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CLINICAL PERSPECTIVE

Acromegaly and Cancer: A Problem

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Since the original description by Pierre Marie over a century ago, acromegaly has been known to be associated with an increased morbidity and mortality. Early epidemiological reviews suggested that this was due largely to cardiovascular, cerebrovascular, respiratory, and metabolic diseases. However, more recently, studies such as that by Ezzat and Melmed (1) have suggested that these patients currently are also at increased risk for cancer, particularly colorectal; some suggestions have been made that there is a risk of breast, prostate, and possibly hematological malignancies (2, 3) (Table 1). Some of the difficulty in determining the true incidence of cancer in this condition results from the relative rarity of acromegaly itself, which makes it difficult for individual centers to gather sufficient numbers of patients for statistical analysis. A further important factor is that it is only with improved treatment of the other complications that patients with acromegaly are now surviving long enough to reach the age of increased cancer risk. In the early series by Wright *et al.* (64) and Alexander *et al.* (65), approximately 50% of patients had died before the age of 60 yr; it is clearly inappropriate to use early reviews to draw conclusions relating to cancer risk in patients exposed to current improved practice because patients are now living much longer, and the development of malignancy in these patients appears to be age related. The establishment of the true prevalence of cancer in acromegaly requires current data and will become clearer with multicenter analysis, such as that of acromegaly registers being collated in the United Kingdom and U.S.

Colorectal cancer and tubulo-villous adenomas

Colorectal cancer. Of all cancers, evidence is strongest for an increased risk in acromegaly of colorectal cancer (Table 2), and this is now regarded by many researchers and consensus working groups as being a major complication of this disease (1–7). The cancer surveillance program at St. Bartholomew's Hospital was initiated after the publication of one of the earliest reports detailing an increased prevalence of colonic neoplasia by Ezzat and Melmed (8). In that study of 26 patients, 3 had colorectal cancer, and 8 had tubulo-villous adenomas. Of the 155 asymptomatic patients with acromegaly aged over 50 yr investigated at St. Bartholomew's Hospital with full-length colonoscopic examination, 10 (6.5%) have been found to have adenocarcinoma. Although, in common with several other series, this study did not include asymptomatic matched controls, the relative risk can be assessed by comparison with published series of screened asymptomatic nonacromegalic patients (Table 3). These analyses give a relative risk of between 6.8- and 18.3-fold. That this increased risk is not restricted to our center is supported by grouping all of the prospective series of colonoscopic screening of patients with acromegaly: a total of 25 cancers have been detected in 681 patients (3.7%), compared with a rate of 0.5% among control subjects in those series with concurrent control groups (relative risk, 13.4; $P < 0.00001$). Even a recent study that reported no increased rate of colorectal neoplasia recorded cancers in 2.6% of asymptomatic patients with acromegaly (9). An increasing amount of data suggests that the prevalence of colorectal cancer is significantly increased in acromegaly, and in common with other researchers, we regard these patients as being at high risk of developing this malignancy (1, 3, 4, 6, 10).

Tubulo-villous adenomas

In nonacromegalic patients, the majority of colorectal cancers arise from tubular adenomas, a process that is thought to take approximately 10 yr. Particularly bad prognostic signs are a severe degree of cellular dysplasia within the adenoma and a size greater than 10 mm. In common with colorectal cancer, numerous studies have demonstrated an increased prevalence of these premalignant polyps in acromegaly with rates of between 9–40%. Several reasons account for these variations. As in the general population, age is a major determinant of their prevalence in acromegaly (9, 11–13); in one large series adenomas occurred in only 8% of patients aged less than 40 yr, 12% of those aged 40–49 yr, 26% of those aged 50–59 yr, 30% of those aged 60–69 yr, and 33% of those over 70 yr of age (13). Series that have recorded a lower overall prevalence rate in acromegaly have often studied younger patients than those that report an increased age-related prevalence (14). Another important variable is the need to visualize the entire colon. In some series the cecum was reached in only about 70% of patients (14, 15); improved visualization to the cecum is associated with a higher prevalence rate, as the lesions occur at the right side

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TABLE 1. Retrospective epidemiological reviews of occurrence of malignant disease in patients with acromegaly

Author	No. of patients	Relative risk of malignant disease	Type of cancers reported (no. of patients)
Mortality studies			
Wright *et al.*, 1970 (64)	194	M + F, 1.38:1 F (65–75 yr) 5:1[a]	Bronchus (3); colorectal (2; gastric (2);); thyroid (2); fibrosarcoma (1)
Alexander *et al.*, 1980 (65)	164	M 4.6:1[b] F 0.43:1	NR
Nabarro *et al.*, 1987 (44)	47	M + F 0.95:1	NR
Bengtsson *et al.*, 1988 (66)	62	M + F 2.67:1[b] F 3.33:1[b]	Breast (3); haematological (3); bronchus (2); ependtmoma (1); carcinoid (1); melanoma (1); renal (1); gastric (1); adrenal (1); prostate (1)
Ritchie *et al.*, 1990 (47)	36	NR	Colorectal (4); bronchus (3); breast (1); pancreas (1); oesophagus (1); biliary tree (1)
Orme *et al.*, 1998 (28)	1239	M + F 1.16:1 (breast, 1.6:1) (colorectal, 2.47:1[b])	Breast (13); colorectal (16); bronchus (13); others (41)
Studies detailing occurrence of malignancy in acromegaly			
Nabarro *et al.*, 1987 (44)	256	F 1.86:1 (breast, 4.23:1[b])	Breast (11); bronchus (3); colorectal (2); ovary (2); haematological (2); prostate (1); small intestine (1); thyroid (1); fibrosarcoma (1); astrocytoma (1); renal (1)
Barzilay *et al.*, 1991 (74)	87	M + F 2.5:1	Thyroid (2); haematological (1); breast (1); sarcoma (1); ovarian (1); colorectal (1)
Ron *et al.*, 1991 (67)	1041	M + F 1.6:1 (esophagus, 2.22:1) (stomach, 1.6:1)	Bronchus (22); colorectal (14); oesophagus (7); haematological (7); gastric (4); melanoma (3); small intestine (1); pancreas (1)
Cheung *et al.*, 1997 (68)	50	M 1.2:1 F 4.3:1[c]	Breast (2); renal (2); colorectal (1); melanoma (1); parotid (1); prostate (1)
Orme *et al.*, 1998 (28)	1239	M + F 0.76:1	Colorectal (16); breast (14); bronchus (6); others (42)
Popovic *et al.*, 1998 (7)	220	3.39:1[b]	Breast (4); cervix (4); haematological (3); thyroid (3); colorectal (2); pancreas (2); skin (2); renal (1); bladder (1); ovarian (1)

M, Male; F, female; NR, not recorded.
[a] $P < 0.05$.
[b] $P < 0.01$.
[c] $P < 0.001$.

of the colon more often than is usually found in other patient groups (13, 16, 17).

In common with the data on cancer, the absence of simultaneous control groups in some series of patients with acromegaly has been used to play down the significance of the findings. However, comparison of these data with those from series with matched control groups confirm the increased prevalence in acromegaly (Table 2). Grouping of these various studies gives an overall prevalence rate in acromegaly of 21% compared with 9% for controls (relative risk, 2.36, 95% confidence interval, 1.8–3.1; $P < 0.0001$). This mean prevalence among controls accords with the 9–10% reported in a number of published series of colonoscopic screenings of asymptomatic nonacromegalic patients. However, a recent large scale study of nonacromegalic subjects found a higher rate of 37% (18). There are several reasons for the discrepancy relating to the latter study: 1) the patients were all males, and males are known to have an increased incidence of colorectal neoplasia; and 2) there was a marked selection bias in that of the available 17,732 patients, only 3,196 were selected for screening, 50% of whom had been referred by their medical practitioner for unspecified reasons. There was also a positive selection toward those with a family history of colonic cancer. That this study overestimated the prevalence of adenoma detected by colonoscopy in the general population is indicated by a simultaneously published study of colonoscopic screening of almost 2,000 asymptomatic subjects among whom the prevalence rate was again 9.6% (19).

The majority of studies report an increased prevalence of colonic adenomas in acromegaly, but a recent study published in this journal failed to do so (9). Indeed, the observed prevalence in that report is the lowest of all series of patients with acromegaly. However, many of the patients were studied at an earlier age (mean, 54.8 yr; range, 25–82 yr). If the prevalence of tubulo-villous adenomas is assessed only in those patients reported in this study over the age of 50 yr, the prevalence is 20%, not different from that in other series of patients with acromegaly and clearly greater than the generally accepted control prevalence of around 9%. Despite the claim to the contrary, these observations confirm the increased risk of colonic neoplasms in the older patients with acromegaly. Furthermore, the autopsy-based second control group is not comparable to the group of acromegalic patients; not only are the subjects elderly, but the resected bowel obtained at autopsy is washed several times and repeatedly examined in optimal lighting, often under a microscope, and lesions as small as 1 mm are recorded. This is far different from the *in vivo* situation in acromegalic patients, in whom the colon is larger, more cavernous, and with frequently difficult visualization (10, 20). Indeed, such limitations are likely to underestimate the true prevalence rate in acromegaly.

Characteristics of colorectal neoplasia in acromegaly. In addition to its increased overall incidence, there is evidence that colorectal neoplasia in acromegaly has different characteristics compared with those in the general population. The lesions are more likely to be right sided, with up to 68% of adenomas

TABLE 2. Retrospective and prospective studies of screening for colorectal neoplasia in patients with acromegaly

Author	Patients with acromegaly					Control subjects				
	No. of patients	Mean age (yr)	No. with tubular adenomas (%)	No. with hyperplastic polyps (%)	No. with cancer (%)	No. of subjects	Mean age (yr)	No. with tubular adenomas (%)	No. with hyperplastic polyps (%)	No. with cancer (%)
Retrospective studies										
Klein *et al.*, 1982 (22)	27	53			2 (7.5)					
Pines *et al.*, 1985 (72)	48	61			3 (6)					
Ziel *et al.*, 1988 (73)	3	57			2 (66)					
Brunner *et al.*, 1990 (70)	13	NR			0 (0)					
Ron *et al.*, 1991 (67)	1041	61			13 (1.3)					
Prospective studies										
Klein *et al.*, 1982 (22)	17	49	5 (29)	3 (18)	2 (12)					
Ituarte *et al.*, 1984 (69)	12	56	2 (15)	1 (8)	3 (20)					
Brunner *et al.*, 1990 (70)	29	NR	4 (14)		2 (7)					
Ezzat *et al.*, 1991 (8)	23	47	8 (35)	1 (4)	0 (0)					
Ladas *et al.*, 1994 (14)	54	47	5 (9)	11 (20)	0 (0)					
Vasen *et al.*, 1994 (15)	49	54	11 (22)	5 (10)	0 (0)	57	54	5 (8.7)	2 (3.5)	0
Terzolo *et al.*, 1994 (11)	31	52	12 (38)	8 (26)	1 (3)	236	50	34 (140)	24 (10)	0
Delhougene *et al.*, 1995 (12)	103	51	23 (22)	25 (24)	0 (0)	138	53	11 (8)	6 (4.4)	0
Colao *et al.*, 1997 (17)	50	NR	11 (22)	12 (24)	1 (2)	318	NR	18 (5.7)	20 (6.3)	4 (1.2)
Jenkins *et al.*, 1997 (13)[a]	155	63	40 (26)	37 (24)	10 (6.5)					
Archambeaud-Mouveroux *et al.*, 1998 (23)	16	53		4 (25)	2 (12)				(4)	
Tzoiti *et al.*, 2000 (21)	20	51	8 (40)	2 (10)	1 (5)	47	50	3 (6)	6 (13)	0
Renehan *et al.*, 2000 (9)	122	55	11 (9)	18 (16)	3 (2.6)					
Total (prospective studies)	681		140 (21)	127 (19)	25 (3.7)	796		71 (9)	58 (7)	4 (0.5)

[a] Represents the current data from St. Bartholomew's Hospital of patients aged over 50 yr.

TABLE 3. Relative risk of the prevalence of colorectal cancer (CRC) in patients with acromegaly determined by comparison of prevalence rates from St. Bartholomew's Hospital and other published series to large scale screening studies of asymptomatic nonacromegalic subjects

Published series of colonoscopic screening of asymptomatic subjects without acromegaly			Relative risk of colorectal cancer in acromegaly obtained by comparison with St. Bartholomew's Hospital data and other published series of acromegalic patients	
Author	No. of subjects screened	No. of subjects (%) with CRC	St. Bartholomew's series (>50 yr) CRC = 10/155 patients	All series combined[a] CRC = 25/681 patients
Rex *et al.*, 1993 (71)	621 (>50 yr)	3 (0.4)	13.4 (4.0–44) [<0.00001]	7.6 (2.4–23.6) [<0.00006]
Imperiale *et al.*, 2000 (19)	1994 (>50 yr)	7 (0.3)	18.3 (7.3–45.9) [$<3.6 \times 10^{-8}$]	10.4 (4.6–23.5) [$<5.0 \times 10^{-10}$]
Lieberman *et al.*, 2000 (18)	3196 (50–75 yr)	30 (0.9)	6.8 (3.4–13.5) [<0.00001]	3.9 (2.3–6.6) [<0.000001]

Ninety-five percent confidence intervals are in *parentheses*; *P* values are in *brackets*.
[a] Refs. 8, 9, 11–15, 17, 21–23, 69, and 70.

being situated in the ascending or transverse colon (9, 12, 15, 17, 21); 3 of the 10 carcinomas in the Bart's series were at the cecum. The adenomas also tend to be larger, with 1 series reporting a mean diameter of 18 mm compared with 9 mm in controls ($P < 0.001$) (9, 15, 17). Several groups have also reported that the adenomas tend to be more dysplastic, with up to 64% being classified as moderately to severely dysplastic (9, 17). Finally, the adenomas are more often multiple in patients with acromegaly (9, 11, 12, 21–23). These altered characteristics suggest that not only do adenomas occur more frequently in acromegaly, but they behave more aggressively, with an increased tendency for malignant progression.

Influence of serum GH and insulin-like growth factor I (IGF-I) on colorectal neoplasia. In nonacromegalic subjects, the colonic epithelium is arranged in crypts, with actively dividing cells located at the base that then move up the crypt toward the lumenal surface to undergo apoptosis. Increased proliferation is the preliminary step in adenoma formation, leading to an increased chance of an oncogenic mutation in the adenomatosis polyposis coli gene, the initial mutation in colorectal tumorigenesis. IGF-I is a known mitogen in many tissues and stimulates the growth of colorectal cancer cells *in vitro* (24, 25). We and others have shown increased proliferation of the colonic epithelium in acromegaly, proportional to serum IGF-I levels (26, 27). However, some studies of patients with acromegaly have shown no association between serum IGF-I levels and the presence of neoplasia (11), whereas others have shown a significant association (9, 15, 17), including a large retrospective review that demonstrated a positive association between mortality from colorectal cancer in acromegaly and disease activity (28). There is uncertainty as to how long adenomas/carcinomas have actually been present when detected at the time of colonoscopy; therefore, the relationship between IGF-I levels and development of the adenoma is uncertain. A clearer prospective study has been provided in patients who have had removal of adenomas at an initial colonoscopy followed by review with a second colonoscopic evaluation at intervals after the original screening examination. We recently completed this for 66 of our original cohort of patients at a mean interval of 33 months (range, 3–76 months). Newly developed adenomas were detected in 14% of patients, and their occurrence was significantly related to both serum GH ($P < 0.05$) and IGF-I levels ($P < 0.005$). This would be consistent with the idea that a raised IGF-I level is relevant at the time that the adenoma develops rather than when it is subsequently discovered and that elevated circulating GH/IGF-I is implicated in colorectal tumorigenesis in acromegaly (29). This is in keeping with recent epidemiological studies in nonacromegalic subjects that have demonstrated a positive association between the development of colorectal cancer and serum IGF-I levels in the upper, rather than the lower, part of the normal range (30, 31).

In addition to its proliferative actions, IGF-I exerts marked antiapoptotic effects in a variety of tissues (32, 33). IGF-I prevents butyrate-induced apoptosis in HT-29 and Caco-2 colorectal cancer cells, and the increased colonic epithelial proliferation in acromegaly is accompanied by significantly reduced apoptosis and a disordered pattern of the Bcl-2 family of apoptotic proteins (34). The precise mechanisms by which IGF-I might cause these effects remain uncertain. One possibility involves the inappropriate induction of c-*myc* transcription. Both GH and IGF-I have been shown to activate c-*myc* transcription *in vivo*, and this gene is up-regulated in 70–90% of colorectal cancers at an early stage (35, 36). c-*myc* is regarded as playing a central role in sporadic colorectal tumorigenesis regulating the transcription of numerous genes that are intimately involved in proliferation, apoptosis, angiogenesis, and metastases.

In addition to GH and IGF-I, alterations in the intracolonic environment might also play a role in the development of neoplasia in acromegaly. One such factor relates to bile acids and, in particular, the unconjugated secondary bile acid, deoxycholic acid (DCA). This is formed in the cecum by bacterial deconjugation and dehydroxylation of the primary bile acid, cholic acid. Serum levels of unconjugated DCA have been shown to reflect intraluminal concentrations and are much higher in nonacromegalic patients with colorectal neoplasia than in age-matched normal subjects (37, 38). Levels of serum unconjugated DCA are, on the average, 3 times higher in acromegaly than in nonacromegalic control subjects; patients with acromegaly and colonic neoplasia have even higher levels than those without neoplasms (39). The mechanisms for this increase in DCA concentrations relate both to a prolonged colonic transit and an increased intraluminal bacterial activity (40).

Guidelines for colonoscopic screening. In the nonacromegalic population, it has been demonstrated that colonoscopic

screening and removal of adenomas reduce the incidence of subsequent carcinoma, thus suggesting that colorectal cancer is to some extent a preventable disease (41). As patients with acromegaly are at increased risk of colonic cancer, they should be offered regular colonoscopic screening (5, 6, 42). The question arises as to when this should begin and how often it should be repeated. In nonacromegalic subjects, a single sigmoidoscopy at the age of 55 yr has been proposed by some authorities as being sufficient (43). We believe that this is inadequate and that patients with acromegaly should be regarded as a high risk group, similar to patients with a strong family history of colorectal cancer (10). In our series of repeat colonoscopic evaluations, all but two of the patients with new adenoma had had an adenoma at the original screening (29). Our youngest patient with a carcinoma was aged 58 yr, and our youngest patient with an adenoma was 40 yr. We suggest that it would be prudent to offer routine surveillance similar to other at risk groups. A conservative approach would be initial screening at the age of 40 yr with subsequent reevaluation intervals dependent on the colonoscopic findings and disease activity. When an adenoma is found, or if the serum IGF-I level is still elevated, repeat screening should occur after 3 yr. A normal full-length screening colonoscopy or the presence of a hyperplastic polyp should warrant screening at 5-yr intervals. Naturally, these preliminary guidelines will need to be amended in the light of further data.

There are several practical issues that determine the success of colonoscopy in patients with acromegaly. Their increased colonic length and circumference, as well as prolonged colonic transit time mean that standard bowel preparation is usually inadequate (20, 40). In the authors' experience, 6 L Kleen-Prep (Norgine, Harefield, UK) instead of the usual 3 L are generally required, with 2 L given at 6, 4, and 2 h before the procedure, with a liquid only diet for the preceding 24 h. In view of the technical difficulties of the examination, an experienced colonoscopist should perform the procedure, as in inexperienced hands the cecum is reached in only approximately 75% of cases (10). This is particularly important given the propensity toward right-sided lesions.

In conclusion, a number of studies have confirmed that acromegaly is associated with an increased prevalence of colorectal neoplasia, and as such, these patients should be regarded as being at high risk for developing this complication. Regular colonoscopic screening and polypectomy will reduce the incidence of subsequent carcinoma among these patients. The demonstration of a clear relation to serum GH and IGF-I levels is further indication for more aggressive management of the underlying acromegaly.

Other malignancies

Breast carcinoma. In addition to colorectal cancer, a number of reviews have indicated that patients with acromegaly may be also at increased risk of developing breast carcinoma (7, 44–47) with one study suggesting a 4-fold increase in risk (44). Determining the true incidence, however, is made more difficult by the restriction to female patients, which halves the number of patients at any single center. This has to some extent been overcome by a large multicenter retrospective review of more than 1200 patients that demonstrated an almost 2-fold increase in mortality from breast carcinoma, although other clinical studies in acromegalic patients are limited (28). There is also circumstantial evidence to suggest that patients with acromegaly might be at increased risk of developing breast cancer. Two early epidemiological studies have related the GH/IGF-I axis to breast carcinoma in the general population, in that patients with breast carcinoma had significantly higher serum GH or IGF-I levels compared with subjects without carcinoma (48, 49). A subsequent prospective review showed that a serum IGF-I level in the upper part of the normal range was associated with a significant increased risk of developing this cancer (50). Further prospective studies are required to establish whether there is truly an increased risk.

Some of the earliest work relating the GH/IGF-I axis to breast carcinoma was provided in the 1950s by Moon *et al.*, who demonstrated the occurrence of mammary neoplastic change in female rats injected long term with GH (51). It has also long been known that hypophysectomy is associated with disease remission in patients with metastatic breast carcinoma, even in previously ovariectomized women (52). *In vitro*, IGF-I causes marked proliferation of human breast cancer cell lines (53–55), results complemented by *in vivo* experiments using infusions of GH and/or IGF-I to monkeys (56). Significant increases in the size of the mammary glands and proliferation of the epithelium were observed in response to both GH (3- to 4-fold) and the combination of GH and IGF-I (4- to 5-fold). These changes correlated with serum GH/IGF-I levels, which were comparable to those seen in acromegaly. Further evidence is suggested by transgenic human GH mice, which have elevated plasma GH levels and an increased incidence of mammary tumors (57). Conversely, other models have used the *lit* mouse, in which there is a functional defect of the GHRH receptor and decreased serum GH levels (58). Transplantation of human breast cancer cells into these mice results in approximately 50% decreased cancer growth compared with controls.

The number of studies showing an increase in breast cancer incidence in females with acromegaly is limited, but there is some evidence relating the GH/IGF-I axis and breast cancer in the nonacromegalic population. Further studies are required.

Prostate cancer. Evidence linking prostatic carcinoma and acromegaly is circumstantial. This may be because the disease is limited to elderly men, and it has not been until recently that these patients with acromegaly have survived long enough to become available for epidemiological studies. Significant prostatic enlargement has been demonstrated in young (<40-yr-old) patients with acromegaly compared with age-matched controls (mean volume, 28 *vs.* 18 mL, respectively; $P < 0.001$), with a higher than expected prevalence of micro- and macrocalcification (59). This hyperplasia resolved with lowering of GH levels. In a recent cross-sectional survey of acromegalic men aged over 50 yr, an elevated serum prostate-specific antigen was detected in 17%, which represented 46% of those aged over 65 yr, with one patient having a metastatic prostate cancer (60). In a

retrospective review of nonacromegalic men, those with histologically proven prostate carcinoma were found to have serum IGF-I levels higher than control levels, although still within the normal range (61, 62). The relative risk was estimated at 1.9 for each 60 mg/mL increment in serum IGF-I, but increased almost 7-fold in the presence of a higher serum testosterone level. These findings were supported by a recent prospective study in which a serum IGF-I level in the upper quintile of the normal range was associated with a significantly increased risk of developing prostate cancer, which was increased to almost 18-fold for men aged over 60 yr of age (63).

Thus, although direct evidence is limited, these data suggest that the incidence of prostatic carcinoma in male patients with acromegaly may be increased, although well controlled studies have not been published. Given this, increased surveillance of these patients is warranted, with the highest theoretical risk being in elderly men with persistent elevated serum IGF-I who are receiving testosterone replacement.

Conclusions

In summary, the evidence of an increased risk of colorectal cancer in acromegaly is now strong. Such patients should be considered as a high risk group for the development of this neoplasia, which is related to disease activity. These patients should be offered regular colonoscopic screening, although the optimal frequency of this has yet to be finally determined. Determination of the pathogenesis of colorectal cancer in these patients will offer significant information about the role of the GH/IGF-I axis in colorectal tumorigenesis in the general population. There is circumstantial evidence suggesting that breast and prostate malignancies may also be increased in acromegaly, but the true incidence will await the outcome of large scale epidemiological studies. As cancer is generally a disease of increasing age; the current trend toward improved survival of patients with acromegaly may reveal an increased prevalence of cancer in the future.

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