

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

**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

*Terms of use:*

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(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) <sup>1</sup>. Given that elevated levels of IGF1  
7 inhibit apoptosis and promote cell proliferation in many tissues <sup>2</sup>, 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 <sup>3</sup>.

12 Whether cancer should be considered part of the clinical manifestations of acromegaly remains  
13 matter of controversy <sup>4, 5</sup>. 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 <sup>6-8</sup>. Second, studies used different  
17 methodological approaches and heterogeneous patient populations, such as sex-specific series <sup>9, 10</sup>  
18 or hospitalized patients <sup>9, 11</sup>. 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) <sup>12</sup>. Population-based studies are theoretically more  
21 robust, but should have a nationwide dimension and availability of accurate cancer registry data <sup>13</sup>.  
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 <sup>1</sup>.

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 <sup>14</sup>. 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

39 Massimo Terzolo, Soraya Puglisi, Giuseppe Reimondo.

40 *Internal Medicine, Department of Clinical and Biological Sciences, San Luigi Gonzaga Hospital, Orbassano,*  
41 *University of Turin, Italy*

42

43 Address correspondence to:

44 Soraya Puglisi, MD

45 Internal Medicine, Department of Clinical and Biological Sciences, San Luigi Gonzaga Hospital,

46 Regione Gonzole 10, 10043 Orbassano, Italy; tel: +39 011 9026292, fax: +39 011 6705456

47 e-mail: sorayapuglisi@yahoo.com

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 years<sup>15</sup>. 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 diagnosis<sup>15</sup>.

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.<sup>16</sup>, 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<sup>17, 18</sup>. Kim et al.<sup>19</sup> 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.<sup>20</sup>  
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.<sup>21</sup> 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 without<sup>21</sup>.

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,  $P < 0.001$ )<sup>5</sup>. Similar findings have been  
97 reported in other European studies<sup>11, 22</sup>, 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%)<sup>23</sup>. 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 <sup>24, 25</sup>. 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 <sup>25</sup>. 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 <sup>19</sup>. 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 <sup>26</sup>, 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 <sup>27</sup>, 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 <sup>28</sup> 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 <sup>26</sup>, 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 <sup>29</sup> and the Acromegaly Consensus Group <sup>30</sup> 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 <sup>31 32</sup>, and it is held that the risk of malignancy may be associated with an increase in  
153 nodule volume <sup>33</sup>. 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%<sup>15</sup>.

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 years<sup>34</sup>. 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 mortality<sup>35</sup>. 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 polyposis<sup>34</sup>. 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 neoplasms<sup>36-38</sup>. 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 acromegaly<sup>39</sup>. 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 <sup>40</sup>.  
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 <sup>41</sup>. Moreover, expression of IGF1, IGF1R and of their mRNA were higher in colorectal  
185 cancer than in colon adenoma and normal tissues <sup>42</sup>. 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 <sup>42</sup>. 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 <sup>43</sup>.

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) <sup>44</sup>. More recently, the same group  
194 demonstrated that in colon cells, GH inhibited the DNA damage repair pathways thus promoting  
195 chromosomal instability <sup>45</sup>. Another study using cells with disrupted IGF-1R, to block IGF1 effect,  
196 showed that GH induces colon DNA damage independently of IGF1 <sup>46</sup>. 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 <sup>47-49</sup>. Conversely, elevated  
205 levels of IGF binding protein-3 (IGFBP-3) have been associated with a lower risk of cancer <sup>47, 48</sup>,

206 although the strength of association is inferior <sup>3</sup>. 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 <sup>50,51</sup>, and an elevated IGF1/IGFBP-3 ratio may lead to enhanced cancer  
209 risk in acromegaly <sup>47,52</sup>.

210 Rokkas et al <sup>53</sup> 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 <sup>54</sup>. 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 <sup>28</sup> 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)<sup>5</sup>. 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 cancer<sup>5</sup>. 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**<sup>7-11, 28, 55-77</sup>).

233 Most studies failed to demonstrate any relationship between activity of acromegaly and risk of  
234 colorectal cancer<sup>54, 78</sup>. 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.<sup>79</sup> 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 colonoscopy<sup>54</sup>. Patients with colonic neoplasms at the repeat colonoscopy had increased  
245 IGF1 levels than patients without<sup>54</sup>.

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 aggressive<sup>54</sup>.

253 There is substantial agreement between Endocrine Scientific Societies<sup>29, 30, 80, 81</sup> 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 mortality<sup>82</sup>. 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 diverticula<sup>83</sup>. 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<sup>54, 79</sup> 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 **years<sup>54</sup>, 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 indicated<sup>34</sup>.**

276 **2: AGAINST**

277

278 Dimopoulou C<sup>1</sup>, Stalla GK<sup>1,2</sup>

279

280 <sup>1</sup> *Medicover Neuroendocrinology, Munich, Germany*

281 <sup>2</sup> *Medizinische Klinik und Poliklinik IV der Ludwig-Maximilians-Universität München, Munich, Germany*

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<sup>84, 85</sup>. 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 neoplasia<sup>13</sup>. 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 far<sup>12</sup>.

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 ambiguous<sup>86</sup>.  
302 In two larger series from the United Kingdom<sup>63</sup> and Germany<sup>7</sup>, 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 population<sup>87</sup>. 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 not<sup>28</sup>.

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 discussed<sup>28</sup>.  
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 available<sup>28</sup>. 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 disease<sup>88</sup>. 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 growth<sup>89</sup>.

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%<sup>73, 90, 91</sup>. 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 incidence<sup>28</sup>. 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)<sup>88</sup>. 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 anticipated<sup>92</sup>.

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<sup>93, 94</sup>. Differences regarding cancer incidence may be due to geographical, ethnic



350 or environmental reasons such as iodine intake or the prevalence of thyroid autoimmunity<sup>92</sup>. 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 unsatisfactory<sup>26</sup>. 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 malignancy<sup>92</sup>. 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 cancer<sup>95</sup>.

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 nodule<sup>29</sup>. Other authors also consider it rational to perform periodic  
365 ultrasonographic evaluation in acromegaly, follow by fine needle aspiration biopsies of suspect  
366 nodules<sup>96</sup>. 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 levels<sup>89</sup>. **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 life<sup>4</sup>. 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%)<sup>23</sup>.

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<sup>6, 7</sup>. 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 ( $P = .41$ )<sup>7</sup>.

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 polyps<sup>97</sup>. Increased fasting insulin levels seem to be associated with an 8.6- to 14.8-fold  
398 increased risk of presenting with colonic adenomas<sup>98</sup>. 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 complaints<sup>54</sup>.

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 studies<sup>99</sup>. 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 acromegaly<sup>53</sup>.

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 overestimated<sup>100</sup>. 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)<sup>100</sup>. 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 weighed<sup>101</sup>.

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 patients<sup>102</sup>. 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 modest<sup>102</sup>.

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 guidelines<sup>102</sup>.

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 proposed<sup>86</sup>. 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 acromegaly<sup>103</sup>.

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 levels<sup>79</sup>.

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 Society<sup>29</sup>, 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 examiner<sup>86</sup>. 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 proposed<sup>99</sup>.

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 small<sup>104</sup>.

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 far<sup>105</sup>.

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 bias<sup>4</sup>.

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 practice<sup>106</sup>.

528

529

### 530 ***Disclosure***

531 The authors have nothing to disclose.

532

### 533 ***Funding***

534 There was no funding for this article.

535

- 537 1. O'Reilly KE, Rojo F, She QB, Solit D, Mills GB, Smith D, Lane H, Hofmann F, Hicklin DJ,  
538 Ludwig DL, et al. mTOR inhibition induces upstream receptor tyrosine kinase signaling and  
539 activates Akt. *Cancer Res* 2006 **66** 1500-1508.
- 540 2. Melmed S. Medical progress: Acromegaly. *N Engl J Med* 2006 **355** 2558-2573.
- 541 3. Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM & Egger M. Insulin-like  
542 growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-  
543 regression analysis. *Lancet* 2004 **363** 1346-1353.
- 544 4. Boguszewski CL & Ayuk J. MANAGEMENT OF ENDOCRINE DISEASE: Acromegaly  
545 and cancer: an old debate revisited. *Eur J Endocrinol* 2016 **175** R147-156.
- 546 5. Terzolo M, Reimondo G, Berchialla P, Ferrante E, Malchiodi E, De Marinis L, Pivonello R,  
547 Grottoli S, Losa M, Cannavo S, et al. Acromegaly is associated with increased cancer risk: a  
548 survey in Italy. *Endocr Relat Cancer* 2017 **24** 495-504.
- 549 6. Kauppinen-Makelin R, Sane T, Valimaki MJ, Markkanen H, Niskanen L, Ebeling T,  
550 Jaatinen P, Juonala M, Finnish Acromegaly Study G & Pukkala E. Increased cancer  
551 incidence in acromegaly--a nationwide survey. *Clin Endocrinol (Oxf)* 2010 **72** 278-279.
- 552 7. Petroff D, Tonjes A, Grussendorf M, Droste M, Dimopoulou C, Stalla G, Jaurisch-Hancke C,  
553 Mai M, Schopohl J & Schofl C. The Incidence of Cancer Among Acromegaly Patients:  
554 Results From the German Acromegaly Registry. *J Clin Endocrinol Metab* 2015 **100** 3894-  
555 3902.
- 556 8. Cheng S, Gomez K, Serri O, Chik C & Ezzat S. The role of diabetes in acromegaly  
557 associated neoplasia. *PLoS One* 2015 **10** e0127276.
- 558 9. Ron E, Gridley G, Hrubec Z, Page W, Arora S & Fraumeni JF, Jr. Acromegaly and  
559 gastrointestinal cancer. *Cancer* 1991 **68** 1673-1677.
- 560 10. Alexander L, Appleton D, Hall R, Ross WM & Wilkinson R. Epidemiology of acromegaly  
561 in the Newcastle region. *Clin Endocrinol (Oxf)* 1980 **12** 71-79.
- 562 11. Baris D, Gridley G, Ron E, Weiderpass E, Mellekjær L, Ekblom A, Olsen JH, Baron JA &  
563 Fraumeni JF. Acromegaly and cancer risk: a cohort study in Sweden and Denmark. *Cancer*  
564 *Causes Control* 2002 **13** 395-400.
- 565 12. Renehan AG & Brennan BM. Acromegaly, growth hormone and cancer risk. *Best Pract Res*  
566 *Clin Endocrinol Metab* 2008 **22** 639-657.
- 567 13. Loeper S & Ezzat S. Acromegaly: re-thinking the cancer risk. *Rev Endocr Metab Disord*  
568 2008 **9** 41-58.
- 569 14. Gadelha MR, Kasuki L, Lim DST & Fleseriu M. Systemic Complications of Acromegaly  
570 and the Impact of the Current Treatment Landscape: An Update. *Endocr Rev* 2019 **40** 268-  
571 332.
- 572 15. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F,  
573 Randolph GW, Sawka AM, Schlumberger M, et al. 2015 American Thyroid Association  
574 Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated  
575 Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid  
576 Nodules and Differentiated Thyroid Cancer. *Thyroid* 2016 **26** 1-133.
- 577 16. Yashiro T, Ohba Y, Murakami H, Obara T, Tsushima T, Fujimoto Y, Shizume K & Ito K.  
578 Expression of insulin-like growth factor receptors in primary human thyroid neoplasms.  
579 *Acta Endocrinol (Copenh)* 1989 **121** 112-120.
- 580 17. Maiorano E, Ciampolillo A, Viale G, Maisonneuve P, Ambrosi A, Triggiani V, Marra E &  
581 Perlino E. Insulin-like growth factor 1 expression in thyroid tumors. *Appl Immunohistochem*  
582 *Mol Morphol* 2000 **8** 110-119.
- 583 18. Gydee H, O'Neill JT, Patel A, Bauer AJ, Tuttle RM & Francis GL. Differentiated thyroid  
584 carcinomas from children and adolescents express IGF-I and the IGF-I receptor (IGF-I-R).

- 585 Cancers with the most intense IGF-I-R expression may be more aggressive. *Pediatr Res*  
586 2004 **55** 709-715.
- 587 19. Kim HK, Lee JS, Park MH, Cho JS, Yoon JH, Kim SJ & Kang HC. Tumorigenesis of  
588 papillary thyroid cancer is not BRAF-dependent in patients with acromegaly. *PLoS One*  
589 2014 **9** e110241.
- 590 20. Aydin K, Aydin C, Dagdelen S, Tezel GG & Erbas T. Genetic Alterations in Differentiated  
591 Thyroid Cancer Patients with Acromegaly. *Exp Clin Endocrinol Diabetes* 2016 **124** 198-  
592 202.
- 593 21. Keskin FE, Ozkaya HM, Ferahman S, Haliloglu O, Karatas A, Aksoy F & Kadioglu P. The  
594 Role of Different Molecular Markers in Papillary Thyroid Cancer Patients with Acromegaly.  
595 *Exp Clin Endocrinol Diabetes* 2019 **127** 437-444.
- 596 22. Wolinski K, Stangierski A, Dyrda K, Nowicka K, Pelka M, Iqbal A, Car A, Lazizi M,  
597 Bednarek N, Czarnywojtek A, et al. Risk of malignant neoplasms in acromegaly: a case-  
598 control study. *J Endocrinol Invest* 2017 **40** 319-322.
- 599 23. Lai NB, Garg D, Heaney AP, Bergsneider M & Leung AM. NO BENEFIT OF  
600 DEDICATED THYROID NODULE SCREENING IN PATIENTS WITH  
601 ACROMEGALY. *Endocr Pract* 2019.
- 602 24. Ahn HS, Kim HJ & Welch HG. Korea's thyroid-cancer "epidemic"--screening and  
603 overdiagnosis. *N Engl J Med* 2014 **371** 1765-1767.
- 604 25. Shin S, Park SE, Kim SY, Hyun MK, Kim SW, Kwon JW, Kim Y, Kim WB, Na DG, Park  
605 HA, et al. Effectiveness of ultrasonographic screening for thyroid cancer: round-table  
606 conference in the National Evidence- based Healthcare Collaborating Agency (NECA) in  
607 conjunction with the Korean Thyroid Association. *Asian Pac J Cancer Prev* 2014 **15** 5107-  
608 5110.
- 609 26. Wolinski K, Czarnywojtek A & Ruchala M. Risk of thyroid nodular disease and thyroid  
610 cancer in patients with acromegaly--meta-analysis and systematic review. *PLoS One* 2014 **9**  
611 e88787.
- 612 27. Woliński K, Stangierski A, Gurgul E, Bromińska B, Czarnywojtek A, Lodyga M & Ruchala  
613 M. Thyroid lesions in patients with acromegaly - case-control study and update to the meta-  
614 analysis. *Endokrynol Pol* 2017 **68** 2-6.
- 615 28. Dal J, Leisner MZ, Hermansen K, Farkas DK, Bengtsen M, Kistorp C, Nielsen EH,  
616 Andersen M, Feldt-Rasmussen U, Dekkers OM, et al. Cancer Incidence in Patients With  
617 Acromegaly: A Cohort Study and Meta-Analysis of the Literature. *J Clin Endocrinol Metab*  
618 2018 **103** 2182-2188.
- 619 29. Katznelson L, Laws ER, Melmed S, Molitch ME, Murad MH, Utz A, Wass JA & Society E.  
620 Acromegaly: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2014  
621 **99** 3933-3951.
- 622 30. Giustina A, Barkan A, Beckers A, Biermasz N, Biller BMK, Boguszewski C, Bolanowski  
623 M, Bonert V, Bronstein MD, Casanueva FF, et al. A Consensus on the Diagnosis and  
624 Treatment of Acromegaly Comorbidities: An Update. *J Clin Endocrinol Metab* 2019.
- 625 31. Kan S, Kizilgul M, Celik B, Beysel S, Caliskan M, Apaydin M, Ucan B & Cakal E. The  
626 effect of disease activity on thyroid nodules in patients with acromegaly. *Endocr J* 2019 **66**  
627 301-307.
- 628 32. Dogansen SC, Salmaslioglu A, Yalin GY, Tanrikulu S & Yarman S. Evaluation of the  
629 natural course of thyroid nodules in patients with acromegaly. *Pituitary* 2019 **22** 29-36.
- 630 33. Angell TE, Vyas CM, Medici M, Wang Z, Barletta JA, Benson CB, Cibas ES, Cho NL,  
631 Doherty GM, Doubilet PM, et al. Differential Growth Rates of Benign vs. Malignant  
632 Thyroid Nodules. *J Clin Endocrinol Metab* 2017 **102** 4642-4647.
- 633 34. Qaseem A, Crandall CJ, Mustafa RA, Hicks LA, Wilt TJ & Physicians CGCotACo.  
634 Screening for Colorectal Cancer in Asymptomatic Average-Risk Adults: A Guidance  
635 Statement From the American College of Physicians. *Ann Intern Med* 2019 **171** 643-654.



- 636 35. Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, Waye JD,  
637 Schapiro M, Bond JH & Panish JF. Prevention of colorectal cancer by colonoscopic  
638 polypectomy. The National Polyp Study Workgroup. *N Engl J Med* 1993 **329** 1977-1981.
- 639 36. MOON HD, SIMPSON ME, LI CH & EVANS HM. Neoplasms in rats treated with  
640 pituitary growth hormone; pulmonary and lymphatic tissues. *Cancer Res* 1950 **10** 297-308.
- 641 37. Pollak MN, Polychronakos C, Yousefi S & Richard M. Characterization of insulin-like  
642 growth factor I (IGF-I) receptors of human breast cancer cells. *Biochem Biophys Res*  
643 *Commun* 1988 **154** 326-331.
- 644 38. Cats A, Dullaart RP, Kleibeuker JH, Kuipers F, Sluiter WJ, Hardonk MJ & de Vries EG.  
645 Increased epithelial cell proliferation in the colon of patients with acromegaly. *Cancer Res*  
646 1996 **56** 523-526.
- 647 39. Bogazzi F, Russo D, Locci MT, Chifenti B, Ultimieri F, Raggi F, Cosci C, Sardella C, Costa  
648 A, Gasperi M, et al. Apoptosis is reduced in the colonic mucosa of patients with  
649 acromegaly. *Clin Endocrinol (Oxf)* 2005 **63** 683-688.
- 650 40. Dutta P, Bhansali A, Vaiphei K, Dutta U, Ravi Kumar P, Masoodi S, Mukherjee KK, Varma  
651 A & Kochhar R. Colonic neoplasia in acromegaly: increased proliferation or decreased  
652 apoptosis? *Pituitary* 2012 **15** 166-173.
- 653 41. Zhang R, Xu GL, Li Y, He LJ, Chen LM, Wang GB, Lin SY, Luo GY, Gao XY & Shan  
654 HB. The role of insulin-like growth factor 1 and its receptor in the formation and  
655 development of colorectal carcinoma. *J Int Med Res* 2013 **41** 1228-1235.
- 656 42. Han L, Zhang GF, Cheng YH & Zhao QC. Correlations of insulin-like growth factor I and  
657 insulin-like growth factor I receptor with the clinicopathological features and prognosis of  
658 patients with colon cancer. *Jpn J Clin Oncol* 2016 **46** 1127-1134.
- 659 43. Shiratsuchi I, Akagi Y, Kawahara A, Kinugasa T, Romeo K, Yoshida T, Ryu Y, Gotanda Y,  
660 Kage M & Shirouzu K. Expression of IGF-1 and IGF-1R and their relation to  
661 clinicopathological factors in colorectal cancer. *Anticancer Res* 2011 **31** 2541-2545.
- 662 44. Chesnokova V, Zonis S, Zhou C, Recouvreux MV, Ben-Shlomo A, Araki T, Barrett R,  
663 Workman M, Wawrowsky K, Ljubimov VA, et al. Growth hormone is permissive for  
664 neoplastic colon growth. *Proc Natl Acad Sci U S A* 2016 **113** E3250-3259.
- 665 45. Chesnokova V, Zonis S, Barrett R, Kameda H, Wawrowsky K, Ben-Shlomo A, Yamamoto  
666 M, Gleeson J, Bresee C, Gorbunova V & Melmed S. Excess growth hormone suppresses  
667 DNA damage repair in epithelial cells. *JCI Insight* 2019 **4**.
- 668 46. Chesnokova V, Zonis S, Barrett RJ, Gleeson JP & Melmed S. Growth Hormone Induces  
669 Colon DNA Damage Independent of IGF-1. *Endocrinology* 2019 **160** 1439-1447.
- 670 47. Ma J, Pollak MN, Giovannucci E, Chan JM, Tao Y, Hennekens CH & Stampfer MJ.  
671 Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth  
672 factor (IGF)-I and IGF-binding protein-3. *J Natl Cancer Inst* 1999 **91** 620-625.
- 673 48. Giovannucci E, Pollak MN, Platz EA, Willett WC, Stampfer MJ, Majeed N, Colditz GA,  
674 Speizer FE & Hankinson SE. A prospective study of plasma insulin-like growth factor-1 and  
675 binding protein-3 and risk of colorectal neoplasia in women. *Cancer Epidemiol Biomarkers*  
676 *Prev* 2000 **9** 345-349.
- 677 49. Kaaks R, Toniolo P, Akhmedkhanov A, Lukanova A, Biessy C, Dechaud H, Rinaldi S,  
678 Zeleniuch-Jacquotte A, Shore RE & Riboli E. Serum C-peptide, insulin-like growth factor  
679 (IGF)-I, IGF-binding proteins, and colorectal cancer risk in women. *J Natl Cancer Inst* 2000  
680 **92** 1592-1600.
- 681 50. Juul A, Pedersen SA, Sørensen S, Winkler K, Jørgensen JO, Christiansen JS & Skakkebaek  
682 NE. Growth hormone (GH) treatment increases serum insulin-like growth factor binding  
683 protein-3, bone isoenzyme alkaline phosphatase and forearm bone mineral content in young  
684 adults with GH deficiency of childhood onset. *Eur J Endocrinol* 1994 **131** 41-49.

- 685 51. Ghigo E, Aimaretti G, Maccario M, Fanciulli G, Arvat E, Minuto F, Giordano G, Delitala G  
686 & Camanni F. Dose-response study of GH effects on circulating IGF-I and IGFBP-3 levels  
687 in healthy young men and women. *Am J Physiol* 1999 **276** E1009-1013.
- 688 52. Giovannucci E & Pollak M. Risk of cancer after growth-hormone treatment. *Lancet* 2002  
689 **360** 268-269.
- 690 53. Rokkas T, Pistiolas D, Sechopoulos P, Margantinis G & Koukoulis G. Risk of colorectal  
691 neoplasm in patients with acromegaly: a meta-analysis. *World J Gastroenterol* 2008 **14**  
692 3484-3489.
- 693 54. Terzolo M, Reimondo G, Gasperi M, Cozzi R, Pivonello R, Vitale G, Scillitani A, Attanasio  
694 R, Cecconi E, Daffara F, et al. Colonoscopic screening and follow-up in patients with  
695 acromegaly: a multicenter study in Italy. *J Clin Endocrinol Metab* 2005 **90** 84-90.
- 696 55. MUSTACCHI P & SHIMKIN MB. Occurrence of cancer in acromegaly and in  
697 hypopituitarism. *Cancer* 1957 **10** 100-104.
- 698 56. Wright AD, Hill DM, Lowy C & Fraser TR. Mortality in acromegaly. *Q J Med* 1970 **39** 1-  
699 16.
- 700 57. Bengtsson BA, Edén S, Ernest I, Odén A & Sjögren B. Epidemiology and long-term  
701 survival in acromegaly. A study of 166 cases diagnosed between 1955 and 1984. *Acta Med*  
702 *Scand* 1988 **223** 327-335.
- 703 58. Nabarro JD. Acromegaly. *Clin Endocrinol (Oxf)* 1987 **26** 481-512.
- 704 59. Pines A, Rozen P, Ron E & Gilat T. Gastrointestinal tumors in acromegalic patients. *Am J*  
705 *Gastroenterol* 1985 **80** 266-269.
- 706 60. Barzilay J, Heatley GJ & Cushing GW. Benign and malignant tumors in patients with  
707 acromegaly. *Arch Intern Med* 1991 **151** 1629-1632.
- 708 61. Rajasoorya C, Holdaway IM, Wrightson P, Scott DJ & Ibbertson HK. Determinants of  
709 clinical outcome and survival in acromegaly. *Clin Endocrinol (Oxf)* 1994 **41** 95-102.
- 710 62. Cheung NW & Boyages SC. Increased incidence of neoplasia in females with acromegaly.  
711 *Clin Endocrinol (Oxf)* 1997 **47** 323-327.
- 712 63. Orme SM, McNally RJ, Cartwright RA & Belchetz PE. Mortality and cancer incidence in  
713 acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. *J Clin*  
714 *Endocrinol Metab* 1998 **83** 2730-2734.
- 715 64. Popovic V, Damjanovic S, Micic D, Nesovic M, Djurovic M, Petakov M, Obradovic S,  
716 Zoric S, Simic M, Penezic Z et al. Increased incidence of neoplasia in patients with pituitary  
717 adenomas. The Pituitary Study Group. *Clin Endocrinol (Oxf)* 1998 **49** 441-445.
- 718 65. Higuchi Y, Saeki N, Iuchi T, Uchino Y, Tatsuno I, Uchida D, Tanaka T, Noguchi Y,  
719 Nakamura S, Yasuda T, et al. Incidence of malignant tumors in patients with acromegaly.  
720 *Endocr J* 2000 **47 Suppl** S57-60.
- 721 66. Holdaway IM, Rajasoorya RC & Gamble GD. Factors influencing mortality in acromegaly.  
722 *J Clin Endocrinol Metab* 2004 **89** 667-674.
- 723 67. Ayuk J, Clayton RN, Holder G, Sheppard MC, Stewart PM & Bates AS. Growth hormone  
724 and pituitary radiotherapy, but not serum insulin-like growth factor-I concentrations, predict  
725 excess mortality in patients with acromegaly. *J Clin Endocrinol Metab* 2004 **89** 1613-1617.
- 726 68. Kurimoto M, Fukuda I, Hizuka N & Takano K. The prevalence of benign and malignant  
727 tumors in patients with acromegaly at a single institute. *Endocr J* 2008 **55** 67-71.
- 728 69. Gullu BE, Celik O, Gazioglu N & Kadioglu P. Thyroid cancer is the most common cancer  
729 associated with acromegaly. *Pituitary* 2010 **13** 242-248.
- 730 70. Baldys-Waligórska A, Krzentowska A, Gołkowski F, Sokołowski G & Hubalewska-  
731 Dydejczyk A. The prevalence of benign and malignant neoplasms in acromegalic patients.  
732 *Endokrynol Pol* 2010 **61** 29-34.
- 733 71. Kauppinen-Mäkelin R, Sane T, Reunanen A, Välimäki MJ, Niskanen L, Markkanen H,  
734 Löyttyniemi E, Ebeling T, Jaatinen P, Laine H, et al. A nationwide survey of mortality in  
735 acromegaly. *J Clin Endocrinol Metab* 2005 **90** 4081-4086.

- 736 72. Arosio M, Reimondo G, Malchiodi E, Berchiolla P, Borraccino A, De Marinis L, Pivonello  
737 R, Grottole S, Losa M, Cannavò S, et al. Predictors of morbidity and mortality in  
738 acromegaly: an Italian survey. *Eur J Endocrinol* 2012 **167** 189-198.
- 739 73. Dagdelen S, Cinar N & Erbas T. Increased thyroid cancer risk in acromegaly. *Pituitary* 2014  
740 **17** 299-306.
- 741 74. Mercado M, Gonzalez B, Vargas G, Ramirez C, de los Monteros AL, Sosa E, Jarvis P,  
742 Roldan P, Mendoza V, López-Félix B et al. Successful mortality reduction and control of  
743 comorbidities in patients with acromegaly followed at a highly specialized multidisciplinary  
744 clinic. *J Clin Endocrinol Metab* 2014 **99** 4438-4446.
- 745 75. Dal J, Feldt-Rasmussen U, Andersen M, Kristensen L, Laurberg P, Pedersen L, Dekkers  
746 OM, Sørensen HT & Jørgensen JO. Acromegaly incidence, prevalence, complications and  
747 long-term prognosis: a nationwide cohort study. *Eur J Endocrinol* 2016 **175** 181-190.
- 748 76. Maione L, Brue T, Beckers A, Delemer B, Petrossians P, Borson-Chazot F, Chabre O,  
749 François P, Bertherat J, Cortet-Rudelli C, et al. Changes in the management and  
750 comorbidities of acromegaly over three decades: the French Acromegaly Registry. *Eur J*  
751 *Endocrinol* 2017 **176** 645-655.
- 752 77. Esposito D, Ragnarsson O, Granfeldt D, Marlow T, Johannsson G & Olsson DS. Decreasing  
753 mortality and changes in treatment patterns in patients with acromegaly from a nationwide  
754 study. *Eur J Endocrinol* 2018 **178** 459-469.
- 755 78. Jenkins PJ, Fairclough PD, Richards T, Lowe DG, Monson J, Grossman A, Wass JA &  
756 Besser M. Acromegaly, colonic polyps and carcinoma. *Clin Endocrinol (Oxf)* 1997 **47** 17-  
757 22.
- 758 79. Dworakowska D, Gueorguiev M, Kelly P, Monson JP, Besser GM, Chew SL, Akker SA,  
759 Drake WM, Fairclough PD, Grossman AB et al. Repeated colonoscopic screening of  
760 patients with acromegaly: 15-year experience identifies those at risk of new colonic  
761 neoplasia and allows for effective screening guidelines. *Eur J Endocrinol* 2010 **163** 21-28.
- 762 80. Katznelson L, Atkinson JL, Cook DM, Ezzat SZ, Hamrahian AH, Miller KK &  
763 Endocrinologists AAoC. American Association of Clinical Endocrinologists medical  
764 guidelines for clinical practice for the diagnosis and treatment of acromegaly--2011 update.  
765 *Endocr Pract* 2011 **17 Suppl 4** 1-44.
- 766 81. Melmed S, Casanueva FF, Klibanski A, Bronstein MD, Chanson P, Lamberts SW,  
767 Strasburger CJ, Wass JA & Giustina A. A consensus on the diagnosis and treatment of  
768 acromegaly complications. *Pituitary* 2013 **16** 294-302.
- 769 82. Løberg M, Kalager M, Holme Ø, Hoff G, Adami HO & Bretthauer M. Long-term  
770 colorectal-cancer mortality after adenoma removal. *N Engl J Med* 2014 **371** 799-807.
- 771 83. Wassenaar MJ, Cazemier M, Biermasz NR, Pereira AM, Roelfsema F, Smit JW, Hommes  
772 DW, Felt-Bersma RJ & Romijn JA. Acromegaly is associated with an increased prevalence  
773 of colonic diverticula: a case-control study. *J Clin Endocrinol Metab* 2010 **95** 2073-2079.
- 774 84. Jenkins PJ. Acromegaly and cancer. *Horm Res* 2004 **62 Suppl 1** 108-115.
- 775 85. Jenkins PJ. Cancers associated with acromegaly. *Neuroendocrinology* 2006 **83** 218-223.
- 776 86. Dworakowska D & Grossman AB. Colonic Cancer and Acromegaly. *Front Endocrinol*  
777 *(Lausanne)* 2019 **10** 390.
- 778 87. Tirosh A & Shimon I. Complications of acromegaly: thyroid and colon. *Pituitary* 2017 **20**  
779 70-75.
- 780 88. Gasperi M, Martino E, Manetti L, Arosio M, Porretti S, Faglia G, Mariotti S, Colao AM,  
781 Lombardi G, Baldelli R, et al. Prevalence of thyroid diseases in patients with acromegaly:  
782 results of an Italian multi-center study. *J Endocrinol Invest* 2002 **25** 240-245.
- 783 89. Siegel G & Tomer Y. Is there an association between acromegaly and thyroid carcinoma? A  
784 critical review of the literature. *Endocr Res* 2005 **31** 51-58.

- 785 90. Tita P, Ambrosio MR, Scollo C, Carta A, Gangemi P, Bondanelli M, Vigneri R, degli Uberti  
786 EC & Pezzino V. High prevalence of differentiated thyroid carcinoma in acromegaly. *Clin*  
787 *Endocrinol (Oxf)* 2005 **63** 161-167.
- 788 91. Kaldrymidis D, Papadakis G, Tsakonas G, Kaldrymidis P, Flaskas T, Seretis A, Pantazi E,  
789 Kostoglou-Athanassiou I, Peppas M, Roussou P et al. High incidence of thyroid cancer  
790 among patients with acromegaly. *J BUON* 2016 **21** 989-993.
- 791 92. Reverter JL, Fajardo C, Resmini E, Salinas I, Mora M, Llatjos M, Sesmiolo G, Rius F,  
792 Halperin I, Webb SM, et al. Benign and malignant nodular thyroid disease in acromegaly. Is  
793 a routine thyroid ultrasound evaluation advisable? *PLoS One* 2014 **9** e104174.
- 794 93. Ferlay J, Autier P, Boniol M, Heanue M, Colombet M & Boyle P. Estimates of the cancer  
795 incidence and mortality in Europe in 2006. *Ann Oncol* 2007 **18** 581-592.
- 796 94. Rego-Iraeta A, Perez-Mendez LF, Mantinan B & Garcia-Mayor RV. Time trends for thyroid  
797 cancer in northwestern Spain: true rise in the incidence of micro and larger forms of  
798 papillary thyroid carcinoma. *Thyroid* 2009 **19** 333-340.
- 799 95. Davies L & Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-  
800 2002. *JAMA* 2006 **295** 2164-2167.
- 801 96. Marchisotti FG, Umeda LM, Zach PL, Saldanha MD, First OS & Liberman B. [Acromegaly  
802 and thyroid disease: prevalence of thyroid cancer]. *Arq Bras Endocrinol Metabol* 2005 **49**  
803 843-849.
- 804 97. Parolin M, Dassie F, Russo L, Mazzocut S, Ferrata M, De Carlo E, Mioni R, Fallo F, Vettor  
805 R, Martini C et al. Guidelines versus real life practice: the case of colonoscopy in  
806 acromegaly. *Pituitary* 2018 **21** 16-24.
- 807 98. Colao A, Pivonello R, Auriemma RS, Galdiero M, Ferone D, Minuto F, Marzullo P &  
808 Lombardi G. The association of fasting insulin concentrations and colonic neoplasms in  
809 acromegaly: a colonoscopy-based study in 210 patients. *J Clin Endocrinol Metab* 2007 **92**  
810 3854-3860.
- 811 99. Lois K, Bukowczan J, Perros P, Jones S, Gunn M & James RA. The role of colonoscopic  
812 screening in acromegaly revisited: review of current literature and practice guidelines.  
813 *Pituitary* 2015 **18** 568-574.
- 814 100. Renehan AG, O'Dwyer S T & Shalet SM. Colorectal neoplasia in acromegaly: the reported  
815 increased prevalence is overestimated. *Gut* 2000 **46** 440-441.
- 816 101. Renehan AG, O'Dwyer ST & Shalet SM. Guidelines for colonoscopic screening in  
817 acromegaly are inconsistent with those for other high risk groups. *Gut* 2003 **52** 1071-1072;  
818 author reply 1072.
- 819 102. Renehan AG & Shalet SM. Acromegaly and colorectal cancer: risk assessment should be  
820 based on population-based studies. *J Clin Endocrinol Metab* 2002 **87** 1909; author reply  
821 1909.
- 822 103. Bogazzi F, Cosci C, Sardella C, Costa A, Manetti L, Gasperi M, Rossi G, Bartalena L &  
823 Martino E. Identification of acromegalic patients at risk of developing colonic adenomas. *J*  
824 *Clin Endocrinol Metab* 2006 **91** 1351-1356.
- 825 104. Cairns SR, Scholefield JH, Steele RJ, Dunlop MG, Thomas HJ, Evans GD, Eaden JA,  
826 Rutter MD, Atkin WP, Saunders BP, et al. Guidelines for colorectal cancer screening and  
827 surveillance in moderate and high risk groups (update from 2002). *Gut* 2010 **59** 666-689.
- 828 105. Melmed S. Acromegaly and cancer: not a problem? *J Clin Endocrinol Metab* 2001 **86** 2929-  
829 2934.
- 830 106. Perry I, Stewart PM & Kane K. Colorectal screening guidelines in acromegaly. *Gut* 2003 **52**  
831 1387; author reply 1387.

832

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 **1<sup>55</sup>; 2<sup>56</sup>; 3<sup>10</sup>; 4<sup>57</sup>; 5<sup>58</sup>; 6<sup>59</sup>; 7<sup>60</sup>; 8<sup>9</sup>; 9<sup>61</sup>; 10<sup>62</sup>; 11<sup>63</sup>; 12<sup>64</sup>; 13<sup>65</sup>; 14<sup>11</sup>; 15<sup>66</sup>; 16<sup>67</sup>; 17<sup>68</sup>; 18<sup>69</sup>; 19<sup>70</sup>; 20<sup>71</sup>;**  
840 **21<sup>72</sup>; 22<sup>73</sup>; 23<sup>74</sup>; 24<sup>7</sup>; 25<sup>8</sup>; 26<sup>75</sup>; 27<sup>76</sup>; 28<sup>28</sup>; 29<sup>77</sup>.**

841

842