Provisional chapter

Colorectal Neoplasm in Acromegaly: Epidemiology and Underlying Mechanisms

Masaaki Yamamoto and Yutaka Takahashi

Additional information is available at the end of the chapter

Abstract

Acromegaly is characterized by autonomous growth hormone (GH) secretion from the pituitary somatotroph adenoma and increased levels of serum insulin-like growth factor I (IGF-I). These conditions are associated with increased morbidity and mortality due to metabolic conditions, cardiovascular diseases, and malignant neoplasms. Among neoplasms, while colorectal neoplasms are a well-known comorbidity in patients with acromegaly, the prevalence of colorectal benign or malignant tumors varies among studies. Although several underlying mechanisms have been proposed, recent studies have unveiled new insights into tumorigenesis. This review focused on the epidemiological studies of colorectal neoplasm in acromegaly and recent advances in the elucidation of the underlying mechanisms.

Keywords: acromegaly, colon polyp, colon cancer, GH, IGF-I

1. Introduction

Acromegaly is characterized by excess levels of insulin-like growth factor I (IGF-I) derived from autonomous growth hormone (GH) secretion from the pituitary somatotroph adenoma, which results in acral enlargement, coarse facial features, and visceromegaly [1, 2]. Even worse, acromegalic patients exhibit a shorter life span than healthy subjects owing to various comorbidities such as diabetes; hypertension; and cardiovascular, cerebrovascular, and respiratory diseases [1]. Malignant neoplasms in several organs including the thyroid, breast, prostate, pancreas, and digestive tract are also widely recognized as representative complications [1, 3, 4]. Even among those, patients with acromegaly are well known to have a significantly higher prevalence of colon neoplasms than the general population. Recent evidence suggests

that even benign neoplasms such as adenoma and hyperplasia may have the potential to develop into malignant adenocarcinoma, which potentially affects the prognosis of acromegalic patients [5–7]. Recent guidelines recommend that while acromegalic patients are necessary to undergo colonoscopy regularly, they often face difficulties throughout colonoscopy intubation owing to distinctive features of acromegaly such as elongation of the colon [8]. Recently, the molecular mechanism behind colon tumorigenesis associated with the GH-IGF-I excess has been elucidated. In this chapter, we review the epidemiological evidence, protocol of follow-up colonoscopy, and underlying mechanism of GH/IGF-I-associated colon tumorigenesis in patients with acromegaly.

2. Epidemiology in colorectal neoplasms in acromegaly

Klein et al. first demonstrated an increased prevalence of colon polyps in patients with acromegaly in 1982, reporting a prevalence of colorectal adenomatous polyps of approximately 30% in 17 patients with acromegaly [9]. Several subsequent reports also showed that colonic neoplasms were more frequently observed in 47% of patients with acromegaly, compared to the control with colonic lesions in 40% of asymptomatic males >50 years [10]. A cohort study identified 1041 male patients as having acromegaly from over 4 million men from the database of the United States Veterans Administration, which revealed a prevalence of acromegaly to be 277 cases/million [11]. In this study, 13 acromegalic patients had colonic cancer, which indicates a significantly higher prevalence than in the control group (SIR: 3.1; 95% CI 1.7–5.1) [11]. The UK registry of acromegaly diagnosed 16 patients as having colorectal cancer from a total of 1239 patients with acromegaly. Although this study did not show any significant change in the frequency of colorectal carcinoma compared to healthy subjects, the mortality rate of colon cancer was higher even though the overall mortality rate due to cancer was not increased [4]. An investigation of the incidence of cancer in 1643 hospitalized acromegalic patients in North Europe was performed, and the estimated standardized incidence ratio (SIR) was 2.6 (95% confidence interval [CI] 1.6–3.8) for overall colorectal cancer and 2.5 (95% CI 1.3–4.2) for rectal carcinoma [12]. Terzolo et al. performed colonoscopy to screen for colorectal tumors in 235 patients with acromegaly and compared the prevalence of colorectal tumors in this cohort with the prevalence in a control population who had no past and family history of colonic disease. Patients with acromegaly exhibited a higher prevalence of colon adenomas (acromegaly; 23.4% vs. control; 14.6%; $P = 0.001$), hyperplastic polyps (19.1% vs. 9.4%; $P = 0.003$), and cancer (4.3% vs. 0.9%; $P = 0.036$) [13]. The risk factor for colon cancer in acromegaly was young age, whereas there was no association between the prevalence of colon neoplasms and serum IGF-1 levels or disease duration [13]. Delhougne et al. reported similar results of acromegalic patients showing an increased prevalence of adenomatous (22.3% vs. 8%; $P = 0.0024$) and hyperplastic polyps (24.3% vs. 4.4%; $P < 0.001$) compared to a control group [14]. In particular, younger people (younger than 55 years old) and men had a higher prevalence of adenomatous polyp than those in the control group (20.3% vs. 3.0%; $P < 0.0026$) [14]. Our recent study revealed that 57 Japanese acromegalic patients also exhibited a higher prevalence of colon adenomas (31.6% vs. 2.5%; $P < 0.0001$) and hyperplastic polyps (38.6% vs. 6.7%; $P < 0.0001$) than the historical control group with irritable bowel syndrome [15].

Furthermore, colon cancer in patients with acromegaly exhibited an increased odds ratio of 14.5 (95% CI 5.8–23.3) compared to that in the general Japanese population [15].

Thus, numerous studies documented evidence regarding risk of colorectal tumors in acromegalic patients, and several meta-analyses have demonstrated an increased prevalence of colorectal tumors including benign polyps and carcinomas. A German review meta-analyzed 9 eligible papers with strict inclusion criteria from 106 studies. As benign polyps, the pooled ORs with 95% CI of hyperplastic polyps and colon adenomas were 3.7 (95% CI; 2.6–5.3) and 2.5 (95% CI; 1.9–3.4), respectively. In terms of colon cancer, the pooled OR with 95% CI was 4.4 (1.5–12.4) [16]. The second study meta-analyzed 14 papers to determine the incidence of colorectal cancer [17]. After exclusion criteria was <10 expected cases, standardized incidence ratios (SIRs) were obtained from eight studies and the pooled SIR was 2.6 (95% CI; 1.7–4.0), which demonstrated an increased prevalence of colorectal cancer [18]. While the prevalence of colorectal cancer in female was significantly increased (SIR 1.86; 95% CI, 1.06–3.28 $P = 0.03$), male patients had no change (SIR 1.44; 95% CI, 0.72–2.88 $P = 0.31$) [17]. An analysis of patients with acromegaly including male and female patients revealed that the SIR of colorectal cancer with 95% CI was significantly elevated (SIR 1.67; 95% CI, 1.07–2.58, P = 0.022) [17]. Taken together, these meta-analyses demonstrated an increased risk of colorectal cancer in patients with acromegaly. There was a large variance in SIRs among studies from 1.4 [4] to 18.2 [3] and the difference in SIRs was observed depends on single center trials (SIR 7.3) and multicenter or population-based trials (SIR 2.0 and 2.2, respectively). In addition, two meta-analyses demonstrated that Japanese cohorts exhibited obviously higher prevalence of colorectal cancer in acromegalic patients than in other countries, suggesting that there may be an ethnic difference [16, 18].

3. Follow-up colonoscopy based on guidelines

Although some studies described the frequency of colonoscopy for the follow-up in patients with acromegaly, there is still controversy on the appropriate follow-up [13, 19, 20]. The guidelines in 2002 recommended that colonoscopy should be performed every 3–5 years considering the past history of colon neoplasms and family history [21]. The next revision in 2009 suggested that colonoscopy should be performed at least once upon diagnosis in all patients with acromegaly. If colon polyps were detected in patients with acromegaly at the first screening, they should be carefully followed up based on the guidelines of screening and surveillance for general colorectal cancer [22–24]. However, several groups still appealed the importance of repeated colonoscopy on a regular basis for acromegalic patients [25–27]. Dworakowska et al. reported that patients who were diagnosed as having adenomatous polyp at first screening had a higher risk of developing a new lesion at the subsequent follow-up colonoscopy. Additionally, patients with poor IGF-I control had a 7.5-fold higher risk of a subsequent adenoma even if patients had a normal colon at the first screening [20].

The British Society of Gastroenterology and the Association of Coloproctology for Great Britain and Ireland in 2010 classified acromegalic patients as having a moderate to high risk of colorectal cancer on the update of the 2002 guidance, which suggested performing

colonoscopy screening in those 40 years of age or older on a regular basis [28]. The frequency of repeat colonoscopy should be modified depending on the conditions of the initial screening and the activity of acromegaly. If the initial screening test showed negative results and IGF-I level was within normal range, the next colonoscopy will be scheduled 5–10 years later. When adenomatous polyps were detected at initial screening or higher IGF-I levels were noted, follow-up colonoscopy should be performed every 3 years [28]. The medical guidelines of the American Association of Clinical Endocrinologists (2011) and the Acromegaly Consensus Group (2013) state a similar recommendation that acromegalic patients should undergo initial colonoscopy at the time of diagnosis. If persistently elevated IGF-I level, abnormal findings by colonoscopy, or a family history of colon cancer is noted, follow-up colonoscopy should be performed more frequently. If not, a follow-up colonoscopy should be recommended every 10 years [29, 30].

Although current recommendations for surveillance colonoscopy in acromegaly may differ slightly among each study, collectively, it is deemed necessary to perform follow-up colonoscopy for cases with poor control of IGF-I and adenomatous polyps at least every 5 years according to five independent statements [20, 28, 29, 31]. Although an updated consensus from the Acromegaly Consensus Group in 2019 still recommends screening by colonoscopy at the time of diagnosis, they toned down the recommendation in terms of follow-up colonoscopy on a regular basis because there is no evidence linking screening frequency to colon cancer mortality rates [32, 33]. As acromegalic patients live longer than before owing to the improvement of biochemical control by advances in the treatment strategy, aging seems to be a more reliable indicator of cancer in patients with acromegaly than GH/IGF-I excess [34].

4. Underlying mechanism of colon neoplasm in acromegaly

4.1. GH signal

Secreted GH interacts with the GH receptor (GHR) that belongs to the class I cytokine receptor family, which is mainly expressed in the liver, fat, and muscle [35]. Consequently, phosphorylated GHR induces janus kinase 2 (JAK2) phosphorylation, which results in tyrosine phosphorylation of STAT5 (signal transducer and activator of transcription 5). STAT5 is the physiologically essential transcription factor for GH-dependent body growth, lipid metabolism, and sex-specific gene expression [36]. Recent studies have revealed that STAT5 plays an important role in tumorigenesis, especially cell proliferation and exertion of the anti-apoptotic property [37]. The phosphorylated STAT5 is associated with the development of malignant neoplasms including malignant prostate neoplasms, malignant breast neoplasms, and leukemia [37–39]. In colorectal cancer, the expression level of STAT5B is higher than in the normal colon tissue, and also correlates with the TNM stage [40]. Furthermore, phosphorylated STAT5 in colon adenocarcinomas is associated with a poor prognosis [41]. The phosphorylation of STAT5 is suppressed by suppressor of cytokine signaling-2 (SOCS2) in the GH signaling pathway [42]. A previous paper reported that SOCS2-knockout exhibited the development of hyperplastic mucosa and polyps in bovine GH-transgenic mice [43] Furthermore,

d3GHR polymorphism caused the signaling enhancement, which resulted in increasing the risk of colon adenoma regardless of circulating IGF-I concentration compared to intact GHR in acromegalic patients [44]. Recently, we reported that the GH area under the curve in the oral glucose tolerance test exhibited higher prevalence in colon cancer patients than in colonic benign tumor patients [15]. These data suggest the significance of excessive GH signaling in the development of epithelium-adenoma-carcinoma, independent of IGF-I signaling [45].

4.2. IGF-I signal

Bowel enlargement in acromegalic patients is observed associated with accumulative excessive GH and IGF-I [46–48]. Enhanced proliferation of colonic epithelial cells and reduced apoptosis of the colonic mucosa were observed in patients with acromegaly [47, 49]. Interestingly, an increased proliferation rate of colonic epithelium cells was correlated with circulating IGF1 levels [50]. IGF-I receptor knockout mice exhibited a decreased cell proliferation and increased apoptosis [1]. The IGF-I/IGF-IR system also plays an important role in the promotion of cell adhesion, migration, and tumor microenvironment including the angiogenesis in the tumor [51]. The IGF-IR mRNA expression level in the colon cancer tissue was associated with paracrine/autocrine effects [1]. Even in those with normal IGF-I levels, there was a positive association between circulating IGF-I levels and the risk of colorectal cancer in a meta-analysis of 19 epidemiological studies [52]. However, several previous studies suggested that the classification based on the type of colorectal neoplasms or with/without colorectal neoplasms did not correlate with serum IGF-I levels [13, 15, 53, 54]. Taken together, elevated levels of serum IGF-I may also involve colorectal tumorigenesis, but it still needs further investigation.

4.3. Local GH action in the colon

In terms of direct action of GH as a novel insight, it has recently been reported that locally expressed GH in the colon is a precursor to colon cancer. Excessive GH leads to cell survival with downregulation of tumor suppressor genes such as p53 and APC, which results in neoplastic colon growth [55]. GH suppressed DNA damage response (DDR) by inhibiting phosphorylated ataxia telangiectasia mutated (ATM), checkpoint kinase 2 (Chk2), and p53. They also elucidated that GH significantly increased unrepaired DNA damage in colon epithelial cells, and colon cancer cell lines of xenografted mice with GH overexpression exhibited more metastases compared to colon cancer cell lines of control mice [56], and these mechanisms were observed independent of IGF-I action [57].

5. Underlying mechanism of hyperplastic polyp in acromegaly

As mentioned above, various mechanisms are involved in tumorigenesis of colorectal neoplasms. These mechanisms can account for the tumorigenesis of colorectal adenomatous polyps or adenocarcinomas, but not hyperplastic polyps. As a noteworthy fact, hyperplastic polyps are basically considered as benign neoplasms, while colorectal adenoma is widely

recognized as pre-malignant conditions based on the presence of the adenoma-carcinoma sequence. Indeed, hyperplastic polyps are described by a superficial serrated architecture and variably elongated crypts with proliferation confined to the lower portion of the crypt [58]. However, *k-ras* or *BRAF* mutations and microsatellite instability, which cause the malignant colorectal tumors, are detected in hyperplastic polyps [6]. In this aspect, hyperplastic polyps may need to be carefully diagnosed with histological examination in acromegaly. Acromegalic patients exhibited accelerated mucosal proliferation in the colon tissue compared to normal subjects [47, 59], which might involve in an increased prevalence of hyperplastic polyps. Further investigation is needed to elucidate the potential risk and underlying mechanism of the development of hyperplastic polyps in acromegaly.

6. Conclusion

Colorectal neoplasm, especially adenocarcinoma, is a life-threatening comorbidity of acromegaly. Accumulating data clearly demonstrate the increased prevalence of colorectal polyps and cancer in patients with acromegaly even among different races and countries. Although the appropriate follow-up protocol of colonoscopy remains controversial, different guidelines state that cases with poor control IGF-I and adenomatous polyps should be classified as having a high risk of colon cancer. In terms of molecular mechanisms, both GH and IGF-I are implicated in colon cancer development.

Author details

Masaaki Yamamoto[1] and Yutaka Takahashi[2]*

*Address all correspondence to: takahash@med.kobe-u.ac.jp

1 Division of Diabetes and Endocrinology, Kobe University Hospital, Kobe, Japan

2 Division of Diabetes and Endocrinology, Kobe University Graduate School of Medicine, Kobe, Japan

References

[1] Colao A et al. Systemic complications of acromegaly: Epidemiology, pathogenesis, and management. Endocrine Reviews. 2004;**25**(1):102-152

[2] Melmed S. Acromegaly pathogenesis and treatment. The Journal of Clinical Investigation. 2009;**119**(11):3189-3202

[3] Kurimoto M et al. The prevalence of benign and malignant tumors in patients with acromegaly at a single institute. Endocrine Journal. 2008;**55**(1):67-71

[4] Orme SM et al. Mortality and cancer incidence in acromegaly: A retrospective cohort study. The Journal of Clinical Endocrinology and Metabolism. 1998;**83**(8):2730-2734

[5] Jass JR et al. Emerging concepts in colorectal neoplasia. Gastroenterology. 2002;**123**(3): 862-876

[6] Snover DC et al. Serrated polyps of the large intestine: A morphologic and molecular review of an evolving concept. American Journal of Clinical Pathology. 2005;**124**(3):380-391

[7] Torlakovic E et al. Morphologic reappraisal of serrated colorectal polyps. The American Journal of Surgical Pathology. 2003;**27**(1):65-81

[8] Iwamuro M et al. Colonoscopy examination requires a longer time in patients with acromegaly than in other individuals. Endocrine Journal. 2018;**65**(2):151-157

[9] Klein I et al. Colonic polyps in patients with acromegaly. Annals of Internal Medicine. 1982;**97**(1):27-30

[10] Melmed S. Acromegaly and cancer: Not a problem? The Journal of Clinical Endocrinology and Metabolism. 2001;**86**(7):2929-2934

[11] Ron E et al. Acromegaly and gastrointestinal cancer. Cancer. 1991;**68**(8):1673-1677

[12] Baris D et al. Acromegaly and cancer risk: A cohort study in Sweden and Denmark. Cancer Causes & Control. 2002;**13**(5):395-400

[13] Terzolo M et al. Colonoscopic screening and follow-up in patients with acromegaly: A multicenter study in Italy. The Journal of Clinical Endocrinology and Metabolism. 2005;**90**(1):84-90

[14] Delhougne B et al. The prevalence of colonic polyps in acromegaly: A colonoscopic and pathological study in 103 patients. The Journal of Clinical Endocrinology and Metabolism. 1995;**80**(11):3223-3226

[15] Yamamoto M et al. The prevalence and associated factors of colorectal neoplasms in acromegaly: A single center based study. Pituitary. 2015;**18**(3):343-351

[16] Rokkas T et al. Risk of colorectal neoplasm in patients with acromegaly: A meta-analysis. World Journal of Gastroenterology. 2008;**14**(22):3484-3489

[17] Terzolo M et al. Acromegaly is associated with increased cancer risk: A survey in Italy. Endocrine-Related Cancer. 2017;**24**(9):495-504

[18] Dal J et al. Cancer incidence in patients with acromegaly: A cohort study and meta-analysis of the literature. The Journal of Clinical Endocrinology and Metabolism. 2018;**103**(6): 2182-2188

[19] Parolin M et al. Guidelines versus real life practice: The case of colonoscopy in acromegaly. Pituitary. 2018;**21**(1):16-24

[20] Dworakowska D et al. Repeated colonoscopic screening of patients with acromegaly: 15-year experience identifies those at risk of new colonic neoplasia and allows for effective screening guidelines. European Journal of Endocrinology. 2010;**163**(1):21-28

[21] Melmed S et al. Guidelines for acromegaly management. The Journal of Clinical Endocrinology and Metabolism. 2002;**87**(9):4054-4058

[22] Melmed S et al. Guidelines for acromegaly management: An update. The Journal of Clinical Endocrinology and Metabolism. 2009;**94**(5):1509-1517

[23] Sung JJ et al. Asia Pacific consensus recommendations for colorectal cancer screening. Gut. 2008;**57**(8):1166-1176

[24] Levin B et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: A joint guideline from the American Cancer Society, the US multi-society task force on colorectal Cancer, and the American College of Radiology. Gastroenterology. 2008;**134**(5):1570-1595

[25] Jenkins PJ et al. Insulin-like growth factor I and the development of colorectal neoplasia in acromegaly. The Journal of Clinical Endocrinology and Metabolism. 2000;**85**(9):3218-3221

[26] Jenkins PJ, Fairclough PD. Colorectal neoplasia in acromegaly. Clinical Endocrinology. 2001;**55**(6):727-729

[27] Perry I, Stewart PM, Kane K. Colorectal screening guidelines in acromegaly. Gut. 2003;**52**(9):1387. author reply 1387

[28] Cairns SR et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut. 2010;**59**(5):666-689

[29] Melmed S et al. A consensus on the diagnosis and treatment of acromegaly complications. Pituitary. 2013;**16**(3):294-302

[30] Katznelson L et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of acromegaly—2011 update. Endocrine Practice. 2011;**17**(Suppl 4):1-44

[31] Giustina A et al. Expert consensus document: A consensus on the medical treatment of acromegaly. Nature Reviews. Endocrinology. 2014;**10**(4):243-248

[32] Lois K et al. The role of colonoscopic screening in acromegaly revisited: Review of current literature and practice guidelines. Pituitary. 2015;**18**(4):568-574

[33] Giustina A et al. A consensus on the diagnosis and treatment of acromegaly comorbidities: An update. The Journal of Clinical Endocrinology and Metabolism. 2019. (in press)

[34] Bolfi F et al. Mortality in acromegaly decreased in the last decade: A systematic review and meta-analysis. European Journal of Endocrinology. 2018;**179**(1):59-71

[35] Brown RJ et al. Model for growth hormone receptor activation based on subunit rotation within a receptor dimer. Nature Structural & Molecular Biology. 2005;**12**(9):814-821

[36] Lanning NJ, Carter-Su C. Recent advances in growth hormone signaling. Reviews in Endocrine & Metabolic Disorders. 2006;**7**(4):225-235

[37] Ferbeyre G, Moriggl R. The role of Stat5 transcription factors as tumor suppressors or oncogenes. Biochimica et Biophysica Acta. 2011;**1815**(1):104-114

[38] Nevalainen MT et al. Signal transducer and activator of transcription-5 activation and breast cancer prognosis. Journal of Clinical Oncology. 2004;**22**(11):2053-2060

[39] Tan SH, Nevalainen MT. Signal transducer and activator of transcription 5A/B in prostate and breast cancers. Endocrine-Related Cancer. 2008;**15**(2):367-390

[40] Du W et al. STAT5 isoforms regulate colorectal cancer cell apoptosis via reduction of mitochondrial membrane potential and generation of reactive oxygen species. Journal of Cellular Physiology. 2012;**227**(6):2421-2429

[41] Mao YL et al. Phospho-STAT5 expression is associated with poor prognosis of human colonic adenocarcinoma. Pathology Oncology Research. 2011;**17**(2):333-339

[42] Favre H et al. Dual effects of suppressor of cytokine signaling (SOCS-2) on growth hormone signal transduction. FEBS Letters. 1999;**453**(1-2):63-66

[43] Michaylira CZ et al. Haplotype insufficiency for suppressor of cytokine signaling-2 enhances intestinal growth and promotes polyp formation in growth hormone-transgenic mice. Endocrinology. 2006;**147**(4):1632-1641

[44] Wassenaar MJ et al. Acromegaly is associated with an increased prevalence of colonic diverticula: A case-control study. The Journal of Clinical Endocrinology and Metabolism. 2010;**95**(5):2073-2079

[45] Vogelstein B et al. Genetic alterations during colorectal-tumor development. The New England Journal of Medicine. 1988;**319**(9):525-532

[46] Reinmuth N et al. Blockade of insulin-like growth factor I receptor function inhibits growth and angiogenesis of colon cancer. Clinical Cancer Research. 2002;**8**(10):3259-3269

[47] Cats A et al. Increased epithelial cell proliferation in the colon of patients with acromegaly. Cancer Research. 1996;**56**(3):523-526

[48] Ewton DZ et al. Insulin-like growth factor-I has a biphasic effect on colon carcinoma cells through transient inactivation of forkhead1, initially mitogenic, then mediating growth arrest and differentiation. International Journal of Cancer. 2002;**98**(5):665-673

[49] Bogazzi F et al. Apoptosis is reduced in the colonic mucosa of patients with acromegaly. Clinical Endocrinology. 2005;**63**(6):683-688

[50] Gonzalez B et al. The prevalence of colonic polyps in patients with acromegaly: A case-control, nested in a cohort colonoscopic study. Endocrine Practice. 2017;**23**(5):594-599

[51] Baserga R. The contradictions of the insulin-like growth factor 1 receptor. Oncogene. 2000;**19**(49):5574-5581

[52] Chi F et al. Circulation insulin-like growth factor peptides and colorectal cancer risk: An updated systematic review and meta-analysis. Molecular Biology Reports. 2013;**40**(5): 3583-3590

[53] Colao A et al. The association of fasting insulin concentrations and colonic neoplasms in acromegaly: A colonoscopy-based study in 210 patients. The Journal of Clinical Endocrinology and Metabolism. 2007;**92**(10):3854-3860

[54] Renehan AG et al. The prevalence and characteristics of colorectal neoplasia in acromegaly. The Journal of Clinical Endocrinology and Metabolism. 2000;**85**(9):3417-3424

[55] Chesnokova V et al. Growth hormone is permissive for neoplastic colon growth. Proceedings of the National Academy of Sciences of the United States of America. 2016; **113**(23):E3250-E3259

[56] Chesnokova V et al. Excess growth hormone suppresses DNA damage repair in epithelial cells. JCI Insight. 2019;**4**(3):e125762

[57] Chesnokova V et al. Growth hormone induces Colon DNA damage independent of IGF-1. Endocrinology. 2019;**160**(6):1439-1447

[58] Williams GT. Metaplastic (hyperplastic) polyps of the large bowel: Benign neoplasms after all? Gut. 1997;**40**(5):691-692

[59] Jenkins PJ. Acromegaly and colon cancer. Growth Hormone & IGF Research. 2000;**10** (Suppl A):S35-S36