

# Growth Hormone's Links to Cancer

Cesar Luiz Boguszewski<sup>1</sup> and Margaret Cristina da Silva Boguszewski<sup>2</sup>

<sup>1</sup>Department of Internal Medicine, Endocrine Division (SEMPR), University Hospital, Federal University of Parana, 80030-110 Curitiba, Brazil; and <sup>2</sup>Department of Pediatrics, Endocrine Division (SEMPR), University Hospital, Federal University of Parana, 80030-110 Curitiba, Brazil

**ORCID numbers:** 0000-0001-7285-7941 (C. L. Boguszewski); 0000-0002-5306-0715 (M. C. d. S. Boguszewski).

**ABSTRACT** Several components of the GH axis are involved in tumor progression, and GH-induced intracellular signaling has been strongly associated with breast cancer susceptibility in genome-wide association studies. In the general population, high IGF-I levels and low IGF-binding protein-3 levels within the normal range are associated with the development of common malignancies, and components of the GH-IGF signaling system exhibit correlations with clinical, histopathological, and therapeutic parameters in cancer patients. Despite promising findings in preclinical studies, anticancer therapies targeting the GH-IGF signaling system have led to disappointing results in clinical trials. There is substantial evidence for some degree of protection against tumor development in several animal models and in patients with genetic defects associated with GH deficiency or resistance. In contrast, the link between GH excess and cancer risk in acromegaly patients is much less clear, and cancer screening in acromegaly has been a highly controversial issue. Recent studies have shown that increased life expectancy in acromegaly patients who attain normal GH and IGF-I levels is associated with more deaths due to age-related cancers. Replacement GH therapy in GH deficiency hypopituitary adults and short children has been shown to be safe when no other risk factors for malignancy are present. Nevertheless, the use of GH in cancer survivors and in short children with RASopathies, chromosomal breakage syndromes, or DNA-repair disorders should be carefully evaluated owing to an increased risk of recurrence, primary cancer, or second neoplasia in these individuals. (*Endocrine Reviews* 40: 558 – 574, 2019)

**G**H is a protein synthesized by the somatotroph cells of the anterior pituitary and represents 800-fold the amount of any of the other pituitary hormones (1, 2). Also, GH can be locally secreted by many other extrapituitary human tissues, where it exerts autocrine or paracrine actions (3). At target cells, two distinct sites of GH bind to the extracellular domains of the predimerized GH receptor (GHR) (4, 5). Activation of the GHR triggers tyrosine phosphorylation of receptor-associated Janus kinase-2 and other substrates, such as signal transducer and activator of transcription (STAT)5, which are mediators of genomic GH actions and might be involved in oncogenesis (6). Additionally, GH activates other mitogenic pathways, such as MAPK/ERK, Ras-like GTPases, and insulin (INS) receptor substrate/phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt), and it interacts with focal adhesion kinases that permits the GH signal to be propagated through multiple alternate intracellular transduction pathways

(7, 8). GH has recently been shown to modify the tissue expression of miRNAs, which in turn regulate key components of the GH signaling system, implying a novel regulatory mechanism of GH expression and action (9).

GH is a main regulator of hepatic IGF-I production, which modulates GH release in a feedback loop (10). Several hormones and regulators of food intake and energy balance, such as INS, ghrelin, adipokines, free fatty acids, estrogen, thyroid hormones, and glucocorticoids, also influence pituitary GH secretion and hepatic IGF-I output (11). The liver is also the main source of IGF-II, which is secreted in a GH-independent manner in response to nutritional and hormonal factors (12). Both IGFs exert autocrine and paracrine effects in many extrahepatic tissues. Although IGF-I and IGF-II elicit similar biological responses, their expression patterns differ, with IGF-II preferentially expressed in a wide variety of tissues during fetal development and IGF-I mostly expressed

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### ESSENTIAL POINTS

- GH-induced intracellular signaling pathways are the third most highly associated with breast cancer susceptibility
- Attenuation of GH and IGF effects in mice and humans protect against cancer
- Age-related cancers are becoming a leading cause of death in acromegaly patients with biochemically controlled disease
- GH therapy is safe in children without risk factors for cancer
- Anticancer therapies targeting the GH-IGF system have yet to prove their usefulness

in the liver after birth, with a progressive age-related decline after puberty (12–14).

The IGF signaling mechanisms involve a complex system formed by three ligands (IGF-I, IGF-II, and INS), six membrane receptors [IGF-IR, IGF-IIR, INS receptor (INS-R), and the IGF-I/INS hybrid receptors], six high-affinity binding proteins [IGF-binding protein (IGFBP)-1 to IGFBP-6], a family of lower affinity IGFBP-related proteins, and several proteases (14–16). Upon binding to IGFs, IGF-IR undergoes autophosphorylation, followed by binding and phosphorylation of INS-R substrate proteins and recruitment of other effectors responsible to ultimately activate MAPK and PI3K/Akt signaling cascades. The MAPK pathway involves Ras/ERK activity and is mainly associated with the mitogenic effects of IGFs and INS, whereas PI3K/Akt mediate metabolic and cell growth responses, the latter via the mammalian target of rapamycin pathway (14, 16–18). In contrast, following binding to its receptor, IGF-II is internalized and degraded, without transducing intracellular signals, a

process that reduces its tissue availability and prevents its activity via IGF-IR and INS-R (12). Although GH and IGF-I effects are frequently interconnected, GH also exerts IGF-I-independent actions in muscle, bone, and adipose tissue, sometimes involving other intermediates, such as hepatocyte growth factor in the liver, fibroblast growth factor in the chondrocyte, epidermal growth factor in the kidney, or interleukins in bone and immune cells (19). Additionally, GH promotes lipolysis, blocks lipogenesis, and has diabetogenic effects, whereas IGF-I has opposing effects on glucose and lipid metabolism (7, 20).

A wealth of evidence linking GH and carcinogenesis has been produced from experimental, epidemiological, genetic, and clinical studies, both in animal models and humans. Consequently, several components of the GH signaling system have been investigated as targets for new cancer therapies. The same reasoning has served as the rationale for the debate on cancer risk during GH therapy and in patients with acromegaly.

### GH-IGF-I Axis in Cancer

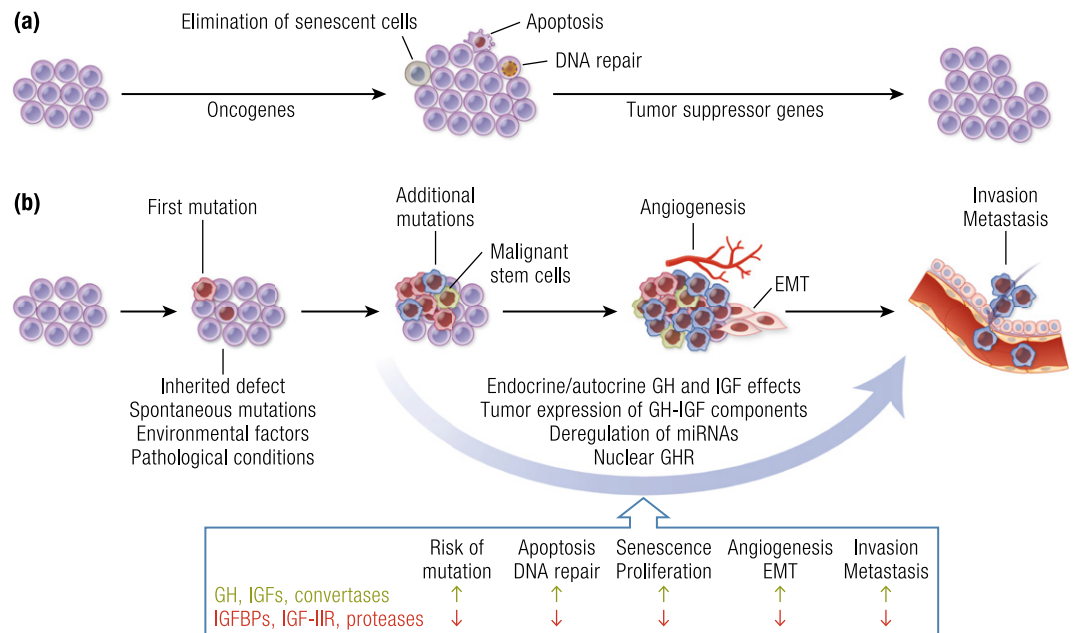
Malignant transformation of normal to cancer cells involves disruption of key cellular processes (Fig. 1). Growth factors do not directly lead to malignant transformation, but they can help to increase the risk of mutation by reducing time for DNA repair during rapid progression of the cell cycle. In rodents, GH/IGF-I influences cellular DNA repair capacity during a critical period during early life, presumably by transcriptional control of genes involved in DNA repair (21). However, the components of the GH-IGF system might exert contrasting effects in these events. Although GH, IGFs, and convertases may favor tumor development by promoting cell proliferation, the epithelial-to-mesenchymal transition (EMT), and angiogenesis, as well as by inhibiting apoptosis, other factors, such as IGFBPs, proteases, and IGF-IIR, may protect against tumor progression by inhibiting mitogenesis and stimulating apoptosis (14, 18, 22–24). Curiously, GH stimulates both IGF-I and IGFBP-3 production, simultaneously inducing signaling pathways for cell growth that compete with others for cell

death. Considering that GH is able to disrupt the balance of these opposed forces, potentially leading to development of neoplasia, how and when GH is involved in this process are key questions that remain unanswered. The whole picture is complicated by the effects of autocrine/paracrine GH, IGFs, and IGFBPs through their local production by neoplastic cells (and other cells in the tumor micro-environment), the tumor expression of GHRH, GHRH receptor (GHRH-R), and its splice variant SV1, IGF-IR and IGF-IIR, deregulation of miRNAs induced by GH and IGFs, and the presence of nuclear GHR, all of which may participate in the progression of various malignancies (7, 25–27).

#### Breast cancer

Endocrine and autocrine/paracrine GH influences growth of the normal mammary glands and the process of lactation, acting both alone and in conjunction with estrogen and progesterone (28, 29). In humans, GH can also bind and activate the prolactin receptor (PRLR), and in breast cancer cells, GHR may form heterodimers with the PRLR, modulating GH signal transduction (9).

**Figure 1.** Schematic representation of (a) mechanisms involved in normal cell growth and (b) the role of the GH-IGF system in cancer development. Normal cell growth is controlled by the balance between genes that promote cell proliferation (oncogenes) and tumor suppressor genes that break cell division. Apoptosis, DNA repair, and elimination of senescent cells are mechanisms that protect against neoplasia. Accumulated mutations in normal cells due to genetic, environmental, or pathological factors disrupt these protective mechanisms, resulting in uncontrolled proliferation of neoplastic cells. As tumor progresses, cells grow rapidly and autonomously and may acquire properties of invasion and metastasis, which are facilitated by the EMT, the presence of malignant stem cells, and angiogenesis. GH, IGFs, and convertases may favor tumor development by increasing the risk of mutation, stimulating cell proliferation, senescence, EMT, angiogenesis, invasion, and metastasis, and by inhibiting apoptosis and DNA repair. IGFBPs, IGF-IIR, and proteases may exert opposite effects and protect against cancer. Additionally, tumor expression and autocrine effects of several components of the GH-IGF system, deregulation of miRNAs induced by GH and IGFs, and the presence of nuclear GHR are other events that might contribute to malignant transformation and progression.



Many effects of GH on mammary development are mediated by IGF-I, particularly locally produced IGF-I, but GH can also exert IGF-I-independent proliferative effects in breast cancer cell lines (28, 30). GH has been shown to enhance breast cancer cell proliferation, survival, migration, invasion, and vascularization, to promote stemness of breast cancer stem cells, and to induce chemoresistance, favoring metastatic growth even in estrogen receptor-negative mammary carcinomas (29, 31–33). Interestingly, gene expression may be differently regulated in breast cancer cells by exogenous and autocrine GH, with the latter promoting a more aggressive cellular phenotype (26, 34). In humans, higher GHR expression has been observed in breast cancer cells, and tumor expression of GH has been positively associated with metastatic breast cancer and poor prognosis (35, 36). Overexpression of IGF-I and IGF-IR has also been documented in human breast carcinomas and correlated to malignant progression and prognosis in some, but not all, studies (14, 37). Of note, a genome-wide association study has identified GH-induced intracellular signaling pathways as the third most highly associated with breast cancer susceptibility among 421 pathways containing 3962 genes (38).

### Prostate cancer

Prostate cancer growth is mainly driven by androgen signaling, although the GH-IGF system might exert a permissive role in human prostate carcinogenesis (39). In contrast to breast cancer, exogenous GH seems to be responsible for more aggressive behavior than autocrine GH in prostate cancer cell lines (40). Nevertheless, both autocrine and exogenous GHs appear to enhance the metastatic potential of prostate cancer cells by stimulating cellular motility and invasiveness (41). Prostate-specific antigen, a marker of prostate cancer progression, is a protease that cleaves IGFBP-3 and acts as a comitogen with IGF-I (42). GH-induced IGF-I has been implicated in prostate cancer progression and activation of the androgen receptor (AR) in a ligand-independent manner (43, 44). Increased GH and GHR mRNA and protein coexpression have been documented in human prostate cancer, biopsy specimens, and in both androgen-sensitive and androgen-insensitive human prostate cancer cell lines (40, 45–47). Additionally, the PRLR is also expressed in human prostate cancer specimens and both GH and PRL have been linked to increased STAT5 activity, particularly in high histological-grade cancers (48, 49). STAT5 acts synergistically with AR signaling to promote growth and

metastatic behavior of the prostate tumor cells (50, 51). Activation of the AR, in turn, induces suppressor of cytokine signaling-2 that acts as a tumor suppressor by mediating the crosstalk with GH signaling pathways (52). GH can favor the expression of splice variants of the AR that are associated with resistance to androgen deprivation therapy. In aggressive, castration-resistant prostate cancer, GH expression following androgen deprivation therapy or AR inhibition has been linked to cancer progression by bypassing androgen growth requirements (44). Taken together, these findings support an endocrine/autocrine interaction between androgens and components of the GH signaling system, particularly in advanced stages of prostate cancer.

### Colorectal cancer

Most sporadic colorectal cancer (CRC) develops as a result of a multistep process involving numerous genetic mutations that promote a progressive transformation of the normal colonic epithelium to a benign adenoma, severe dysplasia, and, ultimately, an invasive and metastatic cancer. One of the earliest events in CRC carcinogenesis is the inactivation of *APC*, a “gatekeeper” gene that prevents accumulation of mutations and increased cellular proliferation. This is followed by activating mutations of the *KRAS* gene, loss of heterozygosity on 18q, and inactivation of the tumor-suppressor gene *p53*, events that are accompanied by mutations in other signaling pathways, as well as genomic, microsatellite, and epigenetic instability (53, 54). In a subset of CRC, deregulation of IGF-II signaling owing to loss of imprinting of the IGF-II gene has been proposed as a predictive risk factor and initiator of intestinal cancers (55, 56).

In normal colon, GH and GHR are not expressed in significant amounts. In contrast, GH expression is abundant in conditions predisposing to colon cancer and in stromal fibroblasts of the colonic carcinoma, but not within epithelial tumor cells (57, 58). GH expression in CRC is positively correlated with tumor size and lymph node metastasis (58). In turn, GHR is expressed by most colon epithelial cells, mainly intracellularly, with highest mRNA expression in the proliferating and differentiating zones of the colonic crypt (53, 57). Autocrine GH was shown to enhance cancer stem cell-like behavior, oncogenicity, and EMT functions and to promote xenograft growth and local invasion *in vivo* (58). Accordingly, IGFBP-3 inhibits colitis-induced carcinogenesis (59). It has recently been proposed that high GH levels (endocrine, as in acromegaly, or autocrine, as a result of colonic DNA damage or inflammation) suppress *p53*, *APC*, *PTEN*, and apoptosis, and they stimulate EMT, promoting a change in the intestinal mucosal field in favor of a neoplastic colon growth (57). If true, this model would provide a rationale for targeting GH signaling pathways as a potential treatment of CRC.

### Lung cancer

Eleven out of 64 single-nucleotide polymorphisms (SNPs) found to influence susceptibility for lung cancer in white individuals in a genome-wide association study were related to GH-IGF-I genes (60). In particular, a SNP located in the intracellular domain of the GHR resulting in an amino acid change at position 495 from proline to threonine (P495T) was strongly associated with lung cancer risk in white, Chinese, and African American women, in some cases in a redundant interaction with smoking and familial history of cancer (60–62). It was recently shown that P495T prolongs GH signaling by impairment of suppressor of cytokine signaling-2-mediated degradation in human lung cell lines, facilitating lung cancer progression (63). Moreover, the expression of GHRH-R and its splice variant SV1 is dramatically increased in established lung cancer cell lines and in lung malignant tissue (64, 65).

### Other malignancies

The exposure of papillary thyroid cancer cells to GHRH antagonists inhibits proliferation, increases apoptosis, and reduces the activity of matrix metalloproteinase-2, a marker of tumor invasion. *In vivo*, treatment with GHRH antagonist suppresses angiogenesis of engrafted thyroid tumors (66, 67). Moreover, IGF-I may promote progression of thyroid cancer from an occult to a clinically relevant stage by interacting with TSH and INS (68, 69).

In primary human melanoma, the SV1 splice variant of GHRH-R is expressed in high levels, and GHRH antagonists suppress growth of malignant melanoma both *in vitro* and *in vivo* (70, 71). GHR is also expressed in high levels in melanoma cells, and GH signaling pathways are known to drive melanoma progression and act as key mediators of the chemotherapeutic resistance in human melanoma (22, 72). The knockdown of the GHR in melanoma cell lines results in increased response to chemotherapy (73). Similarly, GHR silencing resulted in control of growth, migration, and invasion of pancreatic ductal adenocarcinoma (74). If this mechanism proves to be effective *in vivo*, it could implicate GHR inhibition as a mean of markedly improving the efficacy of antimelanoma drugs or assist in the development of novel anticancer compounds.

Autocrine expression of GH promotes cell proliferation, invasion, and cancer stem cell-like behavior of hepatocellular carcinoma cells through STAT3-dependent inhibition of CLAUDIN-1 expression, a tumor suppressor protein (75). In patients with hepatocellular carcinoma, tumor GH expression has been associated with tumor size and grade, poor relapse-free survival, and overall survival outcomes (76). IGF-RII might also function as a tumor suppressor in liver carcinogenesis, as loss of heterozygosity of the *IGF-RII* gene is found in human hepatocellular tumors accompanied by mutations in the remaining allele that result in formation of a truncated receptor (77).

Oncogenicity of the Janus kinase/STAT3 pathway has been observed in human endometrial cancer cells, where autocrine GH stimulates the EMT, migration, and invasion, effects that can be blocked by inhibition of STAT3 (78). In endometrial carcinoma, autocrine GH appears to be involved with resistance to ionizing radiation-based therapy, suggesting a role for functional antagonism of GH to enhance radiotherapy efficacy (79).

### Epidemiological Studies in the General Population

Serum IGF-I levels at the highest categories and IGFBP-3 levels in the lowest categories of the normal reference ranges have been associated with an increased risk for several prevalent cancers in the normal population. A summary of four meta-analyses found a positive association between IGF-I levels in the highest percentiles of the normal range with an increased risk of prostate, CRC, and breast cancer in both premenopausal and postmenopausal women (80). Serum IGF-I level was also an independent prognostic factor for the progression and survival of patients with hepatocellular carcinoma in a meta-analysis of 20 studies (81). In contrast, the risk of lung cancer was inversely correlated with IGFBP-3 concentrations, but in this case smoking was an important confounding factor, as IGFBP-3 concentrations are significantly reduced in smokers (82). In general, the influence of IGFBP-3 levels in cancer risk is weaker and usually disappears when results are adjusted for IGF-I levels (80).

In the last years, publications emerged from the EPIC cohort that consists of ~520,000 healthy volunteers, aged 35 to 69 years, recruited between 1992 and 2005 in 10 European countries. The EPIC studies confirmed the association of higher circulating IGF-I levels with increased risk of breast cancer, specifically receptor-positive tumors diagnosed in women at  $\geq 50$  years of age (83), and found positive associations with differentiated thyroid carcinoma (84), low-grade gliomas, and acoustic neuromas (85), but not with lymphoma (86), ovarian (87), hepatocellular (88), and pancreatic cancer (89). Positive associations between *IGF-I* and *IGFBP* gene polymorphisms with certain cancers have been reported in specific populations, but most large series failed to demonstrate a substantial impact of any single SNP in these genes on the clinical characteristics, therapeutic responses, or prognosis of patients with cancer (90–98).

### Cancer in GH Deficiency and Resistance

#### Animal models

Natural or experimentally induced repression of the GH-IGF signaling system is commonly associated with significant delayed or decreased occurrence of

spontaneous or chemical-induced neoplastic disease in various animal models, frequently accompanied by significant increases in lifespan (20, 99, 100). One of the most likely pathways contributing to tumor resistance in GH deficiency (GHD) and GH-resistant animals is the reduction in the mammalian target of rapamycin activity (101). Treatment with GH increases cancer rates in these animals, and in some cases, tumor regresses completely when treatment is interrupted (102, 103). GH and IGF-I deficiency genetically induced in adult life in rodents is also characterized by reduced prevalence of malignancies and increased longevity, but in these cases are associated with functional impairments and age-related degenerative diseases (104).

#### Congenital GHD in humans

Congenital GHD in humans is associated with lower incidences of cancer. In a survey of 53 patients with diagnosis of GHRH-R defect, isolated GHD, or IGF-I insensitivity, no case of cancer was observed, whereas 10 malignancies were identified in 88 relatives of the patients (105). Another similar investigation in 116 patients with congenital isolated GHD found one case of basal cell carcinoma in a short boy who was treated with GH and was also suffering from xeroderma pigmentosum, three malignancies in 79 patients with GHRH-R mutations (one patient previously treated with GH), and three malignancies in 113 patients with multiple congenital pituitary hormone deficiency (two previously treated with GH) (106). In this study, 62 cancers at various sites were reported in 883 relatives, a proportion significantly higher than in GHD patients. Of note, these findings indicate that the protection against cancer in human GHD is not absolute, as also confirmed by four cases of skin tumors with one cancer-related death in GH-naïve adult patients with GHD due to GHRH-R mutation (107). In this cohort, there was a fifth case of cancer in a woman who had intermittently received GH therapy from age 11 to 18 years and developed an ependymoma. Prolonged exposure to small amounts of endogenous or exogenous GH and IGF-I may explain the rare cases of cancer observed in this and other GHD kindred (108).

#### Hypopituitarism

Life expectancy is reduced in acquired hypopituitarism due to vascular diseases, and in a pioneer Swedish study, only seven patients died of cancer, a number significantly lower than expected (109). Untreated GHD was suggested as a potential factor to explain both the increased mortality from vascular disease and the protection against cancer in adults with hypopituitarism. Subsequently, small series found no differences in mortality rates due to cancer (110–112), whereas in three of four larger retrospective studies with more than a thousand patients and controls, the risk of having cancer or dying from cancer was

increased in patients with hypopituitarism not receiving GH (113–116). Surprisingly, CRC (which is usually associated with GH excess in acromegaly) was the predominant malignancy and the main cause of death in one study (115). These divergent results are explained by a variety of confounding factors, unrelated to GHD, including differences in sampling size and study design, prevalence of specific cancer types in the control populations, underlying pituitary disease, surgery, radiation, associated morbidities, and inadequate pituitary hormone replacement (117, 118).

### GH resistance in humans (Laron syndrome)

Congenital IGF-I deficiency caused by homozygous mutations in the GHR or GH-induced intracellular signaling molecules (Laron syndrome) acts as a protecting factor against cancer development. Patients with Laron syndrome often die of aging-unrelated causes, such as accidents or alcohol abuse (20, 105, 106). In one study, none of 169 Laron patients had cancer, in contrast with 41 cancers in 250 members of their families (106). Accordingly, not a single case of cancer was reported in another series of 230 patients with Laron syndrome (105). In a cohort of 99 individuals with Laron syndrome living in Loja, Ecuador, only one case of a nonlethal malignancy was identified, whereas the incidence of cancer was 17% in controls from the same region (119). Ecuadorian dwarfs with Laron syndrome had increased INS sensitivity in comparison with their unaffected relatives, and cells treated with their serum exhibited reduced DNA breaks and increased apoptosis (119).

## Cancer Associated With GH-IGF Excess

### Transgenic animals

Transgenic (Tg) GH mice exhibit features of acromegaly and increased incidence of spontaneous and carcinogen-induced hepatocellular carcinoma (120, 121). These effects are likely due to an IGF-I-independent action of GH on hepatocytes, as Tg IGF-I mice do not exhibit such liver abnormalities, but instead have increased bowel length with highly proliferative colonic crypt cells and decreased apoptosis (122–124). The effects of postnatal IGF-II overexpression vary according to the attained circulating levels and the tissue examined, suggesting a more important local than systemic IGF-II action (14, 125, 126). Tg IGF-IR mice show aberrant development of salivary, pancreatic, and mammary adenocarcinomas as early as 6 weeks of age, characterized by a more invasive and metastatic phenotype (127–129). In contrast, IGF-IIR overexpression results in antiproliferative effects in mammary and prostate cancer cell lines and inhibition of tumor formation *in vivo* (14, 130, 131). Systemic and tissue-specific overexpression of all IGFBPs in Tg animals and in experiments using gene transfer and upregulation

is usually associated with reduction or attenuation of tumor growth and vascularity at different tissues, but in some circumstances, IGFBPs may stimulate cell growth and migration either directly or by enhancing IGF-I effects (14, 132–137).

### Acromegaly

In the pioneering study by Mustacchi and Shimkin (138) in 1957, 13 cancers were detected in 223 acromegaly patients followed during 14 years, with not a single case of CRC or thyroid cancer, leading the authors to conclude that “the material analyzed in this report has not disclosed the presence of a definite influence of the pituitary gland on the initiation of cancer in man. If this stimulus exists, it does not seem to be a very potent one.” Since then, studies examining the risk of cancer in patients with acromegaly have continuously led to inconsistent and controversial findings. From the mechanistic point of view, this could be explained by individual factors affecting the balance between GH-stimulated signals for cell growth (IGFs) and cell death (IGFBP-3) that are simultaneously present in acromegaly. From the epidemiological point of view, there are numerous limitations in determining the incidence of a high prevalent and heterogeneous disease, such as cancer, in patients with a rare disease, such as acromegaly (139).

As shown in Table 1, a mean cancer incidence of 9.6% was found in a review of 23 series published between 1957 and 2018, with large variation in cases of CRC and thyroid cancer reported in different settings (138, 140–161). The standardized incidence ratio (SIR), available in 14 series, was increased in five (141, 142, 149, 157, 159), marginally increased in one (146), not increased in four (marginally lower in one) (138, 151, 155, 156), increased only in women in three (144, 154, 160), and increased only in men in one (148). In large series where cancer rates in patients were compared with those in the general population, SIR was increased in the cohorts from the United States (159), Sweden/Denmark (141, 146), Finland (149), and Italy (160), not increased in the United Kingdom (155) and France (151), and marginally lower in Germany (156). Recently, the Liège Acromegaly Survey Database reported on only 64 cancers in 3173 acromegaly patients followed in 10 different countries, showing that the rate of overall or specific cancers was not markedly elevated in relationship to the general populations (162). Thus, data collected during the last 60 years indicate that the effect of prolonged GH excess in carcinogenesis in acromegaly is, at best, marginally increased and its clinical impact is modest (139). Nevertheless, recommendations for cancer screening, particularly CRC and thyroid cancer, in asymptomatic patients have divided opinions among the experts, a topic that we and others recently revisited (139, 163–165). In the most recent consensus statement, it was recommended that cancer screening in acromegaly should follow the same protocols as for the

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*“...the effect of prolonged GH excess in carcinogenesis in acromegaly is, at best, marginally increased...”*

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**Table 1. Cancer Incidence and Cases of Colorectal (CRC) and Thyroid Malignancies in Acromegaly Studies**

Study (Reference)	Year	Country	Patients (N)	Cancers (N)	Prevalence (%)	Overall SIR	CRC (N)	Thyroid (N)
Mustacchi and Shinkin (138)	1957	United States	223	13	5.8	Not increased	0	0
Baldys-Waligórska <i>et al.</i> (140)	2010	Poland	101	12	11.9	NA	2	3
Baris <i>et al.</i> (141)	2002	Sweden and Denmark	1634	177	10.8	Increased	36	3
Barzilay <i>et al.</i> (142)	1991	United States	87	7	8	Increased	1	2
Cheng <i>et al.</i> (143)	2015	Canada	408	55	13.5	NA	NA	NA
Cheung and Boyages (144)	1997	Australia	50	7	14	Increased in women	1	0
Dagdelen <i>et al.</i> (145)	2014	Turkey	160	34	21.3	NA	3	17
Dal <i>et al.</i> (146)	2018	Denmark	529	81	15.3	Marginally increased	10	1
Gullu <i>et al.</i> (147)	2010	Turkey	105	16	15.2	NA	2	5
Higuchi <i>et al.</i> (148)	2000	Japan	44	5	11.4	Increased in men	1	2
Kauppinen-Mäkelin <i>et al.</i> (149)	2010	Finland	331	48	14.5	Increased	6	6
Kurimoto <i>et al.</i> (150)	2008	Japan	140	22	15.7	NA	10	5
Maione <i>et al.</i> (151)	2017	France	999	94	9.4	Not increased	15	18
Mercado <i>et al.</i> (152)	2014	Mexico	442	21	4.8	NA	1	7
Mestron <i>et al.</i> (153)	2004	Spain	1219	90	7.4	NA	15	2
Nabarro (154)	1987	United Kingdom	256	26	10.2	Increased in women	1	1
Orme <i>et al.</i> (155)	1998	United Kingdom	1239	79	6.4	Not increased	16	1
Petroff <i>et al.</i> (156)	2015	Germany	446	46	10.3	Marginally decreased	4	3
Popovic <i>et al.</i> (157)	1998	Serbia	220	23	10.5	Increased	2	3
Ritchie <i>et al.</i> (158)	1990	United Kingdom	131	15	11.4	NA	4	0
Ron <i>et al.</i> (159)	1991	United States	1041	89	8.5	Increased	13	1
Terzolo <i>et al.</i> (160)	2017	Italy	1512	124	8.2	Increased in women	20	13
Wolinski <i>et al.</i> (161)	2017	Poland	200	27	13.5	NA	4	14
Total			11,517	1,111	9.6		167	107

Abbreviations: NA, not available; SIR, standardized incidence ratio.

general population (166). Of note, factors unrelated to GH status affect cancer estimates in acromegaly, such as variable cancer prevalence in the control population among different countries, genetic/epigenetic events in acromegaly, surveillance bias, presence of comorbidities, and disease management (139). The proportion of acromegaly patients who are successfully treated has progressively increased in recent years owing to greater access to multimodal treatment. Currently, many patients with acromegaly have normal life expectancy and, not surprisingly, age has been associated with an increased cancer risk by multivariate analysis in two recent multicenter studies from Canada (143) and Italy (160).

Increased mortality in active acromegaly has traditionally been related to cardiovascular, respiratory, and metabolic complications (118, 155, 167–169).

Nevertheless, a recent 20-year follow-up study is a good example to illustrate the shift on the causes of deaths in acromegaly; whereas 44% of deaths were due to cardiovascular events and 28% were due to cancer in the first decade, the numbers changed to 23% cardiovascular and 35% cancer during the last decade, contrasting with the unchanged proportion of cancer deaths over time in the control group (170). This finding has frequently been accompanied by a decrease and even normalization of mortality rates in acromegaly, with cancer becoming the main cause of death in several studies (151, 152, 171–177) (Table 2). In a meta-analysis of observational studies published before ( $n = 17$ ) and after 2008 ( $n = 9$ ), we found that the standardized mortality ratio (SMR) did not differ from that of the normal population in the last decade, as a result of an

**Table 2. Mortality in Acromegaly in the Last Decade Determined by Treatment Regimens, Disease Activity, and Cancer Deaths**

Study (Reference)	N	No. of Deaths	Mean Age of Death (y)	Only Cx + Rxt SMR (95% CI)	Include SRL SMR (95% CI)	Controlled SMR (95% CI)	Uncontrolled SMR (95% CI)	Cancer Deaths (%)	Cancer SMR (95% CI)
Maione <i>et al.</i> , 2017 (151)	999	41	62.8		1.05 (0.77–1.43)			34	Main cause of death
Mercado <i>et al.</i> , 2014 (152)	442	22	58.6		0.76 (0.50–1.16)	0.46 (0.21–0.96)	0.94 (0.57–1.55)	27.2	Main cause of death
Arosio <i>et al.</i> , 2012 (172)	1512	61	64		1.15 (0.90–1.47)	0.59 (0.37–0.94)	1.93 (1.33–2.78)	36	Main cause of death
Bogazzi <i>et al.</i> , 2013 (173)	438	20	68.8		0.70 (0.45–1.09)			30	—
Colao <i>et al.</i> , 2014 <sup>a</sup> (174)	220	7	61.3		0.66 (0.27–1.36)			42.8	Main cause of death
Colao <i>et al.</i> , 2014 <sup>b</sup> (174)	407	71	61.9	2.01 (1.59–2.54)		1.25 (0.79–1.95)	2.57 (1.96–3.36)	16.9	1.43 (0.81–2.52)
Exposito <i>et al.</i> , 2018 (175)	1089	232	NA	2.93 (2.56–3.35)	0.98 (0.25–3.94)			21.1	1.76 (1.33–2.33)
Sherlock <i>et al.</i> , 2009 (176)	501	162	67	1.69 (1.45–1.97)				22.2	1.21 (0.87–1.68)
Varadhan <i>et al.</i> , 2016 (177)	167	67	71		1.00 (0.57–1.75)			NA	—
Wu <i>et al.</i> , 2010 (178)	142	18	NA	1.93 (1.22–3.05)		0.46 (0.06–3.28)	3.11 (1.68–5.79)	28	—
Total	5917	701	64.4	2.11 (1.54–2.91)	0.98 (0.83–1.15)	0.70 (0.41–1.22)	1.95 (1.25–3.04)	28.7	1.48 (1.15–1.90)

Abbreviations: Cx, surgery; NA, not available; Rxt, radiotherapy; SMR, standardized mortality ratio; SRL, somatostatin receptor ligand.

<sup>a</sup>Italian cohort.

<sup>b</sup>Bulgarian cohort.

increased proportion of acromegaly patients attaining disease control with multimodal treatment. In parallel, we have confirmed that age-related cancer deaths increased and have become one of the leading causes of mortality in acromegaly (178). Of note, many cancer deaths in recent studies were due to malignancies not commonly related to GH excess in acromegaly (143, 151, 152, 160, 170).

## Cancer in Individuals Treated With GH

### Pediatric population

During the 1980s and 1990s, an association was found between the occurrence of leukemia during or shortly after GH treatment in children with GHD (179–181). Subsequent studies excluding patients with known risk factors for leukemia revealed a cancer incidence comparable to the general population, which was confirmed by postmarketing surveillance studies with large number of GH recipients with no risk factors for malignancy (182–186). Such history linking GH therapy and development of leukemia is illustrative of the numerous pitfalls and concerns in determining the risk of cancer in GH-treated individuals, especially those with known risk factors for neoplasia. Recurrence rates and incidence of *de novo* malignancy were not increased in studies from single or multiple centers where time of GH exposure ranged from a few months to >10 years (187–192). A recent review encompassing safety data from GH registries from different pharmaceutical companies between 1988 and

2016 showed no evidence of increased risk of new malignancy, leukemia, nonleukemic extracranial tumors, or recurrence of intracranial malignancy in GH-treated children with no other risk factors, but it demonstrated an increased risk of a second neoplasm in patients irradiated for a central nervous system (CNS) tumor (193). In a population-based Israeli study, cancer incidence or mortality was not increased in low-risk patients treated with GH during childhood, whereas both cancer mortality and incidence were higher than expected in GH recipients with prior risk factors for malignancies (194). Two meta-analyses involving patients with intracranial tumors (195, 196) and one in pediatric craniopharyngioma (197) found no association of GH therapy with increased risk of tumor recurrence. In contrast, a meta-analysis of 12 long-term studies found that both the overall cancer incidence and relative risk for second neoplasms were significantly increased with GH treatment during childhood, although no increased in mortality rate was observed (198).

More recently, the Safety and Appropriateness of Growth Hormone Treatments in Europe (SAGhE) cohort study, including Belgium, Netherlands, Sweden, Switzerland, United Kingdom, France, Germany, and Italy, was set up to provide long-term safety information on GH treatment independently of pharmaceutical companies. The SAGhE cohort consisted of 24,232 patients born before 1991 to 1995 and treated any time up to a date during 2007 to 2009, most commonly with isolated growth failure (53%), Turner syndrome (13%), and GHD linked to neoplasia (12%)

(199). A preliminary report from the France arm showed no increased mortality due to malignancies in general, but a fivefold increase in deaths due to bone tumors (3 observed vs 0.6 expected) in adults treated with GH during infancy owing to isolated GHD, idiopathic short stature (ISS), and small for gestation age (SGA), conditions classified as low risk for long-term mortality (200). This report was followed by a preliminary data analysis from the Belgium, Netherlands, and Sweden arms of the SAGhE consisting of 46,556 person-years of observation, with no report of death due to cancer (201). Recently, the analysis of the full

SAGhE cohort including 396,344 person-years revealed 251 cancer deaths, and both cancer mortality and incidence significantly increased for several types of malignancies in GH-treated subjects (202). However, the overall cancer risk and mortality were not increased in patients with isolated GHD, ISS, and SGA and no GH dose effect in cancer development was observed in these groups of patients, in which only 21 deaths were reported. Thus, the raised cancer incidence and mortality were largely consequent to tumors in patients given GH after cancer treatment or due to other etiologies, where 230 deaths were reported. In the group of cancer survivors, there were increased SIRs for CRC and bone, soft tissue, ovary, kidney, CNS, and thyroid cancers, melanoma, and leukemia, and increased SMRs for tongue, mouth, pharynx, pancreas, bone, soft tissue, corpus uteri, ovary, kidney, CNS, and thyroid cancers, as well as non-Hodgkin lymphoma and leukemia. In the cancer survivors group, cancer mortality increased significantly with increasing daily GH dose. In patients treated with GH due to other noncancer etiologies different than isolated GHD, ISS and SGA, the incidence of bone and bladder cancer was also increased. Hodgkin lymphoma incidence showed a significant increase with longer follow-up for patients without previous cancer, whereas mortality due to CNS tumors decreased in patients whose underlying diagnosis was cancer (202).

Clearly, the underlying condition to which GH therapy is indicated plays a role in the cancer risk in children. A group of conditions known as "RASopathies," which include Noonan syndrome (NS), neurofibromatosis type 1, NS with multiple lentigines, cardio-facio-cutaneous syndrome, Costello syndrome, capillary malformation–arteriovenous malformation syndrome, and Legius syndrome, has an incidence of ~1 in 1000 live births and an inherited increased risk for malignancies (203–207). Patients with NS have a 3.5- to 8.1-fold increased risk of cancer, particularly acute leukemia and myeloproliferative disorders (208, 209). This finding reinforces the extreme concern related to safety of GH treatment in this group of children (210, 211). The same applies for short children with chromosomal breakage syndromes or DNA-repair disorders, represented by Fanconi anemia (212), ataxia telangiectasia (213), Bloom syndrome (214), Down syndrome (215), and other dysmorphic disorders (216–220). The overlapping clinical features among genetic syndromes and late appearance of their hallmark features make the diagnosis challenging in many cases (221). This was illustrated by the report of a young boy with clinical diagnosis of NS, but no identification of a pathogenic mutation, in whom neurofibromatosis type 1 was genetically confirmed later in the follow-up (222). From another report, two short children had the diagnosis of Bloom syndrome years after GH treatment was started, despite extensive

**Table 3. Medical Conditions Associated With Short Stature and High Risk of Malignancy**

Medical Condition (References)	Special Remarks
Dysmorphic syndromes	Overlapping characteristics between syndromes and late appearance of hallmark features might prevent diagnosis, especially when genetic tests are not available
RASopathies (203–205)	
NS (210, 211)	
Neurofibromatosis type 1 (205)	
NS with multiple lentigines (203, 204)	
Cardio-facio-cutaneous syndrome (204)	
Costello syndrome (204)	
DNA-repair disorders	
Fanconi anemia (212)	
Ataxia telangiectasia (213)	
Bloom syndrome (214)	
Others	Risk of a second malignancy, which may decrease with time
Down syndrome (215)	
Xeroderma pigmentosum, Cockayne syndrome, and trichothiodystrophy (216)	
Kabuki syndrome (217)	
Mulibrey syndrome (218)	
Dubowitz syndrome (219)	
Nijmegen breakage syndrome (220)	
Pediatric cancer survivors	
Medulloblastoma (226)	
Leukemia, retinoblastoma, Hodgkin lymphoma (227)	
	IGF-I levels must be kept in age-appropriate range during GH treatment

and careful diagnostic workup (223). One case was a girl born SGA who had a diagnosis of a non-Hodgkin lymphoma at 14.8 years of age and died 1 year later due to sepsis. The other was a boy with initial diagnosis of Silver-Russell syndrome treated with GH during 5 years before appearance of a photosensitive facial rash that led to the diagnosis of Bloom syndrome.

A recent document from the Pediatric Endocrine Society Drug and Therapeutics Committee made three statements: (i) GH therapy can be safely administered in children without known risk factors for malignancy; (ii) in children with conditions predisposing to cancer, GH use should be defined on an individual basis, with appropriate surveillance for malignancies if therapy is initiated; and (iii) in childhood cancer survivors who are in remission, GH therapy can be used with the understanding that it may increase their risk for second neoplasms (224). Another recent statement from the Growth Hormone Research Society recommends that in high-risk patients, initiation of GH therapy should be discussed with patients and their families (225). In our view, the benefits and risks of GH therapy in cancer survivors need to be carefully scrutinized and proper surveillance should be undertaken during therapy, maintaining IGF-I concentrations always in the age-appropriate range (226, 227). When a dysmorphic syndrome is suspected or confirmed, GH therapy should not be initiated [Table 3 (203–205, 210–220, 226, 227)]. In all other indications, GH therapy is safe and cancer surveillance beyond standard practice is not necessary.

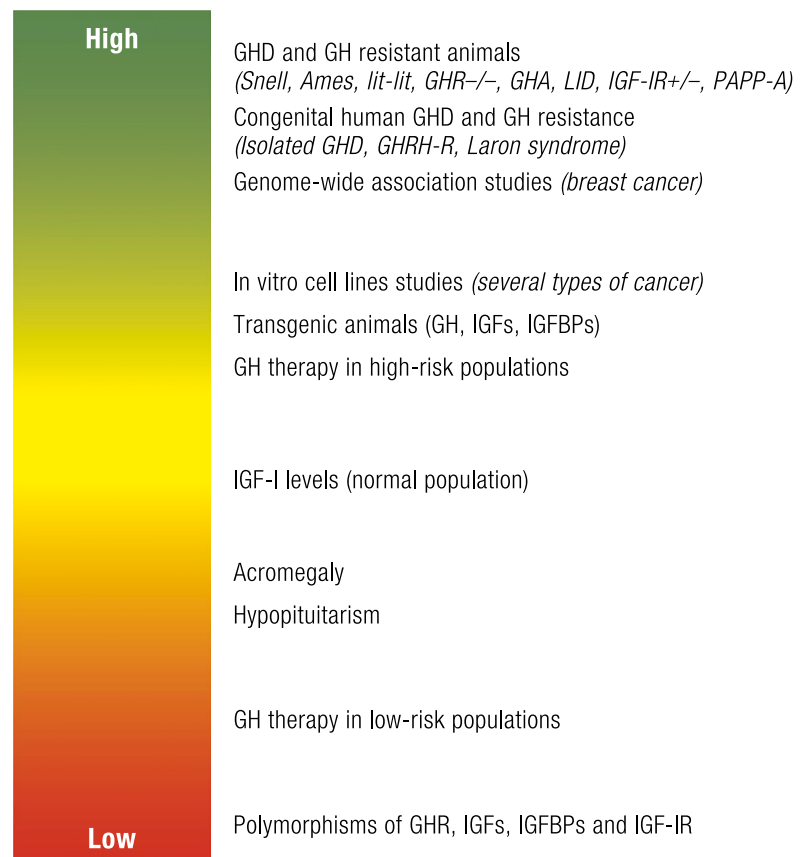
### Adult population

GH therapy in adults is indicated for patients who were diagnosed in childhood with isolated or combined GHD that persists in adult life and for those with acquired GHD in adulthood. In the latter case, GHD is secondary to pituitary or perisellar tumors and/or their treatment in approximately two-third of cases, and it is generally associated with other pituitary hormone deficiencies. Some patients harboring these tumors may present an inherent elevated risk for malignancies (228, 229).

In the Hypopituitary Control and Complications Study, the overall SIR of primary and secondary cancer was not increased in patients receiving GH as adults, except in the subgroups of patients <35 years of age and those with childhood-onset GHD (230). In the Pfizer International Metabolic Database Study, no increase in cancer mortality was observed and the risk of second malignancies was increased only in cancer survivors who had childhood-onset GHD, but not in those with adult-onset GHD (231). Another report from the Swedish arm of Pfizer International Metabolic Database showed a significant increase of SMR associated with late appearance of brain cancer, which was considered to be related to previous radiotherapy

and not with GH therapy (232). In the Dutch National Registry of GH-treated adult patients, SMR due to cancer was not increased (233).

Recently, a Web-based search identified nine studies addressing the risk of *de novo* neoplasia or recurrence/progression of underlying hypothalamic–pituitary tumors in a cohort representing 41,000 adult patient-years on GH therapy (234). There was no evidence from the reviewed studies, some of them having >10 years of follow-up, that GH therapy increases the risk of primary cancer, secondary neoplasia, or recurrence of previous tumors. This observation was confirmed in a meta-analysis of 15 studies published between 1995 and 2015 involving 46,148 patients (235). Surprisingly, a reduced risk of cancer in GHD adults treated with GH was observed in another meta-analysis of two retrospective and seven prospective studies totaling 11,191 participants followed during 2.3 to 14.5 years (236). Taken together, data collected during >30 years of GH replacement in GHD adults have reassured the safety of this therapy, with caution recommended only in cancer



**Figure 2.** Level of evidence linking GH and cancer. The bar colors in the proposal model represent levels of evidence for a direct association of cancer with GH: red (low), yellow (intermediate), green (high). Strength was graded from the red to green level according to the study design: expert opinion, case reports and case series, case-control studies, cohort studies, randomized controlled trials, meta-analysis, and systematic reviews. Quality was graded from the red to green level considering the number of independent publications supporting a relationship with cancer in the same vs in the opposite direction.

survivors with childhood-onset GHD and patients subjected to radiotherapy for brain tumors.

### GHRH–GH–IGF-I Axis as a Target for Cancer Therapy

In recent years, various classes of GHRH antagonists have been synthesized and tested in preclinical studies as anticancer therapy owing to their ability to suppress the GH–IGF-I axis and mainly due to their direct autocrine/paracrine effects on the tumors (27, 237). Nevertheless, no clinical data exist to determine the efficacy and safety of GHRH antagonists in human cancer owing to problems with their bioavailability, short half-life, rapid renal clearance, and lack of *in vivo* stability due to proteolytic degradation (237). Accordingly, despite some promising results in preclinical studies of GHR-targeted agents, such as pegvisomant (a GHR antagonist approved for the treatment of acromegaly), their usefulness in treating human cancer still remains to be proved (22, 26, 73, 100, 238–240).

Several anticancer therapeutic interventions targeting IGF signaling pathways have been tested in preclinical studies and in clinical trials, which have been summarized in several reviews in the past years (16–18, 26, 100, 238–244). These interventions are mainly based on receptor-targeting agents or drugs that reduce ligand bioactivity. Monoclonal antibodies against IGF-IR promote receptor internalization and degradation, whereas monoclonal antibodies that bind both IGFs prevent them from binding and activating their receptors. Tyrosine kinase inhibitors decrease IGF-IR activity by competing for the ATP binding site on the receptor's kinase domain and blocking signal transduction (17). Small interfering RNAs may induce potent IGF-IR gene silencing and inhibition of IGF signaling, thereby enhancing radiosensitivity and chemosensitivity (16). Despite good performance of most agents in preclinical and early clinical studies, phase 2 and 3 trials have been highly disappointed owing to both efficacy and safety issues (16, 17, 245–247). These poor results have been explained by

several factors, such as the expression and pathological importance of IGF, IGF-BPs, and IGF/INS-R isoforms in the different tumors, potency of inhibition, disease stage, toxicity, concomitant therapies, and compensatory mechanisms by other signaling pathways. Also, the homology between IGFI-R and INS-R results in undesirable side effects, such as hyperinsulinemia and hyperglycemia, during therapy with inhibitors of IGFI-R signaling (16, 17, 241). Different strategies have been tested to overcome these limitations, but with no clinical application up to now (248–251).

### Future Directions and Conclusions

Despite substantial advances to unravel the mechanisms linking GH with cancer development, many unanswered questions persist and attempts to extrapolate the findings from experimental or epidemiological studies to clinical care often lead to misconceptions and misinterpretations. The quality and the strength of evidence vary substantially among the studies and divergent results are common (Fig. 2). Thus, the more a finding is replicated and confirmed, the more valuable it becomes. Following this rule, there is robust evidence that both animals and humans with congenital GHD or GH resistance exhibit protection against several types of cancer, and these models are among the strongest evidence for a role of GH in carcinogenesis. In the opposite direction, GH excess as a cause of cancer in acromegaly has divided opinions for years and, as yet, a direct causal relationship has not been undoubtedly demonstrated. The risk of cancer related to GH therapy has been exhaustively scrutinized and, at present, available data on GH therapy in children without underlying risk factors for cancer, and in GHD adults, are reassuring. However, carefully monitoring is still advised, especially if treatment is initiated in high-risk groups, and more long-term studies on GH-exposed individuals, even years after treatment has been interrupted, are desirable. Finally, the discouraging results with anticancer therapies targeting components of the GH-IGF system reported to date clearly warrant the need for further investigation.

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**Correspondence and Reprint Requests:** Cesar L. Boguszewski, MD, PhD, Department of Internal Medicine, SEMP, Endocrine Division, Federal University of Paraná, Avenida Agostinho Leao Junior 285, 80030-110 Curitiba, State of Paraná, Brazil. E-mail: [clbogus@uol.com.br](mailto:clbogus@uol.com.br).

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## Abbreviations

Akt, protein kinase B; AR, androgen receptor; CNS, central nervous system; CRC, colorectal cancer; EMT, epithelial-to-mesenchymal transition; GHD, GH deficiency; GHR, GH receptor; GHRH-R, GHRH receptor; IGFBP, IGF-binding protein; INS, insulin; INS-R, INS receptor; ISS, idiopathic short stature; NS, Noonan syndrome; PI3K, phosphoinositide 3-kinase; PRLR, prolactin receptor; SAGe, Safety and Appropriateness of Growth Hormone Treatments in Europe; SGA, small for gestational age; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SNP, single-nucleotide polymorphism; STAT, signal transducer and activator of transcription; Tg, transgenic.