THEMATIC REVIEW

The science behind the relations among cancer, height, growth patterns, and growth hormone axis

Cesar Luiz Boguszewski, Margaret Cristina da Silva Boguszewski and Wouter W de Herder

1Department of Internal Medicine, Endocrine Division (SEMPR), University Hospital, Federal University of Parana, Curitiba, Brazil
2Department of Pediatrics, Endocrine Division (SEMPR), University Hospital, Federal University of Parana, Curitiba, Brazil
3Department of Internal Medicine, Sector of Endocrinology, Erasmus Medical Center, Rotterdam, The Netherlands

Correspondence should be addressed to C L Boguszewski: clbogus@uol.com.br

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Abstract

The association between growth hormone (GH) and carcinogenesis has long been postulated. The rationale for this association is that several components of the GH axis play an important role in the regulation of cell proliferation, differentiation, apoptosis, and angiogenesis and have been tested as targets for cancer therapy. Epidemiological and clinical studies have examined the association between height, growth patterns, and insulin-like growth factor 1 (IGF1) levels with the most common types of malignancies, while genome-wide association studies have revealed several height-associated genes linked to cancer and/or metastasis-driving pathways. In this context, a permissive role of the GH–IGF signaling system in the link between height and cancer risk has also been investigated. In animal and human models, genetic defects associated with GH deficiency or resistance are associated with protection from tumor development, while the risk of malignancies in acromegaly or in patients exposed to recombinant GH therapy has long been a matter of concern and scrutiny. In this review, we present a narrative and historical review covering the potential relations among height, growth patterns, GH axis, and cancer.

Key Words
- height
- growth
- growth patterns
- growth hormone
- cancer
- carcinogenesis

Introduction

In the early years of the twentieth century, experiments with pituitary extracts, hypophysectomy in animals, and the first transsphenoidal surgeries in patients with acromegaly paved the way to associate growth with the anterior pituitary (Lindholm 2006, Ranke & Wit 2018, Rogol & Reiter 2022). In 1921, the American anatomist and embryologist Herbert McLean Evans (1882–1971) and the embryologist Joseph Abraham Long (1879–1953) were the first to demonstrate somatic growth in rats that were treated with bovine pituitary extracts, an effect that was later observed also in dogs and other species (Evans & Long 1921). Accordingly, the American endocrinologist Philip Edward Smith (1884–1970) showed a few years later that hypophysectomy in rats caused cessation of growth (Smith 1927). From the 1930s, the Argentinian physiologist Bernardo Alberto Houssay (1887–1971), awarded the Nobel Prize in Physiology or Medicine in 1947, made pivotal contributions related to the interplay between growth
hormone (GH) and glucose homeostasis (Houssay & Biassotti 1930, de Herder 2014). Subsequently, after several decades of research, species-specific pituitary GHs were synthesized by Evans’ disciple, the Chinese-born American chemist Choh Hao Li (1913–1987) and human GH was first isolated at Li’s laboratory in 1956, with subsequent characterization of its structure, physiology, and multiple functions (Li & Papkoff 1956, Barsh et al. 1983, Ranke & Wit 2018, Kopchick et al. 2022) and elucidation of the mechanisms underlying GH–GH receptor binding and activation (Brooks et al. 2014).

The role of GH in stimulating mitosis, cell differentiation, and growth was progressively established, and the demonstration in rats that metastases could be suppressed after hypophysectomy led to treatment of advanced cancers in humans, particularly those of the breast and prostate, with surgical ablation of the pituitary, mainly in the 1950s and early1960s (Bailey 1956). At that time, it was shown that GH action in peripheral tissues could be mediated by another factor, somatomedin-C which was later re-named insulin-like growth factor 1 (IGF1) (Salmon & Daughaday 1957). Figure 1 highlights the main pioneers of the first decades of GH research until the discovery of somatomedins.

Initial experiments after the discovery of somatomedins originated the ‘somatomedin hypothesis’, which stated that pituitary GH did not act directly on its target tissues to promote growth, but instead by stimulating IGF1 production in the liver, which in turn circulates in an endocrine action model to the cartilage and bones (Le Roith et al. 2001). Subsequent evidence, however, has shown that GH directly promotes the differentiation of cartilage cells at the epiphyseal growth plate, while IGF1 is responsible for their clonal expansion (Rogol & Reiter 2022). The degrees of contribution of endocrine IGF1 (produced in the liver) vs that of autocrine/paracrine IGF1 (locally produced in the cartilage) for the promotion of human growth is still a matter of debate (Miller et al. 2022). Although the biological effects of IGF1 are frequently interconnected with those of GH, they also exert separate, individual, and sometimes, opposite actions. For instance, IGF1-independent GH actions are observed in target tissues both in an endocrine and autocrine model, which might involve other players, 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. In addition, GH has diabetogenic effects and promotes lipolysis, while IGF1 shows opposing effects on glucose and lipid homeostasis (Le Roith et al. 2001, Kopchick et al. 2022). Since the discovery of IGF1, novel components of the IGF signaling system – including binding proteins, receptors, proteases, and convertases – were gradually unraveled, but there are still many unanswered questions on their roles in the complex system controlling normal and abnormal cell growth and metabolism (Ranke & Wit 2018, Kopchick et al. 2022, Miller et al. 2022).

Pituitary GH from human cadavers became available for clinical use in the late 1950s with treatment limited to...
children with severe GH deficiency (GHD) (Raben 1958) and via biosynthetic, recombinant DNA technology in the 1980s (Ranke & Wit 2018). Since its introduction, GH therapy has been administered to children with various causes of short stature and in hypopituitary adults with severe GHD, and in parallel, the potential increased risk of cancer in these populations has been a matter of concern and subject to careful scrutiny (Boguszewski & Boguszewski 2019). The same reasoning has served as the rationale for the debate on cancer risk and the need for continued surveillance in patients with acromegaly, who are exposed to elevated GH and IGF1 concentrations during long periods of their lives (Boguszewski & Ayuk 2016).

From 1990 onwards, a substantial amount of epidemiological, observational, genomic-wide association studies, systematic reviews, and meta-analyses have found associations between height, growth patterns, serum IGF1 levels, GH signaling pathways and the incidence of several cancers in the general population (Clayton et al. 2011, Boguszewski et al. 2021). Moreover, cumulative data on a protective effect against tumor development and progression in genetically modified animals and human populations exhibiting disrupted GH production or action have brought a wealth of evidence linking GH and carcinogenesis (Basu et al. 2018). For these reasons, several components of the GH signaling system have been investigated as potential targets for new cancer therapies (Lu et al. 2019). In this article, we present a narrative review of the literature with the main facts linking cancer, height, growth patterns, and growth hormone axis.

The role of GH–IGF1 system in normal and abnormal cell growth

The control of normal cell growth, differentiation, and death is tightly regulated by a complex cascade of molecular events. The repair of defective cells, elimination of accumulated senescent cells, and apoptosis are important mechanisms to remove unwanted cells and protect against neoplasia (Munoz-Espin & Serrano 2014). The key cellular mechanisms involved in the malignant transformation of normal cells were recently reviewed (Boguszewski & Boguszewski 2019, Boguszewski et al. 2022). Briefly, GH–IGFs do not directly cause malignant transformation, but they might act as permissive factors during carcinogenesis, and suppression of their local action might be an important determinant for the unrestrained proliferation of cancer cells (Lu et al. 2019, Kopchick et al. 2022). Additional support for this view is the observation that GH-induced intracellular signaling pathways were the third most highly associated pathway with breast cancer susceptibility in a human genome-wide association study (Menashe et al. 2010).

In contrast, other components of the GH–IGF system, such as insulin-like growth factor binding proteins (IGFBPs), proteases, and insulin-like growth factor 2 (IGF2) receptor, might protect against tumor progression by inhibiting mitogenesis and stimulating apoptosis (Boguszewski & Boguszewski 2019). Intriguingly, both IGF1 and IGFBP-3 production are stimulated by endocrine GH, which may at the same time exert proliferative and anti-proliferative effects in cells. The balance between these two antagonistic effects of pituitary GH may explain why the risk of cancer is not substantially increased in patients with acromegaly or those treated with recombinant GH (Boguszewski & Ayuk 2016, Boguszewski et al. 2022). At certain stages of tumor development, autocrine/paracrine effects of GH, IGFs, and growth factors produced by neoplastic and other local cells in the tumor microenvironment might favor forces toward proliferation and malignant transformation (Chesnokova & Melmed 2019).

Height, growth patterns, and cancer

Birth length and weight, rapid growth in early life (including rapid weight and length gain and early adiposity rebound), growth patterns during childhood, time of maturation, and body segments have been associated with the risks of some types of cancer in adulthood (Okasha et al. 2002, Ahlgren et al. 2004, Troisi et al. 2006, Ruder et al. 2008, Meyle et al. 2016). It was suggested that women who grow faster in childhood, particularly around puberty, and reach a height above the average for their menarche category, are at increased risk for breast cancer (De Stavola et al. 2004). In a recent publication from the Copenhagen School Health Records Register involving 372,636 children born between 1930 and 1989, an association between early life body size and risks of 16 different adult cancers until the age of 85 was examined (Aarestrup et al. 2020). Child height was positively associated with breast, colon, endometrial, glioma, Hodgkin's disease, kidney, melanoma, esophageal (only women), ovarian, prostate, testicular, and thyroid cancer and inversely associated with bladder cancer, while birthweight was associated with bladder, breast, colon, glioma, Hodgkin's disease, liver, kidney, melanoma, ovarian, rectal, testicular, and thyroid cancer. Moreover, it was found that greater
than average increases in childhood BMI or linear growth at ages 7–13 increased risks for several cancers (Aarestrup et al. 2020).

A meeting abstract published in 1967 was likely the first report on the association between height and a specific type of cancer (Fraumeni 1967). The study showed that children with bone tumors, followed at the Children’s Hospital Medical Center in Boston between 1945 and 1965, were significantly taller at the time of diagnosis than a control group of children with other types of cancer. Curiously, the abstract pointed out that this phenomenon was also observed among dogs, with a significantly higher incidence of bone sarcoma in larger breeds. Interestingly, a single IGF1 allele is the major determinant of body size in dogs (Sutter et al. 2007). The relevance of these findings remained unappreciated for many years, but nowadays, the link between height and certain cancers is well established and seems to be evolutionarily conserved. As a matter of fact, the meeting abstract was in line with other studies, and the risk of osteosarcoma was estimated to be more than 60 times higher in large vs small dogs (Tjalma 1966).

In humans, case-control and cohort studies have shown an increased risk of 22% for breast cancer in women measuring 175 cm or more in height compared to women measuring 160 cm or less, a 20% increase in risk for prostate cancer in men measuring 180 cm or more compared to men measuring 170 cm or less, and 20–60% increase in risk for colorectal cancer between these height categories for women and men (Gunnell et al. 2001, Jenkins et al. 2006). An analysis of the relationship between country-specific cancer incidence rates and average adult height was conducted for 24 anatomical cancer sites and the incidence of cancer was associated with tallness in the majority of anatomical sites investigated in both men and women (Jiang et al. 2015). The Million Women Study carried out in the UK collected information on height and other factors relevant to cancer incidence in middle-aged women without previous cancer (Green et al. 2011). The relative risk (RR) for all cancers was 1.16 (95% CI 1.14–1.17) for every 10 cm increase in height, and cancer risk was significantly increased for colon, rectum, melanoma, breast, endometrium, ovary, kidney, central nervous system, non-Hodgkin lymphoma, and leukemia. In the same study, the authors performed meta-analyses of 11 prospective studies and found that height-associated RRs for cancer showed little variation across different populations in Europe, North America, Australasia, and Asia (Green et al. 2011). The positive association between body height and the overall risk of developing various cancers were recently confirmed in a large retrospective study with 784,192 men and women in Germany (Krieg et al. 2022). A study conducted in two twin cohorts from Sweden and one from Finland found that tallest women were at increased risk for breast cancer, with an odds ratio (OR) of 1.8 (95% CI 1.3–2.7), and for ovarian cancer, with an OR of 1.7 (95% CI 0.8–3.5) (Lundqvist et al. 2007). Accordingly, data from the European Prospective Investigation into Cancer and Nutrition (EPIC) study involving 141,896 men showed that those who were taller had an elevated risk of high-grade prostate cancer and prostate cancer death (Perez-Cornago et al. 2017).

In more recent years, the Mendelian randomization (MR) approach was applied to determine more precisely the relationship between height and cancer risk, avoiding the confounders and measurement errors of the observational studies (Glymour et al. 2012). In one study that addressed cancer incidence and mortality by age 60 in 438,870 participants from the UK Biobank resource, the MR approach identified height as a risk factor for being diagnosed with and dying from cancer (Ong et al. 2018). The authors found that each genetically predicted 9 cm increase in height conferred an OR of 1.10 (95% CI 1.07–1.13) and 1.09 (95% CI 1.02–1.16) for diagnosis and death from any cancer, respectively, and for both associations, the effect was stronger in females than in males (Ong et al. 2018).

A meta-analyses of 62 prospective studies and MR analyses, using 423 height-associated genetic variants identified in a genome-wide association study, found increased risks for colorectal and lung cancer, but not for prostate cancer, associated with each 10 cm increase in genetically predicted height (Khankari et al. 2016). In another MR study where 696 genetic variants associated with height were tested, an association between height and colorectal cancer was only detected in women (Thrift et al. 2015). Recently, a within-sibship MR study suggested that the purported effects of height on adulthood disease risk for cancer are unlikely to be explained by demographic or familial factors, but rather was a reflection of an individual-level causal effect (Howe et al. 2022).

**Interplay among height, GH-IGF signaling, and cancer risk**

The MR studies have shed new light on the common underlying genetic pathways affecting both human stature and tumor growth and progression. Height-associated oncogenes and tumor suppressor genes play a crucial role in several steps of cell division, differentiation,
senescence, and programmed death, activities that can also be exploited by tumor cells for cancer growth. Genome-wide association studies have revealed more than a hundred genomic loci linked to human height and 60 of the 88 genes most strongly associated with height are linked to cancer and/or metastasis-driving pathways (Tripaldi et al. 2013). In this context, the GH–IGF signaling system might have a permissive role in the link between height and cancer risk (Fig. 2). Several genetic variants related to the IGF signaling pathway have been related to height (Stefan et al. 2016). Serum IGF1 concentrations and urinary IGF1 excretion were associated with height in children (Juul et al. 1994, Rogers et al. 2006) and high exposure to growth promoters in childhood was pointed out as a potential risk factor for cancer in adulthood (Pollak et al. 2004). In adults, a large European cross-sectional study found a relationship between adult height and serum IGF1 concentrations in men, but not in women, with each 10 cm increase in height corresponding to a 4% increase in IGF1 (Crowe et al. 2011). Like IGF1, IGF2 has also been considered as a potential link between height and cancer development, since it is present in serum in higher concentrations than IGF1, its expression is strongly regulated by nutrition, and also increased in various types of cancers (Bergman et al. 2013, Stefan et al. 2016).

Figure 2
Hypothetical model integrating height, GH–IGF system, and increased cancer risk. Genome-wide association studies have identified around 60 height-associated genes which are strongly linked to oncogenic pathways. High exposure to GH and IGF1 in childhood and high serum IGF1 levels within the normal adult range have been associated with an increased risk of specific cancers. In comparison with short subjects (left), taller individuals (right) might be exposed to higher GH and IGF1 levels in critical periods of life and might present a slightly higher rate of stem cell division and mutations in some tissues. In case of mutations, triggered by modifiable and unmodifiable events, taller individuals would have a lower probability of appropriate DNA repair and apoptosis (red) of damaged cells (orange and purple), which would explain that cancers with high numbers of stem cell divisions, such as melanoma or colon cancer, are more significantly associated with taller adult height. This hypothetical model considers that very small differences in GH and IGF1 exposure over long periods of time would exert a tissue-specific permissive role in transforming a single damaged cell into a clinically significant disease.
Theoretically, the risk of developing cancer should increase with both the number of cells and the lifespan of an organism. As a consequence, increased cancer risk in taller individuals would be related to their high number of cells, but studies in different species have not confirmed a strict correlation between body size and the incidence of cancer, which is known as Peto’s paradox (Tollis et al. 2017). It has claimed, therefore, that is not the total number of body cells that matters, but rather, the variation in the number of stem cells, mutation rates, and metabolism among different organs and tissues that might be of importance in tumorigenesis (Ducasse et al. 2015). In such models, the exposure of stem cells to higher GH and IGF levels during critical periods of life in susceptible tissues of taller individuals would result in a slightly higher rate of cell division and, more importantly, to a lower probability of appropriate apoptotic death of damaged cells, which would accelerate carcinogenesis by increasing the pool of transformed cells available for subsequent hits (Pollak et al. 2004). Following the same rationale, higher exposure to GH–IGF signaling in the early steps of an established cancer could influence the time to transform a single damaged cell into a clinically significant disease (Pollak et al. 2004). In agreement, cancers with high numbers of stem cell divisions, such as melanoma or colon cancer, are more significantly associated with taller adult height than those with fewer stem cell divisions, such as esophageal or lung cancer (Green et al. 2011, Stefan et al. 2016). Despite the clear association of height with certain types of cancer and the potential permissive role of GH–IGF axis, it is obvious that attained adult height does not directly modify cancer risk, and many other modifiable and unmodifiable life factors are also relevant (Renehan 2011). Of note, the GH–IGF1 axis is just one of many regulatory systems that control chondrogenesis in the growth plate, which is the biological process that drives height gain (Baron et al. 2015). Moreover, a study that investigated the relationship between the number of normal stem cell divisions and the risk of 17 cancer types in 69 countries found that two-thirds of the mutations in human cancers occur by random, unpredictable DNA replication errors, unrelated to inherited or environmental risk factors (Tomasetti et al. 2017).

Serum IGF1 levels: do they say anything about cancer risk?

In the last three decades, epidemiological studies have raised the hypothesis that individuals with serum levels of IGF1 at the highest categories of the normal reference range would be at higher risk for several prevalent malignancies, particularly prostate, colorectal, and breast cancer (Clayton et al. 2011, Boguszewski et al. 2021). Of particular interest are the results from the EPIC involving around $20,000 healthy adult volunteers from 10 countries. In this large cohort, higher circulating IGF1 levels were associated with increased risk of receptor-positive breast cancer in women at 50 years of age or older, differentiated thyroid carcinoma, low-grade gliomas and acoustic neuroma, but not with lymphoma, melanoma, ovarian, hepatocellular, and pancreatic cancer (Boguszewski & Boguszewski 2019).

It is important to note, however, that epidemiological studies of cancer risk in the general population have several caveats and are subjected to numerous confounding factors (Boguszewski et al. 2022). When present, the associations are usually weak and have no clinical application, as they do not allow the use of IGF1 measurements in cancer screening or monitoring. These observations should, therefore, be examined with caution, and despite the appropriate rationale underlying the potential links between IGF1 concentrations and cancer risk, it is difficult to establish a causal relationship to ultimately apply these figures in health care.

GH–IGF1-related diseases and cancer risk

Despite the substantial amount of experimental and epidemiological data involving the GH–IGF system in carcinogenesis, it has not been easy to extrapolate these findings to acromegaly, a human disease where peripheral tissues are exposed to pathological high concentrations of GH and IGF1. This topic has been a matter of passionate debate since the first study published by Mustacchi and Shimkin in 1957 and has been subjected to narrative reviews, debate articles, and expert opinions (Boguszewski & Ayuk 2016, Gadelha et al. 2019, Terzolo et al. 2020, Kopchick et al. 2022).

Currently, the main point of discussion is whether thyroid and colorectal cancer screening in acromegaly patients should be different from that in the general population (Tirosh & Shimon 2017, Terzolo et al. 2020). There has been a good agreement that active surveillance has influenced the prevalence of thyroid cancer in acromegaly over the years. There is no evidence that an aggressive and systematic approach to detect small, asymptomatic, low-risk, thyroid malignant nodules has any impact on survival and, indeed, might contribute to unnecessary morbidity and poorer quality of life of...
acromegaly patients (Boguszewski & Ayuk 2016, Tirosh & Shimon 2017). Accordingly, a recent consensus has concluded that thyroid ultrasound should be offered only for patients with a palpable nodular goiter or other risk factors for thyroid cancer, with fine-needle aspiration biopsy performed according to the current guidelines for the investigation of thyroid nodules (Haugen et al. 2016, Giustina et al. 2020).

In relation to colorectal cancer, one side claims that acromegaly patients should be considered as a high-risk group for the development of this malignancy, and colonoscopy should always be performed at the time of diagnosis, while the other side defends that the risks are overestimated in the studies due to several biases, opposing a more proactive surveillance (Terzolo et al. 2020). Experimental studies have pointed out GH as an essential molecular component of the ‘field change’ milieu permissive for neoplastic colon growth (Chesnokova et al. 2016). Intriguingly, however, is the clinical report from a cohort of untreated GH-deficient adults in which colorectal cancer was the predominant malignancy and the main cause of death, speaking against a causal role of excessive GH–IGF1 in the colorectal cancer development (Svensson et al. 2004).

What seems highly controversial may only reflect differences in the epidemiology of colorectal cancer across countries and regions. The incidence and mortality rates of colorectal cancer vary up to 10-fold worldwide, with numbers rising rapidly in many low- and middle-income countries, while decreasing or stabilizing in most developed countries, where rates remain among the highest in the world (Arnold et al. 2017). Age and genetic, ethnic, environmental, and dietary factors are important determinants of colorectal carcinogenesis, which is usually characterized by a malignant transformation of precancerous polyps in a period of approximately 10–15 years (Arnold et al. 2017). The most recent consensus document has stated that there are no conclusive data linking the frequency of screening colonoscopy to colon cancer mortality rates and that cancer-specific mortality rates in acromegaly are generally similar to those numbers observed in the general population (Giustina et al. 2020). In addition, the life expectancy of acromegaly patients has increased over the years and more recent data indicate that cancer incidence and mortality in acromegaly are more related to age than to GH–IGF1 excess, as observed in the general population (Bolli et al. 2018).

On the other side of the coin, many examples of human disorders associated with congenital isolated or combined GHD or GH resistance with severe IGF1 deficiency (Laron syndrome) have found lower incidences or even absence of cancer in these groups of patients (Aguiar-Oliveira & Bartke 2019, Boguszewski & Boguszewski 2019, Werner et al. 2020). One study using cells treated with serum from Ecuadorian patients with Laron syndrome and complete absence of GH action and severe IGF1 deficiency demonstrated increased insulin sensitivity, reduced DNA breaks, and increased apoptosis in comparison with control samples (Guevara-Aguirre et al. 2011). Remarkable, in the Brazilian cohort of patients with isolated congenital GHD due to GHRH-R mutation, circulating GH and IGF1 levels are very low, but not absent, and rare cases of cancer were observed in these individuals (Aguiar-Oliveira & Salvatori 2022). This finding suggests that even prolonged exposure to small amounts of endogenous GH and IGF1 may contribute to carcinogenesis. Of note, these human population studies are in agreement with several animal models in which naturally or experimentally induced suppression of the GH–IGF signaling system has been associated with significant reductions in cancer rates, frequently accompanied by improvement in metabolic indexes and significant increments in their lifespan (Basu et al. 2018, Aguiar-Oliveira & Bartke 2019).

Medical therapies interfering with the IGF1–IGF1 receptor interaction in patients with malignancies

As already mentioned, the IGF1–IGF1 receptor (IGF1R) signaling pathway is critical for cell proliferation, growth, and survival. The IGF1R is, therefore, a potential therapeutic target for patients with malignancies (Lams & Lovly 2015).

Both IGF1 and IGF2 are mitogenic in adrenocortical cancer (ACC), and ACCs express high levels of IGF1R and its messenger RNA. Figitumumab, a human monoclonal IgG2 antibody directed against the IGF1R, thereby blocks IGF1 and IGF2 action in ACC cells (Cohen et al. 2005). In a phase 1 trial, patients with metastatic ACC were treated with this drug and stable disease was observed in 8 out of 14 patients (Haluska et al. 2010). Another human monoclonal IgG1 antibody directed against the IGF1R, cixutumumab, was studied in combination with mitotane in a phase 2 study in patients with metastatic ACC, but this study had to be discontinued due to slow accrual and limited efficacy (Lerario et al. 2014). A phase 3 study of carboplatin, paclitaxel, with or without figitumumab as first-line therapy for metastatic non-small cell lung cancer, was also discontinued early because of failure to show a therapeutic advantage (Langer...
et al. 2014). In parallel, in a phase 1 study in patients with metastatic castration-resistant prostate cancer, the combination of temsirolimus plus cixutumumab showed very limited antitumor activity (McHugh et al. 2020). In a phase 1 trial in 21 patients with advanced sarcomas and other solid tumors, the combination of fitumumab and everolimus induced stable disease in 15 patients and a partial response in 1 patient (Quek et al. 2011). Other monoclonal antibodies against the IGF1R include dalotuzumab, ganitumab, and teprotumumab, but unfortunately, disappointing results have also been obtained with these drugs in patients with breast cancer (Iams & Lovly 2015).

Linsitinib (OSI-906) is an oral small-molecule tyrosine kinase inhibitor of IGF1R. This drug was used in a phase 1 study in 86 patients with advanced solid tumors and 36% of them reached disease stabilization and 1 patient with melanoma achieved a partial response (Puzanov et al. 2015). In a phase 2 trial in patients with wild-type gastrointestinal stromal tumors treated with linsitinib, no objective responses were seen and the progression-free survival estimate at 9 months was 52% (von Mehren et al. 2020). In a phase 2 study in patients with metastatic castration-resistant prostate cancer, linsitinib failed to show activity (Barata et al. 2018).

As shown earlier, targeting the IGF1–IGF1R interaction in patients with cancer, although potentially interesting and being translated from bench to bedside, has generally yielded disappointing results. Ongoing research focuses on identifying patients who might benefit from such therapies either as monotherapy or in combination with other agents (Iams & Lovly 2015). Similarly, despite some promising results in preclinical studies, the usefulness of GHRH antagonists and GHR-targeted agents, as anticancer therapy aiming at suppressing autocrine/paracrine GH effects on the tumors microenvironment, also remains to be proved (Kopchick et al. 2022).

Do we need to be concerned about GH therapy?

Since the introduction and wide availability of recombinant GH, its therapeutic efficacy and safety have been the subject of meticulous scrutiny. While in adults, the approved indication of GH therapy is limited to hypopituitary patients with severe GHD, in children, recombinant GH has been prescribed in different disorders associated with growth failure beyond the classical physiological replacement in GH-deficient individuals (Ranke & Wit 2018, Yuen et al. 2019). Given the mitogenic properties of the GH–IGF system, the short and long-term risks of tumor development in GH-treated subjects have been one of the main concerns (Boguszewski & Boguszewski 2019).

In recent years, this topic has extensively been addressed in workshops held by the Growth Hormone Research Society with the publication of review and consensus documents (Simon et al. 2016, Boguszewski et al. 2021, Boguszewski et al. 2022). As per general rules, it was stated that GH therapy has a good safety profile when used for approved indications and at recommended doses, with no evidence of increased risk of primary tumor or cancer recurrence associated with GH therapy. The effect of GH replacement on the development of secondary neoplasms seems to be of a minor impact compared to host- and tumor treatment-related factors (Boguszewski et al. 2022). Nevertheless, the underlying condition plays a role in the cancer risk related to GH treatment, and it is essential to take this into consideration in specific conditions. Thus, GH is contraindicated in patients with active malignancies and in particular cases of individuals with cancer predisposition syndromes and proven severe GHD, it must be used with extreme caution (Boguszewski et al. 2022). Following these recommendations, cancer surveillance in patients currently or previously treated with GH – including those with pituitary tumor or craniopharyngioma remnants and those with a previous malignancy – does not need to be different than that indicated for the general population (Simon et al. 2016, Rogol & Reiter 2022). Amongst GH-deficient childhood cancer survivors, GH replacement does not seem to increase mortality from cancer, while data on GH-deficient adult cancer survivors are scarce and GH replacement therapy should only be considered for adult patients in remission after careful individual risk/benefit judgment (Boguszewski et al. 2022).

Conclusions

Over the last 65 years, since human GH was first isolated and synthesized, scientists, epidemiologists, and clinicians have produced a vast and valuable collection of scientific documents addressing the association between GH axis and cancer. Despite the intense research and passionate debates, many questions still persist without a definitive answer, since data from experimental and epidemiological studies frequently do not match with findings obtained in clinical studies (Fig. 3). In this context, on the one hand, there is clear evidence that individuals with congenital deficiency or resistance to GH have natural protection against malignant tumors,
while on the other hand, there is no substantial increased risk of malignancies in individuals treated with GH or exposed to excessive amounts of GH in acromegaly. At the present, it seems clear that GH–IGF signaling pathways do not cause cancer but play a role in the tumor microenvironmental during carcinogenesis. Nevertheless, medical interventions directed to the GH–GHR and IGF1–IGF1R systems have yielded disappointing results up to now in the battle against human cancers. Intriguingly, there has been evidence from observational, genomic-wide association studies, systematic reviews, and meta-analyses to support a positive link between human height, growth patterns, and cancer risk, although mechanisms underlying these associations are far from being understood, which might involve the GH–IGF axis to some extent. It is plausible that genetic and epigenetic factors might be a link among anthropometric parameters, metabolic events, and hormone determinants in their interplay on cancer risk, which is certainly a fascinating field for future investigations.

Declaration of interest
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