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Thyroid and colorectal cancer screening in acromegaly patients: Should it be different from that in the general population?

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1769134> since 2022-10-11T12:44:14Z

Published version:

DOI:10.1530/eje-19-1009

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(Article begins on next page)

1 **Thyroid and colorectal cancer screening in acromegaly patients:**
2 **should it be different from that in the general population?**

3

4 ***Introduction***

5 Patients with acromegaly are exposed to persistent excess of growth hormone (GH), which
6 stimulates synthesis of insulin-like growth factor-1 (IGF1) ¹. Given that elevated levels of IGF1
7 inhibit apoptosis and promote cell proliferation in many tissues ², it is biologically plausible to
8 consider acromegalic patients as at increased risk of cancer. The role of GH and, in particular, IGF1
9 in the promotion and development of cancer is well established in preclinical models and
10 population-based studies have detected an association between IGF1 levels and cancer risk such as
11 colorectal, thyroid, breast, and prostate cancer ³.

12 Whether cancer should be considered part of the clinical manifestations of acromegaly remains
13 matter of controversy ^{4, 5}. There are several reasons that may confound interpretation of published
14 research and account for the discrepancies of the results.

15 First, most studies may have insufficient statistical power to detect a moderate increase in risk
16 for different cancer types, and adjust for confounding factors ⁶⁻⁸. Second, studies used different
17 methodological approaches and heterogeneous patient populations, such as sex-specific series ^{9, 10}
18 or hospitalized patients ^{9, 11}. Case-control studies may result in an overestimation of risk, due to
19 their inherent limitations in the capture of events (i.e., ascertainment bias) and identification of
20 matching controls (i.e., well-worried bias) ¹². Population-based studies are theoretically more
21 robust, but should have a nationwide dimension and availability of accurate cancer registry data ¹³.
22 However, it should be taken into account that epidemiology of cancer is not uniform between
23 countries, and even between different regions of the same country, being influenced by lifestyle and
24 the genetic background of the population, as well as by environmental factors ¹.

25 Needless to say that the retrospective nature of the studies, and the fact that some of them date
26 back to more than 40 years ago, make the issue even more challenging. The availability of a more
27 effective, multi-modal treatment of acromegaly has expanded life expectancy of patients, who may
28 now live until the elder age when cancer incidence rises ¹⁴. Therefore, the clinical relevance of the
29 association between acromegaly and cancer may be expected to increase in the future.

30 The literature on an association between acromegaly and cancer is particularly abundant on
31 either colorectal cancer or thyroid cancer, and an endless debate is ongoing whether patients with
32 acromegaly should be submitted to specific oncology screening and surveillance protocols. The aim
33 of the present work is to review the most recent data on the risk of either colorectal or thyroid
34 cancer in acromegaly and discuss the opportunity for specific screening in relation to the accepted
35 procedures in the general population.

36

37 **1. FOR**

38

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48

49 Word count: **2906** words.

50

51 Key words: acromegaly, GH, IGF1, neoplasia

52

53 **THYROID CANCER**

54 *Screening in the general population*

55 Thyroid cancer screening is not recommended in asymptomatic adults at average risk due to: i) the
56 relative rarity of the tumor; ii) the fact that treatment of early thyroid cancer does not seem to confer
57 a better survival to treated patients than untreated ones; iii) the unchanged mortality rate from
58 thyroid cancer despite its increased incidence in the last 10 years¹⁵. In adults at increased risk
59 because of previous exposure to ionizing radiation (especially in childhood), inherited genetic
60 syndromes associated with thyroid cancer, or familial history of thyroid cancer, the American
61 Thyroid Association (ATA) guidelines do not recommend for or against screening. As a matter of
62 fact, there is no evidence that thyroid cancer screening is able to reduce morbidity and mortality
63 although it may lead to earlier diagnosis¹⁵.

64

65 *Acromegaly & thyroid cancer: preclinical evidence*

66 The ATA guidelines do not include acromegaly in the list of conditions at increased risk of thyroid
67 cancer; however, a wealth of experimental and epidemiological data supports this view.

68 Findings of several immunohistochemical studies confirmed the hypothesis of an IGF1-mediated
69 mechanism of cancer promotion in thyroid cells. The first demonstration of the presence of IGF1
70 receptors in human thyroid cells dates back to 1989 by Yashiro et al.¹⁶, who also showed that IGF1
71 binding in neoplastic tissues was significantly higher than in surrounding normal tissues. In the next
72 years, studies demonstrated how the expression of IGF1 and IGF1 receptor was correlated with
73 thyroid cancer aggressiveness^{17, 18}. Kim et al.¹⁹ suggested that in patients with acromegaly a
74 dominant role in the development of papillary thyroid cancer (PTC) could be played by a
75 hyperactive GH-IGF1 axis, rather than the BRAFV600E mutation. The authors found that 15 out of
76 60 acromegalic patients (25%) harbored a PTC, and compared these patients to a control group of
77 16 non-acromegalic patients with PTC. The BRAFV600E mutation was present in only 1/11 (9.1%)
78 of the acromegalic patients compared to 10/16 (62.5%) control patients ($p = 0.007$). In this study,

79 uncontrolled GH-IGF1 secretion was significantly more frequent in the group of acromegalic
80 patients with PTC (60%) than in patients without (28.9%) ($p = 0.030$). Also Aydın K et al.²⁰
81 confirmed that BRAFV600E mutation does not play a causative role in development of
82 differentiated thyroid cancer (DTC) in acromegaly, as BRAFV600E mutation was found in 2/14
83 (14.3%) acromegalic patients with DTC compared to 9/14 (64.3%) non-acromegalic patients with
84 DTC ($p=0.02$). Recently, Keskin et al.²¹ compared protein expressions via immunohistochemical
85 staining in PTC of 13 acromegalic patients and 20 patients without acromegaly, reporting a similar
86 expression of BRAF in the two groups, while IGF1 and Galectine 3 expression was significantly
87 higher in the acromegaly group. Moreover, the 13 acromegalic patients with PTC had higher levels
88 of GH and IGF1 than 300 acromegalic patients without²¹.

89

90 *Acromegaly & thyroid cancer: clinical evidence*

91 This experimental evidence fits well with the epidemiological observation of a higher frequency of
92 thyroid nodules and cancers in acromegaly patients compared to the general population. However,
93 the incidence of thyroid cancer in patients with acromegaly varied considerably in studies done in
94 different countries. In Italy, we evaluated the standard incidence ratios (SIRs) of different cancer
95 types on a nationwide cohort of 1512 acromegalic patients and found a significantly increased
96 incidence of thyroid cancer (SIR 3.99; 95% CI, 2.32–6.87, $P < 0.001$)⁵. Similar findings have been
97 reported in other European studies^{11, 22}, whereas a recent North American study showed that the
98 prevalence of thyroid cancer in acromegalic patients with thyroid nodules was similar to that
99 reported in the general population with thyroid nodules (7-15%)²³. This country-related variability
100 could be related to different dietary iodine intake, which is known to have an influence on thyroid
101 cancer risk, but also to different use of thyroid ultrasonography in the general population.
102 Since proactive thyroid cancer screening with ultrasonography is tied with a greater number of
103 diagnoses, it is conceivable that the elevated frequency of thyroid cancer in acromegalic patients

104 could be due to enhanced use of diagnostic tests. However, a higher frequency of thyroid cancer in
105 acromegalic patients has been also reported in South Korea, where an organized cancer-screening
106 program has been implemented in 1999 that involves screening for asymptomatic thyroid cancer
107 using ultrasound ^{24, 25}. A nationwide survey on 3,633 adults between 20-70 years of age reported
108 that 23.3% of the participants underwent thyroid ultrasonography. The outcome of screening was
109 that 70.7% of tests were normal, while in 23.6% thyroid nodules were detected, and in 1.9% of
110 subjects a thyroid cancer was diagnosed ²⁵. In that country, a study on 60 acromegalic patients, who
111 were evaluated with thyroid ultrasonography, reported that thyroid nodules were detected in 75.0%
112 (45/60) of patients and thyroid cancer in 25.0% (15/60) of them ¹⁹. Despite the small sample of the
113 study, the difference with the general population is striking and cannot be accounted for a more
114 intensive diagnostic testing in patients with acromegaly given that thyroid cancer screening is well
115 practiced in South Korea.

116 However, the issue of a different intensity of screening between the general population and
117 acromegalic patients, which may introduce a possible bias in the detection of thyroid cancer,
118 remains matter of debate. This point has been raised in a meta-analysis and systematic review
119 published in 2014 ²⁶, in which the authors concluded that the amount of reliable papers including
120 controls groups and data on both benign and malignant thyroid nodular disease is unsatisfactory. As
121 a matter of fact, only 5 studies among the 22 initially selected were found to compare the
122 prevalence of thyroid cancer, and 3 studies the prevalence of benign thyroid lesions, in either
123 acromegalic patients or sex- and age-matched control subjects. This meta-analysis showed an odds
124 ratio (OR) of 7.9 (95%CI, 2.8–22.0) for thyroid cancer, and an OR of 3.6 (95%CI, 1.8–7.4) for
125 benign lesions in patients with acromegaly. Moreover, the relative risk (RR) of thyroid cancer in
126 acromegalic patients with thyroid nodules was non-significantly higher (RR 3.2, 95%CI, 0.5–20.1)
127 than in non-acromegalic patients, when assessing the studies that included a concomitant control
128 group. Interestingly, a higher prevalence of nodular goiter and thyroid cancer was found in more
129 recent studies. The pooled prevalence of thyroid cancer was about 3% in the studies published

130 before 2008 and about 6% in studies published since then. The same authors updated the meta-
131 analysis in 2017 ²⁷, confirming that the OR for thyroid cancer and for benign lesions was
132 remarkably increased in patients with acromegaly (4.1; 95%CI, 2.0-8.3 and 3.3; 95%CI, 95% 2.1–
133 5.4, respectively), while the RR for thyroid cancer was non-significantly increased compared with
134 non-acromegalic subjects (2.3; 95%CI, 0.9-6.1, $p = 0.08$).

135 More recently, Dal et al ²⁸ performed a meta-analysis concerning different types of neoplasms in
136 acromegalic patients, including thyroid cancer. Although the inclusion criteria were different
137 compared to the previous meta-analysis ²⁶, a significantly increased prevalence of thyroid cancer in
138 patients with acromegaly was confirmed (pooled SIR = 9.2; 95%CI, 4.2–19.9). However, we still
139 do not know whether thyroid tumors in patients exposed to chronic excess of GH-IGF1 have a
140 different (more aggressive) behavior.

141

142 *Recommendations for screening in patients with acromegaly*

143 For all the abovementioned considerations, it is our opinion that the recommendation of the
144 Endocrine Society Guidelines ²⁹ and the Acromegaly Consensus Group ³⁰ of performing thyroid
145 ultrasonography in case of palpable nodularity should be extended to all patients with acromegaly.
146 The patients in whom thyroid nodules are detected at diagnosis should undergo follow-up
147 surveillance.

148 The plain and uncontroversial evidence of an increased prevalence of benign nodular disease in
149 acromegaly justifies this simple and cost-effective test, which is frequently performed as a point of
150 care ultrasonography. Thyroid ultrasonography is particularly useful in patients with uncontrolled
151 disease, since there is evidence that thyroid nodules may grow significantly in patients with active
152 acromegaly ^{31 32}, and it is held that the risk of malignancy may be associated with an increase in
153 nodule volume ³³. The need of a close monitoring of thyroid nodules in acromegalic patients is in

154 line with the ATA Guidelines that recommend fine needle aspiration biopsy of any nodule that
155 increase in size of more than 20%¹⁵.

156

157 **COLORECTAL CANCER**

158 *Screening in the general population*

159 In the average-risk population, including individuals of 50-75 years of age with no additional risk
160 factors, the recommended screening for colorectal cancer is one of the following: fecal
161 immunochemical testing every 2 years, colonoscopy every 10 years, or sigmoidoscopy every 10
162 years plus fecal immunochemical testing every 2 years³⁴. In fact, it has been demonstrated that
163 colonoscopy screening with the removal of adenomas is an effective strategy for reducing colorectal
164 cancer incidence and mortality³⁵. Screening procedures are different in above-average risk
165 population, as are individuals with family or personal history of colorectal cancer, long-standing
166 history of inflammatory bowel disease or adenomatous polyps, and genetic syndromes such as
167 familial adenomatous polyposis³⁴. Acromegaly is not cited as a condition associated with increased
168 risk; however, experimental and epidemiological data support the view that exposure to chronic
169 GH-IGF1 excess confers an increased risk of colorectal cancer.

170

171 *Acromegaly & colorectal cancer: preclinical evidence*

172 Since the fifties, it is known that elevated levels of serum GH-IGF1 promote development of colon
173 neoplasms³⁶⁻³⁸. Additional evidence has accumulated in the last decades on the role of IGF1 in
174 colorectal tumorigenesis in acromegalic patients. Bogazzi et al. demonstrated that apoptosis was
175 reduced in the colonic mucosa of patients with active acromegaly compared to patients in remission
176 and controls, with an inverse relationship with serum IGF1. The same study showed that expression
177 of PPAR gamma, a tumor suppressor gene involved in colonic tumorigenesis, was reduced in the
178 colonic mucosa of patients with acromegaly³⁹. Moreover, it has been demonstrated that patients
179 with active acromegaly have increased proliferation of colonic epithelial cells, as Ki-67 staining in

180 biopsy samples was significantly higher compared to healthy controls. The same study showed that
181 serum IGF1 levels were associated with increased proliferation in the superficial crypt cells ⁴⁰.
182 Zhang et al. reported that serum IGF1 and mRNA levels for mucosal IGF1 receptors (IGF1R) were
183 significantly higher in patients with adenomatous or neoplastic polyps compared with healthy
184 controls ⁴¹. Moreover, expression of IGF1, IGF1R and of their mRNA were higher in colorectal
185 cancer than in colon adenoma and normal tissues ⁴². Interestingly, expression of IGF1 and IGF1R
186 mRNA was associated with the degree of differentiation, and metastatic spread of colorectal cancer,
187 and was also an independent prognostic factor ⁴². In a prospective study of 210 patients with
188 colorectal cancer, a significant correlation between IGF1 expression and tumor size and depth of
189 invasion was demonstrated ⁴³.

190 In the last few years, studies have shaped better the role of GH in colorectal tumorigenesis,
191 demonstrating that GH suppresses the expression of p53 and p21 in colon cancer cells, whereas the
192 administration of a GH-Receptor antagonist (Pegvisomant) to acromegalic patients increases the
193 expression of p53 and APC (Adenomatous Polyposis Coli) ⁴⁴. More recently, the same group
194 demonstrated that in colon cells, GH inhibited the DNA damage repair pathways thus promoting
195 chromosomal instability ⁴⁵. Another study using cells with disrupted IGF-1R, to block IGF1 effect,
196 showed that GH induces colon DNA damage independently of IGF1 ⁴⁶. All these findings suggest
197 that both IGF1 and GH may act within the cellular microenvironment in colorectal cancer
198 promoting neoplastic growth.

199

200 *Acromegaly & colorectal cancer: clinical evidence*

201 Preclinical findings are in line with clinical evidence from either epidemiological studies in the
202 general population or cohort studies in patients with acromegaly.

203 Several studies in the background population suggested that adults with levels of serum IGF1 at the
204 high end of the normal range have increased risk of colorectal cancer ⁴⁷⁻⁴⁹. Conversely, elevated
205 levels of IGF binding protein-3 (IGFBP-3) have been associated with a lower risk of cancer ^{47, 48},

206 although the strength of association is inferior ³. In acromegalic patients, however, GH excess
207 increases serum IGF1 and, to a lesser extent, IGFBP-3; therefore, the IGF1/IGFBP-3 ratio steeply
208 increases as GH levels raise ^{50,51}, and an elevated IGF1/IGFBP-3 ratio may lead to enhanced cancer
209 risk in acromegaly ^{47,52}.

210 Rokkas et al ⁵³ performed a meta-analysis of colonoscopy studies in acromegaly done before
211 December 2007, and analyzed 9 of 106 potentially eligible studies including 701 acromegalic
212 patients and 1573 controls. The pooled results showed that acromegalic patients have a significantly
213 increased risk of developing hyperplastic colon polyps (OR 3.703; 95%CI, 2.565–5.347), colon
214 adenomas (OR 2.537; 95%CI, 1.914–3.264) and colon cancer (OR 4.351; 95%CI, 1.533–12.354).
215 The meta-analysis included a multicentric Italian study on a cohort of 235 patients with acromegaly
216 and 233 subjects with non-specific abdominal symptoms who served as controls ⁵⁴. The most
217 important colonoscopy findings were adenoma in 55 patients (23.4%) and 34 control subjects
218 (14.6%) with OR 1.7 (95%CI, 1.1-2.5), and colorectal cancer in 10 patients (4.3%) and 2 controls
219 (0.9%) with OR 4.9 (95%CI, 1.1-22.4).

220 More recently, Dal et al ²⁸ performed a population-based study and an accompanying meta-analysis
221 on the risk of different types of cancer in patients with acromegaly. With both approaches the risk
222 of cancer was found to be slightly increased in acromegaly, with a pooled SIR for all cancers from
223 meta-analysis of 1.5 (95%CI, 1.2-1.8). For colorectal cancer, the SIR was 2.6 (95%CI, 1.7–4.0).
224 Considerable heterogeneity was found but no evidence of publication bias. There was no sex-related
225 difference while age-specific patterns were not reported.

226 The main findings of this study are in agreement with our nationwide survey reporting an overall
227 SIR for cancer of 1.41 (95%CI, 1.18-1.68)⁵. For colorectal cancer, we found a SIR of 1.67 (95%CI,
228 1.07-2.58); the risk of cancer was increased in either sex, and both age and family history were
229 factors associated to all-type cancer risk. The number of patients submitted to proactive cancer
230 screening was comparable between patients with and without cancer⁵. The fact that acromegaly
231 confers only a moderately increase in risk of cancer may explain why some less-powered cohort

232 studies have failed to document it (**Figure 1**^{7-11, 28, 55-77}).

233 Most studies failed to demonstrate any relationship between activity of acromegaly and risk of
234 colorectal cancer^{54, 78}. However, this does not argue against the hypothesis that GH and IGF1 are
235 implicated in colorectal tumorigenesis, since a hormonal evaluation at a single point in time in the
236 course of a long-lasting disease such as acromegaly cannot fully reflect the chronic exposure to GH
237 and IGF1 excess. Interestingly, Dworakowska et al.⁷⁹ demonstrated that acromegalic patients with
238 a normal baseline colonoscopy and persistently elevated IGF1 values had a 7.5-fold risk of a
239 subsequent adenoma, compared to those with a normal colonoscopy at the initial screening and
240 controlled disease. Moreover, acromegalic patients with an initial adenoma had a 4.4 to 8.8-fold
241 increased risk of developing a new adenoma at follow-up colonoscopy. These findings are in
242 agreement with a previous study from our group that showed how the presence of a colonic
243 neoplasm (adenoma or cancer) at the screening colonoscopy predicted finding new lesions at
244 follow-up colonoscopy⁵⁴. Patients with colonic neoplasms at the repeat colonoscopy had increased
245 IGF1 levels than patients without⁵⁴.

246

247 *Recommendations for screening in patients with acromegaly*

248 Given this premise, we believe that screening colonoscopy is justified in patients with acromegaly
249 at the time of diagnosis. Colonoscopy should not be deferred in patients younger than 50 years, the
250 age at which screening is recommended in average-risk population. There is indeed evidence that
251 the risk of colon neoplasms may be higher in younger patients, when acromegaly is usually more
252 aggressive⁵⁴.

253 There is substantial agreement between Endocrine Scientific Societies^{29, 30, 80, 81} on the need of
254 colonoscopy at the time of diagnosis of acromegaly. The timeline of repeat colonoscopy varies in
255 relation to the control of GH-IGF1 excess, and follow-up colonoscopy should be performed more
256 frequently than in the general population when acromegaly remains active. Therefore, colonoscopy

257 should be repeated every 5 years whenever a colonic adenoma is found at screening or acromegaly
258 is not properly controlled. Conversely, surveillance colonoscopy is deemed every 10 years.
259 Since most colorectal cancers arises from adenomatous polyps, colonoscopy screening may lead to
260 remove the premalignant lesions reducing the risk of either cancer development or cancer-related
261 mortality⁸². Given that acromegaly is a condition at increased risk of colorectal cancer, we do not
262 see a role for alternative screening modalities that are less effective than colonoscopy. However, it
263 should be considered that attaining an optimal visualization of the whole colon in acromegalic
264 patients may be a demanding task, because of the frequent presence of dolichocolon and colonic
265 diverticula⁸³. Moreover, due to the twisting of the colon in acromegalic patients, a rigorous bowel
266 preparation and an experienced endoscopist are mandatory to limit the risk of missing small lesions.

267 **In conclusion, patients with acromegaly deserve a more stringent surveillance than average-**
268 **risk population, since colonoscopy should be repeated every 5 years in patients with active**
269 **disease and/or previous evidence of colonic neoplasm, while only for patients with controlled**
270 **disease and negative colonoscopy^{54, 79} the time interval of 10 years does apply as in average-**
271 **risk population. Moreover, surveillance should be initiated in patients younger than 50**
272 **years⁵⁴, the age cut-off to recommend screening in average-risk population, and should be**
273 **performed only with colonoscopy, differently from general population in which the**
274 **alternative of fecal immunochemical testing every 2 years, or sigmoidoscopy every 10 years**
275 **plus fecal immunochemical testing every 2 years, is also indicated³⁴.**

276 **2: AGAINST**

277

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279

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282

283 Running title: Thyroid and colorectal cancer screening in acromegaly

284

285 Words: **2805**

286

287 **AGAINST**

288

289 Data regarding cancer incidence among acromegaly patients are inconsistent. A positive association
290 between GH and IGF-1 excess with thyroid, colorectal and other types of cancer has been
291 suggested. However, these associations rely mostly on small epidemiological surveys and
292 circumstantial evidence; large-scale epidemiological studies are lacking^{84, 85}. It has been also
293 hypothesised that acromegaly, independent of hormonal secretion, is a disease that brings with it
294 genetic and/or epigenetic alterations predisposing to neoplasia¹³. In parallel literature, GH
295 replacement therapy has been associated with increased cancer risk/tumour recurrence in children
296 with previously treated malignancies; however, this has not been confirmed so far¹².

297 In order to identify published studies on the risk of cancer in acromegaly and to be able to provide
298 an overview of the controversies surrounding this topic, we searched the PubMed database for
299 publications in English from the last two decades (2000-2019). Although patients with acromegaly
300 have a 2–2.5-fold increased mortality rate - predominantly due to non-cancer related reasons - an
301 accurate assessment of the true incidence of cancer in this group of patients remains ambiguous⁸⁶.
302 In two larger series from the United Kingdom⁶³ and Germany⁷, which have assessed the overall
303 cancer rate in acromegaly in comparison with that in the general population, estimated SIR for
304 several types of malignancies was lower or not different from the general population. Moreover, in
305 a recent review by Tirosh et al., the authors state that thyroid micro-carcinomas are probably over-
306 diagnosed among acromegalic patients, whereas there is no sufficient data to suggest that colon
307 cancer risk is higher in acromegaly compared to that of the general population⁸⁷. Regarding
308 mortality, Dal et al. conducted a nationwide cohort study from 1978 to 2010 including 529
309 acromegaly cases in Denmark; whereas overall mortality was elevated in acromegaly (SIR 1.3; 95%
310 CI, 1.1 to 1.6), cancer-specific mortality was not²⁸.

311 Although some data suggest that overall cancer risk might be slightly elevated in acromegaly
312 compared to the general population, numerous potential sources of bias need to be discussed²⁸.
313 Selection or sample bias is suggested by the fact that the elevated overall cancer incidence risk is
314 more pronounced in single-center studies and lower when studies with less than 10 cases are
315 excluded. Additionally, we have to take into account that patient populations in single centers might
316 represent difficult cases with previous treatment failure and increased comorbidity. It is could also
317 be the case that the comparison group in single-center studies derives from screening programs,
318 which poses the risk of healthy user bias; this is of particular relevance in the context of colorectal
319 cancer, for which screening programs are available²⁸. Surveillance bias or diagnostic workup bias

320 risk can be reduced by excluding cancer cases detected within the first year after diagnosis of
321 acromegaly.

322

323 ***THYROID CANCER***

324

325 ***No increased prevalence***

326

327 Thyroid volume, evaluated by ultrasonography, is known to be higher in acromegaly and correlates
328 to the estimated duration of the disease⁸⁸. While simple and multinodular goiters are more common
329 among acromegalics, reports of thyroid carcinoma are rare, and its true incidence remains unclear.
330 Increased cancer rates in acromegaly are possibly due to increased plasma circulating levels of IGF-
331 I, which is known to promote cellular growth⁸⁹.

332 The exact prevalence of benign and malignant nodular thyroid disease in patients with acromegaly
333 is not known. Numerous studies have reported an increasing incidence of thyroid cancer in the last
334 decade with a prevalence ranging from 5,6% up to 11,8%^{73, 90, 91}. However, this was not the case in
335 all studies. In a meta-analysis of the literature regarding cancer incidence in patients with
336 acromegaly by Dal, no significant difference was detected in thyroid cancer incidence between
337 multicenter studies (pooled SIR = 7.6; 95% CI, 2.4 to 24.5) and population-based studies (pooled
338 SIR = 8.2; 95% CI, 3.6 to 18.7); only two single-center studies evaluated thyroid cancer
339 incidence²⁸. In the largest - to our knowledge - study in this issue performed in Western European
340 countries in the last decade, Gasperi et. al. reported only a slightly increased prevalence of thyroid
341 carcinoma than in the general population (3/258 patients)⁸⁸. The second largest study by Reverter et
342 al. found a 2.4% rate of thyroid malignancy in a series of 123 acromegalic patients, which was
343 lower than previously reported and anticipated⁹².

344

345 ***Sources of bias***

346

347 Numbers should be interpreted taking into account epidemiological data from specific geographical
348 regions, since we know that reported thyroid cancer incidence and prevalence varies considerably in
349 different registries^{93, 94}. Differences regarding cancer incidence may be due to geographical, ethnic

350 or environmental reasons such as iodine intake or the prevalence of thyroid autoimmunity⁹². In a
351 recent meta-analysis and systematic review by Wollinski et al., the authors underline that reliable
352 papers including control groups and data both on the prevalence of thyroid nodular disease and
353 thyroid cancer is rather unsatisfactory²⁶. We should also keep in mind that the number of control
354 subjects is adequate to make a conclusion about thyroid volume and goiter prevalence, but could be
355 insufficient for detection of thyroid malignancy⁹². Additionally, surveillance bias is of particular
356 concern for thyroid cancer, since thyroid volume is enlarged in acromegaly, which may lead to
357 more frequent use of ultrasonography and subsequent overdiagnosis of occult thyroid cancer⁹⁵.

358

359 *Thyroid cancer screening*

360

361 Although thyroid malignancy is supposed to be one of the most commonly found cancers in
362 acromegaly, the majority of guidelines do not mention it. The exception is the report from the
363 Endocrine Society, stating that thyroid ultrasound should be offered to acromegalic patients with a
364 palpable thyroid nodule²⁹. Other authors also consider it rational to perform periodic
365 ultrasonographic evaluation in acromegaly, follow by fine needle aspiration biopsies of suspect
366 nodules⁹⁶. This is also the proposal of Siegel et al. who suggest careful monitoring of goiter and
367 thyroid nodules, including fine-needle aspiration of nodules that are 1 cm or larger in acromegalic
368 patients with persistently elevated IGF-I levels⁸⁹. **In the end, this does not deviate from our common
369 practice in the general, non-acromegalic population.** No evidence exists that an aggressive and
370 systematic approach to detect small, asymptomatic, low-risk, thyroid malignant nodules could affect
371 mortality rates in acromegaly, while it could in fact be accompanied by unnecessary morbidity and
372 poorer quality of life⁴. This was confirmed by a recent retrospective chart review performed
373 between 2006-2015 at the University of California, which revealed no benefit of dedicated thyroid
374 nodule screening in patients newly diagnosed with acromegaly, since the prevalence of thyroid
375 cancer in acromegalic patients and coexisting thyroid nodules was no different to that reported in
376 the general U.S. population with thyroid nodules (7-15%)²³.

377

378

379

380

381 **COLORECTAL CANCER**

382

383 ***No increased prevalence***

384

385 Whether incidence of colorectal cancer is increased in acromegaly, remains a matter of debate in
386 numerous publications. Two of the more recently published population-based studies did not find
387 any excess risk of colorectal cancer in acromegaly^{6, 7}. In detail, the analysis from the German
388 Acromegaly Registry (n=446) showed a slightly - but not significantly lower – overall cancer
389 incidence than in the general population (SIR, 0.75; 95% CI, 0.55 to 1.00; $P = .051$) and was not
390 significantly higher for colorectal, thyroid or other types of cancer. There was not a significant
391 dependence on normal vs elevated IGF-1 ($P = .87$), radiation therapy ($P = .45$), disease duration (P
392 $= .96$), age at diagnosis ($P = .15$), or during a period of high GH and IGF-1 from 8 years before to 2
393 years after diagnosis of acromegaly ($P = .41$)⁷.

394 A retrospective, observational, non-interventional and cross-sectional analysis of 146 acromegalic
395 patients in Padua, Italy revealed an increased general risk for polyps and adenomatous polyps in
396 acromegaly compared to the control population (odds ratio 1.33 and 1.16, respectively), but no
397 cancerous polyps⁹⁷. Increased fasting insulin levels seem to be associated with an 8.6- to 14.8-fold
398 increased risk of presenting with colonic adenomas⁹⁸. In an Italian, multicenter, cross-sectional
399 study, patients with acromegaly (n=235) carried only a moderate increase in the risk of colonic
400 carcinoma occurring at a younger age than in the general population (odds ratio, 4.9; range, 1.1-
401 22.4) compared to patients with non-specific abdominal complaints⁵⁴.

402 The question as to whether the increased risk of colorectal cancers in acromegaly results in
403 increased colorectal cancer-specific mortality in this group remains unanswered. Lois et al.,
404 concluded that although initial studies suggested an increased overall cancer related mortality in
405 acromegaly, this has not been supported by further studies⁹⁹. In the largest meta-analysis of
406 colorectal neoplasia in acromegaly published in 2008, Rokkas et al. concluded that an overall
407 cancer mortality risk was significantly greater only in the subgroup of patients with uncontrolled
408 acromegaly⁵³.

409

410

411

412 ***Sources of bias***

413

414 Although a number of studies suggest an increased prevalence of colorectal cancer in acromegaly,
415 potential sources of bias need to be addressed. Most of the studies are too small to adjust for
416 confounding factors e.g. sex, age and conclusions may rely on inappropriate control groups.
417 Renehan et al. state that colonoscopy-based studies of adenoma prevalence rates in acromegalic
418 patients are misleading and often overestimated¹⁰⁰. This is attributed to the fact that no ideal control
419 population for such studies exists and therefore the choice of controls is often inappropriate. The
420 authors believe that population-based studies on colorectal cancer risk are more consistent; a meta-
421 analysis estimated a pooled risk ratio of 2.04 (95 % CI: 1.32, 3.14)¹⁰⁰. From a clinical point of view,
422 it seems reasonable to perform colonoscopic screening at approximately 55 years of age, but
423 potential risks and benefits should be weighed¹⁰¹.

424 Renehan et al. further believe that risk assessment regarding acromegaly and colorectal cancer
425 should rely on population-based studies, since disease prevalence is underestimated and there are
426 major problems arising from lack of matched age-sex comparisons, the variability in colonoscopy
427 completion rates, and the healthy-user factor in screened controls when comparing with published
428 series of screened asymptomatic non-acromegalic patients¹⁰². We should not forget that
429 colonoscopy is an invasive and potentially harmful investigation and an aggressive screening
430 strategy may be associated with escalating morbidity and mortality, although potential benefits
431 seem modest¹⁰².

432

433 ***Colorectal cancer screening***

434

435 Current guidelines for colorectal cancer screening vary according to cancer risk. Patients with
436 hereditary syndromes are considered at “very high risk” for colorectal cancer and are known to
437 profit from frequent screening, since colorectal cancer deaths are reduced. Individuals with positive
438 family history are considered to be at “high risk” and early colonoscopic screening with regular
439 surveillance is recommended. In “average risk” individuals, screening colonoscopy is proposed at
440 the age of 50 according to the US guidelines (UK guidelines are less specific), while “moderate
441 risk” are those with an increasingly recognized, increased risk, but to a modest extent. Acromegaly
442 seems to fall into this category, which is unfortunately neither mentioned by the US nor the UK
443 guidelines¹⁰².

444 The majority of colon cancers develop as a result of a multistep malignant transformation of benign
445 adenomatous colonic polyps which this takes about 10–15 years in non-acromegalic individuals. A
446 wide range of predisposing factors such as diet, obesity, diabetes, and smoking, as well as genetic
447 and epigenetic mechanisms have been proposed⁸⁶. In order to be able to determine optimal
448 colonoscopy screening in acromegalic patients, we should first identify acromegalic patients who
449 are at risk of developing colonic adenomas. In a prospective study up to 5 years of 79 patients with
450 active acromegaly, Bogazzi et al. suggest that the first colonoscopy helps to identify patients at high
451 risk of developing colonic adenomas. If colonic adenomas are not initially present, it is rather
452 unlikely that they develop thereafter, independently of the metabolic control of the disease. On the
453 other hand, new lesions are frequent and multiple in patients who already have colonic adenomas at
454 baseline, particularly in case of uncontrolled acromegaly¹⁰³.

455 The optimum frequency with which acromegalic patients should undergo colonoscopic screening
456 again remains unclear. In a retrospective study by Dworakowska et al., patients treated at the center
457 underwent at least one up to four surveillance colonoscopies. Repeated colonoscopic screening
458 showed a high prevalence of new adenomatous and hyperplastic colonic polyps, dependent on both
459 the occurrence of previous polyps and elevated IGF1 levels⁷⁹.

460 Current guidelines regarding regular colorectal cancer screening in acromegaly are controversial
461 and are based on a variety of sources: the Acromegaly Consensus Group (ACG) guidelines in 2009,
462 the British Society of Gastroenterology (BSG) in 2010, the American Association of Clinical
463 Endocrinologists (AACE) in 2011, the Pituitary Society in 2013 and the Endocrine Society in 2014.

464 In the most recent guideline by the Endocrine Society²⁹, screening colonoscopy at diagnosis for all
465 acromegalic patients is suggested, but only supported by weak, low quality evidence. **On the other
466 hand, there is no reason for not performing it in patients with first diagnosis of acromegaly over
467 50 years.** It is known that adenoma excision at this age reduces colorectal cancer rates in average-
468 risk individuals, while the risk in acromegalic patients seems to be just above the threshold for non-
469 acromegalic individuals. **In patients with first diagnosis of acromegaly between 40 to 50 years of
470 age, the decision should rely on cancer epidemiology and presence of predisposing factors, which is
471 in the end no different than our common practice in the general population.** In case that the
472 skill of endoscopic team is questionable, other safer screening procedures such as computed
473 tomographic colonography should be considered. **Follow-up for acromegalic patients with a normal
474 initial colonoscopy and controlled disease is comparable to that of the general population.** If a polyp
475 is detected in the first examination, the patient should undergo second colonoscopy within 3–5
476 years, depending on the number, size and histology of the resected lesions. An interval of about 5

477 years seems reasonable, but remains debated, for patients with a normal initial colonoscopy and
478 persistently elevated GH and IGF1 levels.

479

480 *Special issues regarding colonoscopic screening*

481

482 In acromegaly, several practical issues such as increased length of colon (mainly the sigmoid) and
483 increased circumference might influence colonoscopy success. Additionally, colonic transit times
484 are twice longer than in normal individuals and therefore standard bowel preparation is often not
485 enough. The procedure lasts much longer due to the colonic length and circumference, which means
486 that the study should be ideally offered by an experienced examiner⁸⁶. There is general agreement
487 that further studies are needed in order to enlighten optimal technical aspects of colonoscopy in
488 acromegaly. Specific recommendations for large bowel endoscopic screening have been proposed⁹⁹.

489

490 The rare incidence of acromegaly means that assessment of the cost-benefit ratio is difficult. Cairns
491 et al. report the example of the UK, comprising around 2500 patients with acromegaly, of whom
492 about 2,000 are aged 40 years or over. According to current data, about one fourth (500 patients),
493 will have an adenoma and will be offered screening every 3 years, while the rest will be offered
494 colorectal screening every 5 to 10 years. In conclusion, the number of extra examinations in each
495 center due to acromegaly is rather small¹⁰⁴.

496

497 *Concluding remarks*

498

499 The question whether acromegalic patients should undergo more extensive/frequent cancer
500 screening has been debated long and passionately. Although current literature proposes a slightly
501 elevated overall risk of cancer in acromegaly, at the moment growth hormone excess in humans
502 does not seem to present a serious cancer risk. Perhaps, the answer to embrace the different views
503 and to preserve an optimal risk/benefit approach is on ‘the middle way’. Among clinical
504 endocrinologists, Melmed adopts a rather moderate position regarding malignancy risk in
505 acromegaly. He states that fifteen percent of deaths in acromegaly are attributable to malignancies,
506 which is lower than expected in the general population. Uncontrolled acromegaly may be linked to

507 more aggressive neoplasms with potentially increased cancer-associated morbidity and mortality,
508 but no clear evidence for enhanced *de novo* cancer initiation in acromegaly exists so far¹⁰⁵.

509

510 There are many problems and limitations in quantifying the risk of cancer in patients harboring a
511 rare disease. Most studies include small numbers of individuals, with no statistical power to adjust
512 the data for confounding factors, such as age and gender. The comparison between older and more
513 recent series is challenging, as both cancer incidence in the general population and life expectancy
514 in patients with acromegaly have dramatically changed over the past few decades, influencing the
515 prevalence of disease-associated morbidities. In addition, population-based cancer registries and
516 epidemiology may differ from site to site. Finally, the heterogeneity of control populations used
517 presents another source of bias⁴.

518

519 In conclusion, at present there is insufficient data to support an intensive thyroid or colorectal
520 cancer screening in acromegaly. **Patients with acromegaly should undergo regular screening with
521 hormonal and ultrasound evaluation of the thyroid and fine-needle aspiration biopsy when required,
522 comparable to that in the general population. Early colonoscopic screening and subsequent
523 regular surveillance above that of the normal population cannot be supported by the evidence
524 currently available.** Rationale together with potential risk and benefits should be weighed. The
525 increased risk for cancer is modest and the potential risk of invasional screening techniques
526 considerable. Current guidelines may have to be revised before forcing physicians into a not
527 evidence based screening practice¹⁰⁶.

528

529

530 ***Disclosure***

531 The authors have nothing to disclose.

532

533 ***Funding***

534 There was no funding for this article.

535

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833 **Figure 1. Sample size of the population-based studies on acromegaly and cancer. Black bars**
834 **indicate studies showing a positive association between acromegaly and cancer, striped bars**
835 **indicate negative studies, and white bars indicate studies that do not conclude whether an**
836 **association is either present or not. Studies which focus on mortality only are marked by the**
837 **letter M.**

838 **The correspondence between the number of the study and references is as follows:**

839 **1⁵⁵; 2⁵⁶; 3¹⁰; 4⁵⁷; 5⁵⁸; 6⁵⁹; 7⁶⁰; 8⁹; 9⁶¹; 10⁶²; 11⁶³; 12⁶⁴; 13⁶⁵; 14¹¹; 15⁶⁶; 16⁶⁷; 17⁶⁸; 18⁶⁹; 19⁷⁰; 20⁷¹;**
840 **21⁷²; 22⁷³; 23⁷⁴; 24⁷; 25⁸; 26⁷⁵; 27⁷⁶; 28²⁸; 29⁷⁷.**

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