonksen P, Jacobs H, Orme S, Belchetz P.** 1997 Acromegaly and colonic cancer [Comment]. *Clin Endocrinol (Oxf)*. 47:647–648. [\[CrossRef\]](#)[\[Medline\]](#)
63. **Popovic V, Damjanovic S, Micic D, et al.** 1998 Increased incidence of neoplasia in patients with pituitary adenomas. The Pituitary Study Group. *Clin Endocrinol (Oxf)*. 49:441–445. [\[CrossRef\]](#)[\[Medline\]](#)
64. **Pines A, Rozen P, Ron E, Gilat T.** 1985 Gastrointestinal tumors in acromegalic patients. *Am J Gastroenterol*. 80:266–269. [\[Medline\]](#)

65. **Barzilay J, Heatley GJ, Cushing GW.** 1991 Benign and malignant tumors in patients with acromegaly. *Arch Intern Med.* 151:1629–1632.[\[Abstract\]](#)
66. **Colao A, Marzullo P, Spiezia S, et al.** 1999 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.* 84:1986–1991.[\[Abstract/Free Full Text\]](#)
67. **Mustacchi P, Shimkin MB.** 1956 Occurrence of cancer in acromegaly and in hypopituitarism. *Cancer.* 10:100–104.
68. **Harris GW, Donovan BT.** 1966 *The pituitary gland.* Berkeley: University of California Press.
69. **Ron E, Gridley G, Hrubec Z, Page W, Arora S, Fraumeni Jr JF.** 1991 Acromegaly and gastrointestinal cancer [published erratum appears in *Cancer*, 1992, 69:549]. *Cancer.* 68:1673–1677.
70. **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.[\[Abstract/Free Full Text\]](#)