

Acromegaly is a chronic disease caused by the excessive secretion of growth hormone (GH), and as a result, of insulin-like growth factor-1 (IGF-1). Untreated, the condition reduces the patients' life expectancy and leads to a series of complications, among which an increased risk of carcinogenesis is considered most important. This paper is an analysis of the publications on the issue of the formation of neoplasms, both malignant and benign, in acromegalic patients. Although the influence of acromegaly on carcinogenesis remains controversial, a number of studies indicate that the frequency of developing tumors in this patient group is higher. Moreover, numerous publications particularly stress the increased risk of developing neoplasms in patients who had been untreated for a long period of time and show elevated levels of GH and IGF-1. Consequently, a quick diagnosis and the implementation of effective treatment play a key role in the management of this disease.

Key words: neoplasms, cancer, acromegaly, epidemiology.

Risk of neoplasms in acromegaly

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Introduction

Acromegaly is a quite rare chronic disease, the frequency of which is estimated at about 50–70 per million [1]; it is caused by the excessive secretion of growth hormone (GH), and consequently, of insulin-like growth factor-1 (IGF-1). The condition affects both sexes equally, and the average age of the diagnosis is approximately 40 years [2, 3]. Untreated, acromegaly shortens life expectancy by about 10 years [4], leading to a number of complications. Among these, the increased incidence of both malignant and benign tumors is one of the most important. Carcinoma, next to vascular and respiratory diseases, is the third most frequent cause of death in acromegalic patients [5, 6]. Hence, monitoring patients for early detection of potential neoplasms remains a vital part of the treatment.

Pathophysiology

The majority of studies analyzing the causes of the increased tumor incidence in acromegaly patients have dealt with colorectal neoplasms. The most frequently discussed factor was the role of IGF-1, the elevated concentration of which is an effect of the overproduction of growth hormone. IGF-1 is an anti-apoptotic factor, stimulating cell cycle progression (mainly through the MAP kinase pathway), and promoting angiogenesis. Both normal epithelial cells and colorectal cancer cells express IGF-1 receptors; hence, IGF-1 can influence a healthy epithelium, as well as cancer tissue. It has been demonstrated that in acromegalic patients the proliferative zone of the epithelium was extended, and cellular turnover was increased [7]. Animal studies also confirm the significant role of GH and IGF-1 in cancer pathogenesis. In one of the experiments, two distinct lines of transgenic mice were implanted with human breast cancer cells. In the case of the mice characterized by overexpression of GH and IGF-1 receptor agonists, the tumor developed more frequently; on the other hand, in mice with an inactive GH receptor it practically did not develop at all. Moreover, blocking the activity of the growth hormone through antibodies, or transfection leading to the expression of GH antagonists restricted the growth of the implanted tumors. Experimental research proves that cancer cells expressing an inactive IGF-1 receptor are characterized by a significantly decreased ability to metastasize [8]. In fact, much of the IGF-1 in serum is present in the form of a ternary complex with insulin-like growth factor binding protein 3 (IGFBP-3) and the acid-labile subunit (ALS), which due to its high molecular mass (approximately 150 kDa) does not penetrate through the endothelial cells of blood vessels into the target organs. Thus, it is believed that not only the absolute concentration of IGF-1, but also the ratio of IGF-1 to IGFBP-3 concentrations may be of significance for the risk of carcinogenesis [5].

In the case of colorectal cancer, other mechanisms – characteristic of this organ – are also taken into consideration. These, for instance, include prolonged bowel transit, and changes in the microenvironment resulting from, among others, an increased concentration of unconjugated bile acids [9].

Epidemiology

Neoplasms constitute the cause of 15-24% of deaths in acromegalic patients [5, 6]. Tumors also continue to be an increasing problem for this group, as with improved patient care, their lifespan has increased. As a result, this has extended the patients' exposure to elevated levels of IGF-1, consequently creating a higher risk of carcinoma. Nevertheless, the issue of the increased incidence of neoplasms in the course of acromegaly remains a subject of discussion (Table 1).

Although some of the research results discussed here have not demonstrated a higher risk of carcinogenesis in acromegalic patients [11, 14], many studies indicate a relatively high incidence of neoplasms in this patient group [6, 15, 17]. The results depend, to a large extent, on the adopted research methodology. Numerous studies based on retrospective analysis do not demonstrate a higher risk of carcinogenesis, and some of them even point to a lower odds ratio of developing neoplasms in this group [14]. Such conclusions were reached mainly in older analyses, which could be connected with the fact that the patients died prematurely, primarily due to cardiological reasons [11]. However, many prospective analyses, or studies based on screening large cohorts of acromegalic patients for the most common types of tumor, indicate a high percentage of malignant neoplasms [10, 17].

A Polish retrospective study on a group of 101 patients indicates that neoplasm incidence was markedly higher in patients in whom the disease had been uncontrolled for a period of more than five years than in those in whom this period was shorter [6]. These conclusions stress the significance of a quick diagnosis and effective treatment of acromegaly. Additionally, there are data indicating a relationship between the concentration of GH after the administered treatment and the risk of carcinogenesis [10, 19]. The majority of the

studies available have not, however, confirmed a link between the incidence of cancer and the duration of the disease [6, 18]. Few of the available studies have analyzed the total incidence of benign neoplasms in acromegaly; nevertheless, a few research projects imply that these are common. In the Polish retrospective analysis [6], 108 benign neoplasms were detected in a group of 101 patients, 59% of which were thyroid tumors. A retrospective study carried out in Japan on a group of 140 patients revealed nodular goiter in 57% of the subjects, as well as colonic (40%), gastric (23%) and gallbladder polyps (14%) [18].

Colorectal neoplasia

Next to thyroid nodules, colorectal tumors, both benign and malignant, are the most frequently examined group of neoplasms in acromegalic patients. Consequently, the data pointing to the increased incidence of tumors is most reliable in the case of this group of neoplasms.

Colonic adenomas and hyperplastic polyps

Despite the large number of studies carried out, the issue of the increased incidence of colonic adenomas and hyperplastic polyps remains controversial (Table 2). The lack of an appropriate control group is a problem of the majority of the analyses. Since subjecting healthy individuals to colonoscopy raises ethical controversies, the majority of the studies that included a control group involved control subjects suffering from irritable bowel syndrome, or non-specific abdominal symptoms [24]. In turn, comparing the results of a patient group with the data on the incidence of adenomas and hyperplastic polyps obtained from autopsies or screening colonoscopies also raises methodological doubts. On the other hand, some retrospective studies include the number of polyps detected in patients who un-

Table 1. A review of selected studies on the risk of developing malignant neoplasms in acromegalic patients

Author	Year	Patients	Malignant tumors	% of patients	Significantly increased incidence
Prospective					
Gullu <i>et al.</i> [10]	2010	105	16	15.2	not given
Retrospective					
Mustacchi <i>et al.</i> [11]	1957	223	13	5.8	no
Nabarro [3]	1987	256	26	10.2	only in women
Barzilay <i>et al.</i> [12]	1991	87	7	8.0	yes, SIR 2.45
Ron <i>et al.</i> [13]	1991	1041	116	8.5	yes, SIR 1.6
Orme <i>et al.</i> [14]	1998	1239	79	6.4	no
Popovic <i>et al.</i> [15]	1998	220	23	10.5	yes, SIR 3.39
Higuchi <i>et al.</i> [16]	2000	44	5	11.4	only in men
Baris <i>et al.</i> [17]	2002	1634	177	10.8	yes, SIR 1.5
Kurimoto <i>et al.</i> [18]	2008	140	22	15.7	not given
Baldys-Waligórska <i>et al.</i> [6]	2010	101	12	11.9	no control group

SIR – standardized incidence ratio

Table 2. A selection of studies on the incidence ratio of colonic adenomas and hyperplastic polyps in acromegalic patients

Author	Year	Patients	Adenomas	Hyperplastic polyps	Comments
Prospective					
Klein <i>et al.</i> [20]	1982	17	Polyps in 9 patients (53%)	–	–
Jenkins <i>et al.</i> [21]	1997	129	34 (26.5%)	–	–
Renehan <i>et al.</i> [22]	2000	115	11 (9.6%)	18 (16.0%)	No significantly increased risk
Larijani <i>et al.</i> [23]	2007	23	3 (13%)		–
Rokkas <i>et al.</i> – a meta-analysis involving 9 studies with control groups [24]	2008	701 (included in total in the study)	149/641 (23.2% vs. 12.5% in the control group)	128/573 (22.3% vs. 7.4% in the control group)	OR – adenomas 3.3, hyperplastic polyps - 3.6
Retrospective					
Kurimoto <i>et al.</i> [18]	2008	87	35 (40.2%)		–
Dworakowska <i>et al.</i> [25]	2010	254	50 (19.7%)	39 (15.4%)	–
Bałdys-Waligórska <i>et al.</i> [6]	2010	101	13 polyps (12.9%)		–

OR – odds ratio

derwent colonoscopy; the examination, however, was not carried out in all the patients, but only in those for whom additional indications (other than acromegaly itself) existed [18]. Adopting such a research method may falsely overestimate the incidence of lesions in acromegalic patients. Although there are studies which disprove the claim that acromegalic patients suffer from an increased incidence of benign colorectal tumors [22], most investigations support this thesis. A large meta-analysis [24] involving 9 studies (a total of 701 patients) which included control groups has demonstrated a statistically significant higher incidence of both adenomas and hyperplastic polyps in acromegalic patients (odds ratio [OR] 3.3 and 3.6 respectively). Both the above-mentioned meta-analysis and other available prospective studies indicate that adenomas are present in over 20% of acromegalic patients, while benign colonic neoplasms are estimated to be present in 40–55% of cases [20, 21, 24].

Some studies indicate that the adenomas detected in patients suffering from acromegaly are larger (18 mm vs. 9 mm in the control group), and that the speed of their growth is positively correlated with the concentration of plasma IGF-1 [9, 26].

Colorectal cancer

Colorectal cancer is a malignant neoplasm whose rate of incidence in acromegaly has been the subject of numerous studies. Although it would be difficult to assume that the issue has been resolved, many research results indicate that the incidence of this tumor is higher in acromegalic patients. The Rokkas *et al.* meta-analysis [24] – a particularly valuable source due to the large number of subjects (304), prospective character and the inclusion of control groups – claims the colorectal cancer incidence ratio in acromegalic patients equals 4.6%, which is significantly higher than in the case of controls (1.2%, OR = 4.4). Two other British prospective studies report completely divergent results. The first one,

based on a group of 129 patients, indicates a significantly higher (standardized incidence ratio [SIR] = 13.5) incidence of carcinoma [21]. The other one, however, based on a group of 115 subjects, demonstrates a lack of any statistically significant increase in the risk of developing cancer [22]. Also in the case of retrospective analyses, the results are equivocal. Out of three studies involving large cohorts of patients, two indicate a statistically significant increase in the incidence of cancer (SIR 2.6 and 3.1 respectively) [13, 17]; the third one, on the other hand, demonstrates that there is no significant difference between the patient group and the control subjects in the incidence of colorectal carcinoma [14]. The results of smaller studies were even more diverse (Table 3).

Moreover, it has been demonstrated that there is a connection between the risk of developing malignant colorectal neoplasms and the concentration of IGF-1. A prospective study carried out in Italy showed that patients who developed malignant neoplasms in the period between the first and second colonoscopy (the average time between the two was 32.1 months) had noticeably higher levels of IGF-1 than patients who were not diagnosed with such lesions [27]. This bears out the claim that appropriate management in the course of the disease is important taking into consideration the risk of developing neoplasms.

The colonoscopic management of acromegalic patients still remains a controversial issue. According to the 2009 guidelines of the Acromegaly Consensus Group, a colonoscopic examination is indicated upon the diagnosis of the disease, and in the case of a lack of any changes, the patients are to be managed just like the rest of the general population [28]. Most authors agree with the need to carry out a colonoscopy upon the diagnosis [29]; the management of patients with no lesions in the large intestine, however, is more controversial. Nevertheless, some authors claim that with a lack of strong evidence supporting a higher risk of developing colorectal cancer, acromegalic patients should be

Table 3. A selection of studies on the incidence of colorectal cancer in acromegalic patients

Author	Year	Patients	Colorectal cancer	Comments
Jenkins <i>et al.</i> [21]	1997	129	6 (4.7%)	SIR 13.5
Renehan <i>et al.</i> [22]	2000	115	3 (2.6%)	incidence not increased
Rokkas <i>et al.</i> – a meta-analysis involving 9 studies with control groups [24]	2008	701 (involved in total in the study)	14/304 (4.6% vs. 1.2% in the control group)	statistically significant increase, OR 4.4
Gullu <i>et al.</i> [10]	2010	105	2 (1.9%)	no control group
Retrospective				
Mustacchi <i>et al.</i> [11]	1957	223	0 (0%)	–
Ron <i>et al.</i> [13]	1992	1041 observed for an average of 8.3 years	13 (1.2%)	SIR 3.1
Orme <i>et al.</i> [14]	1998	1239	12 (0.9%)	statistically insignificant increase, SIR 1.68
Higuchi <i>et al.</i> [16]	2000	44	1 (2.3%)	no increase in the morbidity
Baris <i>et al.</i> [17]	2002	1634	36 (2.2%)	SIR 2.6
Kurimoto <i>et al.</i> [18]	2008	87	9 (10.3%)	SIR 17.4 for women, 19.0 for men
Dworakowska <i>et al.</i> [25]	2010	254	10 (4.0%)	no control group
Batdys-Waligórska <i>et al.</i> [6]	2010	101	2 (2%)	no control group
Kaappinen-Makelin <i>et al.</i> [19]	2010	331	6 (1.8%)	statistically insignificant increase, SIR 1.9

OR – odds ratio

SIR – standardized incidence ratio

treated according to the guidelines for the general population; i.e. without additional indications, the first colonoscopy should be administered after the age of 50 [30].

Thyroid neoplasms

The analysis of a series of studies involving a total of over 5 000 patients shows that thyroid carcinoma constitutes approximately 6.3% of the malignant tumors diagnosed in acromegalic patients (Table 4). By comparison, this ratio is about 1% in the general population [31]. Any consolidation of the research carried out thus far and reliable estimation of the actual incidence of thyroid cancer in acromegalic patients poses problems due to the varying time of observation and the age of the patients. Thyroid cancer is assumed to be the most frequent type of malignant neoplasm in acromegalic patients [10, 12, 16]. Moreover, in five studies in which particular stress was placed on the detection of thyroid neoplasms (USG, fine needle aspiration biopsy), cancer was detected in as many as 1.2-5.8% of the subjects (Table 5), with some of the lesions being multifocal [32]. On the other hand, three large cohort (1041-1634 patients) retrospective studies did not find such a surprisingly high prevalence of thyroid cancer, which was detected in only 0.1-0.2% of the subjects. Nevertheless, the relative risk of developing malignant thyroid neoplasms in acromegalic patients was estimated to be 2.5-4.3 when compared to the general population; only Baris *et al.* reported a statistically significant result [13, 14, 17]. Data concerning the histological type of the thyroid carcinoma were available in 36 out of 47 cases cited in these studies. Papillary thyroid can-

cer was present in 31 of them (86%), whereas follicular cancer was detected in five patients (14%). Nodular goiter was noted in 54-76% of subjects, and diffuse goiter in 11-24% of acromegalic patients (Table 5).

The reason why malignant thyroid neoplasms develop more frequently in acromegalic patients may be the proliferative and anti-apoptotic effect of IGF-1 on thyrocytes. Indeed, the presence of an IGF-1 receptor in thyroid cancer cells, which has been demonstrated in experimental research, suggests that this may be the case [6, 15]. Other potential causes include pituitary irradiation and genetic diseases, i.e. the Carney syndrome, or multiple endocrine neoplasia type 1 (MEN-1) [17]. Based on the above-mentioned findings, regular thyroid ultrasound as well as biopsy of focal lesions is advised in acromegalic patients [6, 10, 32].

Breast cancer

According to Nabarro, the risk of developing breast cancer in acromegaly increases 4-fold [3]. These findings, however, have not been confirmed by other publications. Nonetheless, Baris *et al.* noted a slightly increased incidence of breast cancer in female acromegalic patients under the age of 50 [17]. This result is consistent with another study which demonstrates that the odds ratio of premenopausal breast cancer is positively correlated with the IGF-1 serum concentration, and negatively correlated with the IGFBP-3 concentration. This stems from the fact that in acromegaly not only is the IGF-1 level elevated, but also the IGF-1 to IGFBP-3 ratio is higher [24, 35]. Moreover, Orme *et al.* noted

Table 4. The incidence of thyroid carcinoma in acromegalic patients in selected studies

Author	Year	Number of patients	Number of malignant tumors	Thyroid cancer		
				Number	% of patients	% of malignant lesions
Prospective						
Gullu <i>et al.</i> [10]	2010	105	16	5	4.8	31.3
Retrospective						
Nabarro [3]	1987	256	26	1	0.4	3.8
Barzilay <i>et al.</i> [12]	1991	87	7	2	2.3	28.6
Ron <i>et al.</i> [13]	1991	1041	89	1	0.1	1.1
Orme <i>et al.</i> [14]	1998	1239	79	1	0.1	1.3
Popovic <i>et al.</i> [15]	1998	220	23	3	1.4	13
Higuchi <i>et al.</i> [16]	2000	44	5	2	4.5	40
Baris <i>et al.</i> [17]	2002	1634	177	3	0.2	1.7
Gasperi <i>et al.</i> [33]	2002	258	not applicable ¹	3	1.2	not applicable ¹
Tita <i>et al.</i> [34]	2005	125	not applicable ¹	7	5.6	not applicable ¹
Kurimoto <i>et al.</i> [18]	2008	140	22	5	3.6	22.7
Kaappinen-Makelin <i>et al.</i> [19]	2009	331	48	6	1.8	12.5
Ruchata <i>et al.</i> [32]	2009	86	not applicable ¹	5	5.8	not applicable ¹
Baldys-Waligórska <i>et al.</i> [6]	2010	101	12	3	3	25

¹The study involved only thyroid cancer cases

Table 5. Thyroid lesions in acromegalic patients detected on the basis of ultrasound examination and fine needle aspiration biopsy in selected studies

Author	Year	Patients	Cancer	Nodular goiter	Diffuse goiter
Prospective					
Gullu <i>et al.</i> [10]	2010	100	5 (5%)	62 (62%)	No data
Retrospective					
Gasperi <i>et al.</i> [33]	2002	258	3 (1.2%)	140 (54%)	47 (18%)
Tita <i>et al.</i> [34]	2005	125	7 (5.6%)	72 (58%)	30 (24%)
Kurimoto <i>et al.</i> [18]	2008	83	4 (4.8%)	47 (57%)	14 (17%)
Ruchata <i>et al.</i> [32]	2009	86	5 (5.8%)	65 (76%)	10 (11%)

a 1.6-fold increase in breast cancer mortality in the group of female acromegalic patients, with the incidence of this type of cancer not surpassing that of the general population. This could suggest a more aggressive clinical course of the disease [14]. Hence, female acromegalic patients should undergo regular mammography screening, even before the age of 50 [19].

Prostatic neoplasms

Epidemiological research has revealed an elevated serum concentration of IGF-1 in prostate cancer patients when compared to the control group [36, 37]. Despite this dependence, a higher incidence of malignant prostate neoplasms in acromegalic patients has not been observed [5]. Hence, further research is needed in order to solve this issue [17]. Gullu *et al.*, in ultrasound examination, detected benign prostatic

hyperplasia in 26 of 39 (67%) male acromegalic patients, with an average age of 44 [10]. Colao *et al.* demonstrated that prostatic hypertrophy as well as structural abnormalities (including calcifications, cysts and nodules) in acromegalic patients aged 26-74 are common [38, 39]. In conclusion, male acromegalic patients require careful monitoring of the prostate, irrespective of their age.

Hematopoietic system neoplasms

Au *et al.* presented three cases of leukemia discovered in a group of 106 patients, and on this basis determined a 69-fold increase in the risk of developing this cancer in acromegalic patients [40]. Popovic *et al.* found 3 instances of hematopoietic hyperplasia (one case of Hodgkin's lymphoma, and two cases of leukemia) in a group of 220 patients [15].

Other studies found either a small (1.2-2.0), statistically insignificant increase in the incidence of hematopoietic neoplasms in acromegalic patients [12, 16, 19], or no instances of such lesions at all [6, 10, 16, 18]. To sum up, the data discussed above are insufficient to claim that there is a correlation between acromegaly and a higher incidence of hematopoietic neoplasms; however, the existence of such a relation cannot be ruled out.

Tumors of the central nervous system

Baris *et al.* found a nearly 3-fold increase in the risk of developing neoplasms of the central nervous system (CNS) in a group of 1634 acromegalic patients, in comparison to the general population. The most common type of tumor was meningioma, diagnosed in three patients [17]. Bałdys-Waligórska *et al.* reported three more cases of meningioma [6]. The higher incidence of CNS neoplasms can be, at least partially, explained by the use of pituitary irradiation in the course of the treatment of acromegaly [17].

Urinary system tumors

According to Baris *et al.* the incidence of renal cancer was 3 times greater in acromegalic patients [17]. The increase in the risk of developing malignant tumors of the urinary system was confirmed by Kaupinnen-Makelin *et al.*, but only within the period of five years from the diagnosis of acromegaly [19]. Ron *et al.*, however, estimated that the prevalence of these neoplasms in acromegalic patients is approximately the same as in the general population [13]. Although the data above are inconclusive, the fact that hypertension and obesity are common in acromegalic patients could contribute to the higher risk of developing renal cancer [41].

Lung cancer

Not only do lung cancer cells express IGF-1-R, but also IGF-1 stimulates their proliferation [42]. Nevertheless, the literature data agree that there is no indication of a higher incidence of lung cancer in the clinical course of acromegaly.

Other neoplasms

Baris *et al.* found a higher incidence of malignant bone tumors in the course of acromegaly. Furthermore, they also observed that the morbidity in the case of small intestine carcinoid tumors was increased; this was, however, limited to patients with the MEN-1 syndrome [17]. According to Ron *et al.*, the incidence of esophageal and gastric cancer was higher in a group of 1041 male acromegalic patients [13]. Finally, Cohen *et al.* detected uterine myomas in 81% of female acromegalic patients [43].

Summary

Summing up the findings of the available research on the incidence of neoplasms in acromegaly, it is possible to claim that the disease in question contributes to a higher morbidity rate in the case of tumors of various organs. This includes both benign and malignant lesions, with the increased risk chiefly referring to colorectal and thyroid neoplasms. Nu-

merous studies have also pointed out that the higher incidence of such lesions is particularly common in patients who had been untreated, or in whom the disease had been badly managed. As a result, this indicates the need to diagnose acromegaly as early as possible, implement appropriate treatment quickly, and continually monitor its effectiveness. What is more, systematic screening of patients for neoplastic lesions should constitute an indispensable element of managing acromegalic patients.

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