

## 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).

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 (5–14). 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 apo-

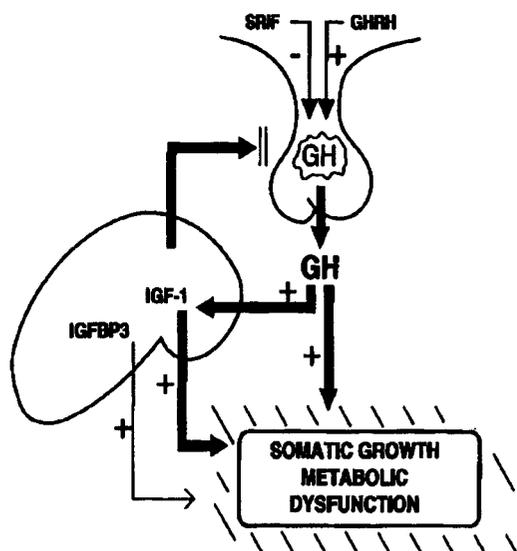
ptotic advantage (16–19). Thus, excess GH, by inducing both IGFBP3 and IGF-I levels, promotes dysregulated cell growth balance characterized by dynamic signals for cell apoptosis *vs.* cell growth advantage (Fig 2).

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.

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, 24–26). 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

Received August 25, 2000. Revision received December 7, 2000. Revision received January 11, 2001. Accepted January 26, 2001.

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Melmed, *N Engl J Med* 322:966, 1990

FIG. 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 Ref. 1.

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

Clinical features in acromegaly		
Features	n	Incidence (%)
Acral enlargement	626	98
Hyperhidrosis	526	70
Menstrual disturbances	318	69
Headaches	809	59
Paresthesias	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.

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

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

Acromegaly: outcome determinants			
Causes of death	%	Survival determinants	P
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.

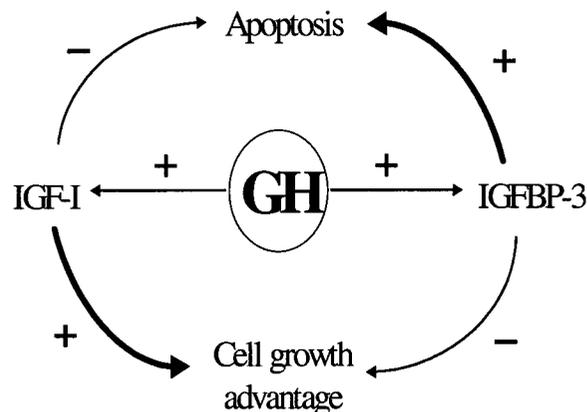


FIG. 2. Balance of GH influences on cell growth regulation. GH stimulates both IGF-I and IGFBP-3, which mediate cell proliferation and cell removal, respectively. Adapted from Refs. 21–23.

high IGFBP-3 levels are concordant with a lower risk for cancer (33–35).

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 phar-

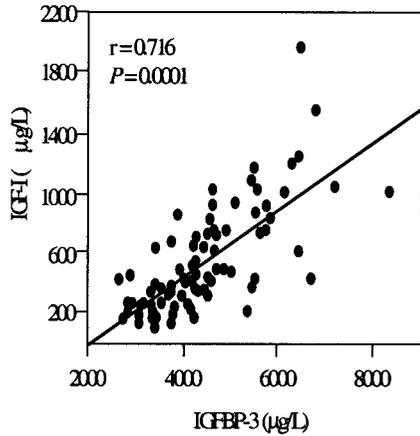


FIG. 3. IGFBP-3 levels are elevated in acromegaly and correlate with IGF-I levels. Adapted from Ref. 20.

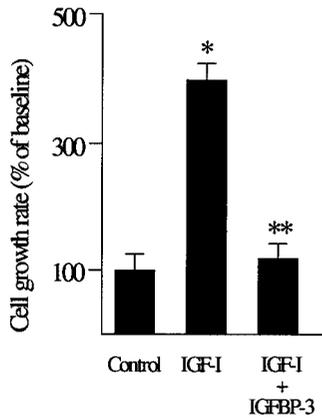


FIG. 4. IGFBP-3 inhibits prostate cancer cell growth. From Ref. 21.

macovigilant 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).

*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 (38–51) (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

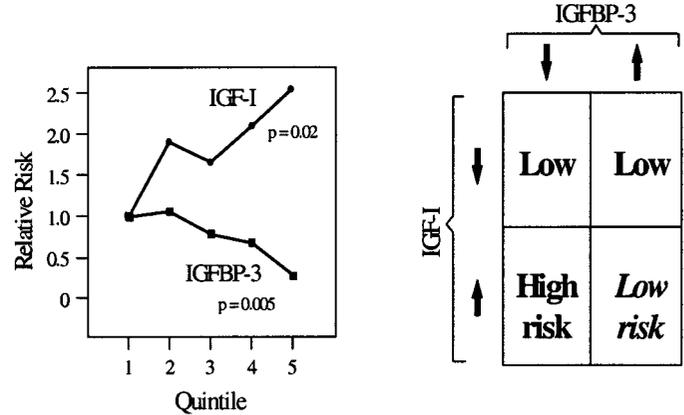


FIG. 5. Relative risk for development of colon cancer. IGF-I and IGFBP-3 levels were measured retrospectively in the general population. Because patients with acromegaly exhibit both elevated IGF-I and IGFBP-3 levels, their relative risk for cancer development seems to be low. Adapted from Ref. 33.

in the GH transgenic model (52–56). 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.

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 (38–47, 50, 51), up to 40% of asymptomatic unselected males over the age of 50 yr in the general population harbor colonic lesions (57–59). 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

**TABLE 3.** Colon polyps in acromegaly

n	Polyps				Total	Carcinoma	Reference
	M/F	Mean age	Adenoma	Hyperplastic			
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 <sup>a</sup>	27	18	45	3	(50)
66 <sup>b</sup>	na	32.7	25	18	43	1	(51)
678			165 (24%)	144 (21%)	309 (45%)	17 (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.

<sup>a</sup> Median age.

<sup>b</sup> Repeat colonoscopy.

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, 63–65), 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 influ-

**TABLE 4.** Acromegaly and cancer incidence: multicenter analysis

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

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

<sup>b</sup> 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.

ence 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 inci-

dence 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.

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*

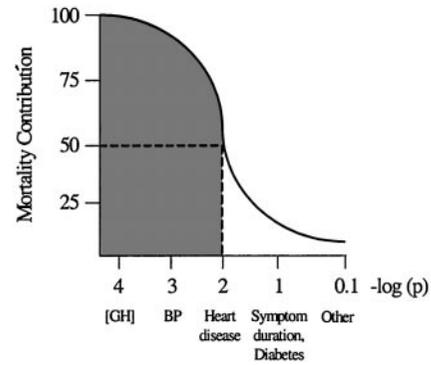
Overall mortality in patients with acromegaly correlates with the degree of GH control, and mortality rates from cancer also stratify according to posttreatment GH levels (70) (Table 5). Overall, if posttreatment GH is controlled, both overall mortality and cancer mortality are unchanged from the control 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.

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

**TABLE 5.** Posttreatment GH levels and mortality in acromegaly

Mortality	Posttreatment GH (ng/mL)			P
	<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.



**FIG. 6.** Depiction of mortality determinants in patients with acromegaly. The x-axis reflects the  $P$  value (log) as calculated from published retrospective reports (8–14).

factors (including cancer) account for relatively low mortality impact (Fig 6).

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). 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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