Best Practice & Research Clinical Endocrinology & Metabolism 31 (2017) 35–47

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

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Controversies in the risk of neoplasia in GH deficiency

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ARTICLE INFO

Article history:
Available online 22 February 2017

Keywords:
GH deficiency
rhGH replacement
cancer
risk factors

Growth hormone (GH) replacement in GH deficient (GHD) children secures normal linear growth, while in GHD adults it improves metabolic status, body composition and quality of life. Safety of GH treatment is an important issue in particular concerning the controversy of potential cancer risk. Unlike in congenital IGF-1 deficiency, there is no complete protection against cancer in GHD patients. Important modifiable risk factors in GHD patients are obesity, insulin resistance, sedentary behavior, circadian rhythm disruption, chronic low grade inflammation and concomitant sex hormone replacement. Age, family history, hereditary cancer predisposition syndromes or cranial irradiation may present non-modifiable risk factors. Quantifying the risk of cancer in relation to GH therapy in adult GHD patients is complex. There is evidence that links GH to cancer occurrence or promotion, but the evidence is progressively weaker when moving from *in vitro* studies to *in vivo* animal studies to epidemiological studies and finally to studies on GH treated patients. GH-IGF inhibition in experimental animals leads to decreased cancer incidence and progression. Epidemiological studies suggest an association of high normal circulating IGF-1 or GH to cancer incidence in general population. Data regarding cancer incidence in acromegaly are inconsistent but thyroid and colorectal neoplasias are the main source of concern.

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http://dx.doi.org/10.1016/j.beem.2017.02.004
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Replacement therapy with rhGH for GHD is generally safe. Overall the rate of *de novo* cancers was not increased in studies of GH-treated GHD patients. Additional caution is mandated in patients with history of cancer, strong family history of cancer and with advancing age. Childhood cancer survivors may be at increased risk for secondary neoplasms compared with general population. In this subgroup GH therapy should be used cautiously and with respect to other risk factors (cranial irradiation etc). We believe that the benefits of GH therapy against the morbidity of untreated GH deficiency outweigh the theoretical cancer risk. Proper monitoring of GH treatment with diligent cancer surveillance remains essential.
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Introduction

Environmental factors and accumulation of genetic alterations are involved in cancer pathogenesis. Various cancers use different growth-regulating pathways. Anatomical site of cancer origin and age at diagnosis vary significantly. Identifying "precancerous lesions" is challenging and today it is recognized that cancer evolves in a stepwise fashion (initiation phase and progression phase) and the sequence of phases may take decades to progress [1].

Growth hormone deficiency (GHD) is a well recognized condition. Treatment with rhGH of GHD children secures normal linear growth and final height, while growth hormone (GH) replacement in adults favorably affects metabolic status, body composition and quality of life. The endocrine community has recently issued a position paper on safety of GH treatment in children and adults in particular concerning the cancer risk. Despite thousands of patients treated with rhGH there is still insufficient evidence for the role of insulin like growth factor 1 (IGF1) in the progression of cancer [2,3].

The controversies between studies that find positive association of IGF 1 and cancer and those that do not, arise from significant limitations of these studies. Experimental studies, epidemiological studies based on the association of endogenous hormones (GH/IGF-I) and cancer, acromegaly (a state of chronic excess of GH/IGF1) and observational studies in children and adults diagnosed with GHD treated with rhGH – each provide some evidence but each have their own limitations. Importantly the extremely heterogeneous genetic background of population exposed to GH therapy with a variety of environmental risk factors must be taken into consideration when assessing cancer risk.

Cancer risk in adult patients with acquired GH deficiency not treated with GH

It is generally accepted that adult GHD is associated with increased mortality due to cardiovascular and cerebrovascular diseases in the untreated state, while the question of malignancy is still controversial. Retrospective studies have presented conflicting results regarding the incidence of malignancy in adult GHD patients. A decreased rate of malignancies in hypopituitary men not replaced with GH has been observed, whereas an increased rate of malignancies was observed in hypopituitary women not treated with GH [4]. Other studies showed an increased rate of malignancy in hypopituitary patients not replaced with GH [5–7]. Patients with non-functioning pituitary adenomas (NFPA) had a 3.91-fold increased incidence of malignant tumors compared with the general population [5]. A retrospective comparison between 1411 hypopituitary adults without GH replacement and the normal population showed an increased rate of malignancies in the hypopituitary patients, with the predominance of colorectal cancer [6]. However, other studies did not report increased rate of malignancy [8–10].

The relatively advanced age of the patients in some studies may possibly explain why an increased incidence of malignant disease was observed [6]. Another explanation of increased incidence of tumors in GHD could be that radiotherapy for pituitary tumors was increasing secondary brain tumors incidence [9]. Two retrospective studies suggest that the association may be due to the underlying genetic instability or may be explained simply by an increased surveillance of these patients [5,11].

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Modifiable cancer risk factors in hypopituitary patients

Obesity and insulin resistance

GHD in adults is characterized by increased prevalence of obesity and in particular with impaired body composition characterized by increased visceral fat as well as with impaired glucose metabolism, hallmarked by insulin resistance and fasting hyperinsulinemia [12]. Increasing evidence associates obesity (linked to hyperinsulinemia) with risk for several cancers: adenocarcinoma of the esophagus and gastric cardia, colorectal cancer, postmenopausal breast cancer, endometrial cancer, and clear cell renal carcinoma [13–15]. Visceral obesity has also been associated to colorectal cancer predisposition [16].

Sedentary life style

Patients with adult GHD are more prone to sedentary lifestyle, due to reduced muscle mass and capacity [17] as well as due to psychological changes such as sense of fatigue, energy loss and depression [18]. Even after adjusting for obesity and diabetes, sedentary behavior (in particular prolonged sitting time while watching TV) was significantly associated with increased risk of colorectal cancer, breast cancer, ovarian cancer and multiple myeloma (particularly in women) [19–21]. Prevalent sedentary behavior was associated with significantly lower BRCA1 mRNA expression, which could translate into more harmful effect in BRCA1 mutation carriers [22].

Circadian rhythm disruption

Quality of life assessment in adult GHD patients has revealed frequent sleep disturbances and fatigue. GHD patients have difficulty falling asleep or sleeping through the night, and are deeply fatigued during the day [18]. Alterations in diurnal rhythmicity were reported in patients treated for NFPA as demonstrated by 24 h monitoring of skin and core body temperature, blood pressure and determining salivary melatonin levels [23]. These observations are attributed to disturbed central or peripheral clock machinery or damage of the hypothalamic SCN caused by suprasellar tumor expansion or by transsphenoidal surgery.

Circadian disruption is associated with an increased risk for breast cancer in women, as demonstrated by a comprehensive meta-analysis [24]. Short duration of sleep was identified as a possible risk factor for the development of early colorectal neoplasia [25].

Chronic low grade inflammation

GHD in adults has been associated with elevated markers of chronic inflammation [26]. Increased IL-6 and TNF-α production from monocytes and increased peripheral serum concentrations of CRP and IL-6 have been found in adult GHD patients [27,28].

Chronic inflammation has been associated with cancer risk and mortality [29]. Chronic local inflammatory states can give rise to several cancer types. Inflammatory bowel disease can lead to colorectal cancer risk; reflux esophagitis to esophageal cancer and chronic pancreatitis to pancreatic cancer.

Cancer risk-behavior and nutrition

Individuals differ in their sensitivity to environmental variations. Smoking and drinking, but also dietary habits all might play a role in causing or modifying cancer risk. Cigarette smoking is a well identified risk factor for lung cancer. Excessive alcohol consumption is a risk factor for pancreatic cancer and oral cancer. A high intake of refined carbohydrates has been associated with an increased risk of cancer [30].

Tobacco smoking and alcohol consumption were less prevalent among GHD patients compared to controls, even in different ethnic and cultural backgrounds (Sweden and Japan) [31,32]. Study in humans with lifetime isolated GHD (IGHD) due to a homozygous mutation in the GHRH receptor gene (Brazilian cohort) pointed that in the absence of GH, estimated energy intake was higher than in controls (corrected for body weight), but IGHD individuals consumed more proteins, less carbohydrates, and equal amount of lipids in comparison to controls and thus seem to have a healthier dietary pattern [33].

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Concomitant sex hormone replacement therapy

Majority of GHD patients receive multiple hormone replacements. Sex steroids are the main focus of concern due to the possible association with breast cancer in women and prostate cancer in men. Testosterone replacement therapy for symptomatic hypogonadism appears to be safe in terms of causing increased PSA levels or risk for prostate cancer. The current data are reassuring although some caution is mandated until studies with longer follow-up are available [34]. Current practice of monthly testosterone-enanthate injections might cause an issue of high variations in serum testosterone levels with periodic exposure to excessive doses. Estrogen replacement in women older than 45 can increase breast cancer risk and should be considered carefully [35]. In both male and female hypopituitary patients requiring gonadal steroid replacement an individualized approach is highly advisable. Patient's age and other risk factors must be taken into full consideration.

Non modifiable cancer risk factors in hypopituitary patients – independent of GH status

Age

Age is one of the most consistent risk factors for neoplasia. The incidence of most malignancies is progressively increasing with age. The incidence of pituitary tumors increases with age (until 75) [36,37]. This association might make GHD patients more prone to cancer risk by the burden of their age, regardless of the subsequent risk introduced by rhGH replacement therapy. The natural decline of the GH/IGF-1 values with age appears to be in sharp contrast with a progressive increase in the occurrence of cancer with aging. This apparent paradox is explained by genomic instability occurring with aging [38].

Family history

Family history of malignancy is an important risk factor for cancer development. Pituitary adenoma patients are found to have a positive family association with some malignancies (breast and colorectal) reported in a study from the Swedish Cancer Database multigenerational registry. The data indicate a twofold increase in cancer risk for persons with a parent or sibling affected by cancer [36,39].

Hereditary syndromes and cranial irradiation

Some of the genetic syndromes responsible for GHD (e.g. MEN-1, MEN-4, Carney complex, Neurofibromatosis-1, von Hippel Lindau disease) are inherently associated with susceptibility to development of other tumors. Patients receiving cranial irradiation for pituitary or other brain tumors are at an increased risk for subsequent malignancy. Increased risk of a late appearance of *de novo* malignant brain tumors in patients who previously received radiotherapy was identified as an important cause of excess mortality in adult patients with hypopituitarism [40].

Congenital GH/IGF-1 deficiency and cancer risk

Patients with congenital hypopituitarism have prolonged life span suggesting that when GH/IGF-1 secretion or action is inhibited, humans live longer and are protected from cancer ("little people of Krk") [41,42]. However there are studies that report reduced longevity in untreated patients with congenital isolated GHD, with the main causes of death being heart and infectious diseases [43]. Large retrospective study on untreated congenital isolated GHD (due to mutation in the GHRH receptor gene) reported that untreated GHD does not affect longevity [44].

Congenital IGF-1 deficiency (Laron syndrome, GH resistance) tends to confer protection against development of malignancies, even if treated with IGF-1 [45,46]. In the large study on 230 Laron syndrome patients (insensitivity to GH), none of them developed cancer, while only one out of 11 patients with congenital IGHD had a basal cell carcinoma [46]. The study on Ecuadorian patients with mutations in the GH receptor gene that lead to severe GH resistance and IGF-1 deficiency reported only one nonlethal malignancy (a papillary serous epithelial tumor of the ovary) [47].

Out of the 79 patients with GHRH-R mutation and 113 with congenital MPHD, six cases of cancer were reported, three with previous rhGH treatment [46]. We recently reported one case of fatal cancerous leptomeningitis from a disseminated ovarian cancer in a patient with familial congenital hypopituitarism due to PROP 1 mutation not treated with GH, but with strong family history for malignancies [48].

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In conclusion, these data indicate the lack of complete protection against cancer in patients with congenital hypopituitarism in comparison with patients with congenital IGF-1 deficiency, with an important role of family history of malignancy.

Animal studies

Animal models provide the best insight into the implications of GH/IGF-1 axis in tumorigenesis. However the genetic homogeneity of the experimental animals and their young age, pose limitations in translating conclusions to humans [3]. From early studies came the evidence that hypopituitary Snell dwarf mice were resistant to various carcinogens and that the growth of transplanted tumors was inhibited in these animals [49]. Transgenic animals exhibiting severely depressed IGF-1 due to either Pit1 knock-out, Prop1 knock-out or GH-receptor deletion, all exhibited reduced tumorigenesis [50–52]. Treatment with GH or IGF-1 in transgenic dwarf rats resulted in significant increase in mammary tumor incidence and reduced average latency in tumor occurrence compared to untreated dwarf animals [53].

The incidence of induced or spontaneous tumors was increased in transgenic animal models of GH excess, IGF-I excess or IGF-1R over-expression [54]. IGF-1 is supposed to have a role in angiogenesis, metastasis and resistance of malignancies to chemotherapeutic treatment [55,56]. Also the impact of locally produced GH in paracrine and autocrine manner has a role in tumorigenesis [57].

In conclusion, gene knock-out and knock-in experiments in laboratory animals can reveal large effects but against a homogenous genetic background. In general, when GH/IGF secretion or action is inhibited, a decreased incidence and rate of progression of cancers has been observed however there is important distinction between most experimental models and clinical cancers in human populations.

Epidemiological studies – endogenous GH/IGF1 levels and cancer risk

Various epidemiological studies have suggested an association with high normal circulating levels of IGF-1 or GH and cancer incidence in general population [54]. Circulating IGF1 levels were found to be positively associated with breast-cancer risk in a recent analysis. Prediagnostic IGF-1 and IGFBP3 concentrations were obtained from 17 prospective studies in 12 countries [58]. The association was not affected by menopausal status, but seemed to be confined to estrogen-receptor-positive tumors [58]. High normal circulating IGF-1 levels were in the past reported to be associated with prostate cancer however in a large study in which 110,000 men were offered PSA testing, IGF-I levels were not associated with PSA detected prostate cancer [59,60].

There are apparent differences when different malignancies are investigated. Thus in the largest prospective study to date no association between IGF-I and epithelial ovarian cancer was found. The conclusion was that pre-diagnostic serum IGF-I concentrations may not influence epithelial ovarian cancer risk [61,62].

The epidemiological studies have important strengths and limitations. Limitations include issues of inconsistent IGF-1 assays, insufficient sample size for cancer subtype analyses to detect an association, unknown nutritional status of subjects, limited follow-up periods and lack of adequate control groups [63].

In conclusion the strength of evidence linking GH to cancer is progressively weaker when moving from *in vitro* studies to *in vivo* animal studies to epidemiological studies and finally to studies on GH treated patients [54] (Fig. 1).

Therapeutic manipulation of GH/IGF-1 axis

Building on the platform of the role of GH/IGF-1 axis in carcinogenesis, manipulation of GH/IGF-1 system has been used as a therapeutic approach in cancer patients, with variable success. Blockade of the IGF-1 receptor or anti-IGF-1 antibody administration is associated with tumor inhibition. In vitro studies with monoclonal antibodies against IGF-1 receptor have demonstrated a decrease of breast cancer proliferation [64] and antitumor effects on esophageal carcinoma [65].

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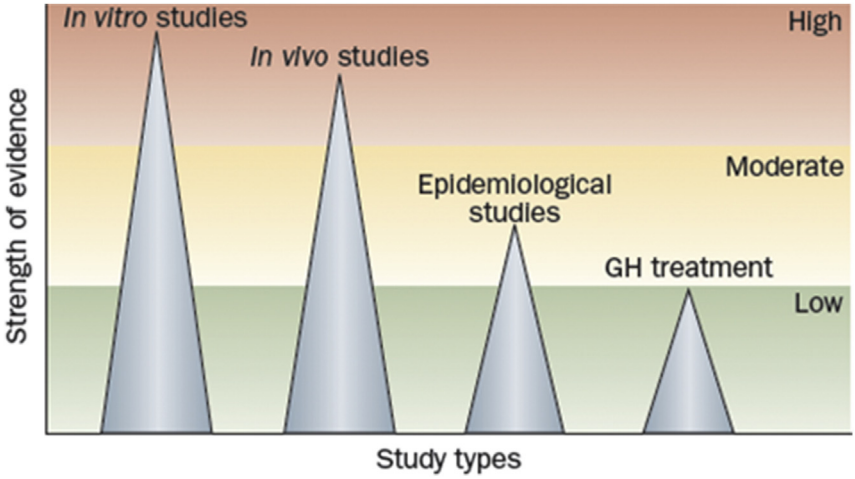

Fig. 1. Illustration of the strength of evidence linking the GH–IGF axis to cancer. The x-axis represents the different types of study, from *in vitro* cell-based studies through to information derived from GH-treated cohorts of patients. The y-axis represents the proposed strength of the link between the GH–IGF axis and cancer in each study setting. (GH – growth hormone, IGF – insulinlike growth factor). (Reprinted by permission from Macmillan Publishers Ltd: Nat Rev Endocrinol (Growth hormone, the insulin-like growth factor axis, insulin and cancer risk. Clayton PE, Banerjee I, Murray PG, Renehan AG. Nat Rev Endocrinol. 2011 Jan; 7(1):11–24), Copyright (2011)).

Antisense RNA against IGF-1 receptor inhibited colon cancer growth *in vivo* [66]. Larger randomized Phase III trials in patients with non-small cell lung cancer, breast cancer and pancreatic cancer, have failed to demonstrate a clear clinical benefit of targeting GH/IGF-1 pathway in combination with conventional therapy [67,68]. The use of monoclonal antibodies targeting the IGF1R in pre-clinical studies has opened high hopes for these agents in prostate cancer treatment. However, initial results from clinical trials of IGF-based therapies for prostate cancer have been disappointing. The final results of many of these clinical studies are still pending [69].

Acromegaly

An increased risk of cancer in patients with chronic GH/IGF-1 excess (acromegaly) is reported by many authors but also disputed by some. Possible mechanisms underlying this association include elevated levels of circulating GH and IGF-I, but several other factors may be relevant such as aging, obesity, insulin resistance, family history of malignancy [3,63,70]. Traditionally, acromegaly has been linked to an increased risk of thyroid cancer, colorectal neoplasias and urinary tract carcinomas [71–74]. There is also a view that an increase in benign neoplasia (such as colonic polyps, breast dysplasias, thyroid nodules) leads to increased diagnostic procedures in acromegalic patients which creates a bias in discovery of some malignant tumors that do not necessarily occur more often. A comprehensive literature review of 12 years (1998–2010) confirmed that overall mortality in acromegaly has decreased, and that overall cancer-related mortality did not increase [75].

Screening for colorectal neoplasias in acromegalic patients is advised in most centers. Most reports point to an increased prevalence of colonic polyps and suggest a more prevalent malignant transformation [76,77]. One study showed a 7.6-fold increased risk of colorectal cancer in acromegaly compared with general population, while other studies reported lower risk of colorectal cancer [72,78,79]. A recent investigation on 446 acromegalic patients from German Acromegaly Registry reported slightly (but not significantly) lower overall cancer incidence compared to the general population [80]. There was no significantly higher incidence for colorectal, breast, thyroid, prostate or lung cancers in acromegalics compared to the general population [80].

Increased risk of thyroid cancer is attributed to acromegaly by some authors and routine neck ultrasound screening is advised [74,81–84]. In the study of Mercado et al., a malignant neoplasm was

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diagnosed in 21/442 (4.7%) patients and thyroid cancer was the most common, followed by breast carcinoma [85].

In conclusion, data regarding cancer incidence among acromegaly patients are inconsistent and remain controversial due to the rarity of the disease, small patient numbers and confounding factors (age, obesity, nutritional status, diabetes mellitus, and family history of malignancy). Periodic thyroid ultrasound examination and screening for colorectal neoplasias should be an important part of follow-up of patients with acromegaly.

Cancer risk in GH treated GHD patients

Risk of de novo *cancers in hypopituitary patients treated with GH*

Available data in children do not indicate an increased risk of new primary cancers in GH recipients, while the data for new cancer risk in adult GH recipients are insufficient (Table 1) [2,63,86]. Analysis of the GH treated patients from the Genentech' National Cooperative Growth Study (NCGS) reported no increased risk for nonleukemic extracranial neoplasms, and the leukemia risk was comparable to that in the general population when subjects with known risk factors for leukemia were excluded [87,88].

Cancer risk data for GH-treated hypopituitary adults are variable. Reports from single centers and large multinational databases generally found no increase in the overall occurrence of *de novo* neoplasia in hypopituitary patients replaced with GH [6,89–93]. There are some studies with opposite result showing that GH treated patients had significantly elevated overall cancer mortality risk, especially for colorectal cancer and Hodgkin's disease [94]. The limitation of this study is a relatively small number of subjects, different GH treatment regimen used at the time (standard daily GH, or doses 2 or 3 times a week) and also lack or inconsistency in serum IGF-1 level monitoring.

Analysis of almost 14,000 GHD adults in KIMS (Pfizer International Metabolic Database) demonstrated a modest increase in mortality rate of GHD adults on GH replacement therapy, but no increased standardized mortality ratio for deaths from malignancies [95]. The large post-marketing surveillance studies which did not find increased cancer risk among GH treated patients, with many patient years of observation, also have some very important limitations. They have relatively short follow-up period, data in the databases are incomplete, patient selection bias is a possibility and control population for comparison is lacking.

In conclusion, overall increased rate of *de novo* cancers was not observed in studies of GH-treated GHD patients.

Risk of recurrence or regrowth of neoplasm in GHD patients treated with GH

Some concerns have been raised about the rhGH safety because of its mitogenic potential. However, most of the published studies on this topic have important limitations [96]. Considering the slow-

Table 1
Majority view of the effect of GH treatment for approved indications on cancer risk in children and adults (including those with a childhood-onset of GH deficiency). The term 'robust' is used when there are multiple independent published sources supporting the statement. The term 'suggestive' is used when there are less than three sources supporting the statement. The term 'insufficient' is used when available publications provide inadequate evidence to support the statement.

Age at onset of GH treatment	New primary cancer	Recurrence of the primary cancer in survivors	Second or subsequent neoplasm in survivors
Child	No evidence for GH treatment effect *Level: robust*	No evidence for GH treatment effect *Level: robust*	Risk present but diminishes with time from onset of GH treatment *Level: suggestive*
Adult	No evidence for GH treatment effect *Level: suggestive*	*Insufficient data available*	*Insufficient data available*

(Reused from Allen DB et al. Eur J Endocrinol February 1, 2016 174 P1–P9. GH safety workshop position paper: a critical appraisal of recombinant human GH therapy in children and adults. Copyright 2016 Allen D et al. http://www.eje-online.org/content/174/2/P1.long).

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growing nature of most of pituitary benign tumors, current position statement is that long-term randomized prospective clinical trials are needed to generate conclusive evidence on the safety of GH treatment in patients with pituitary tumors.

For GHD children there is no significant risk of recurrence of previously known cancer. For the adults data is insufficient (Table 1) [2,97].

A large study by Swerdlow et al. compared 180 children with brain tumors treated with GH and 891 children with brain tumors who received radiotherapy and were not treated with GH [98]. The relative risk of recurrence in those treated with GH compared with untreated patients was small, with no significant trend in relative risk of recurrence with cumulative exposure to rhGH therapy. Data from the Childhood Cancer Survival Study (CCSS) are consistent with the finding that GH does not increase risk of disease recurrence for both primary brain tumors and acute leukemias [99].

Data from the Pfizer International Metabolic Surveillance (KIMS) study demonstrated that there was no increase in the rate of regrowth of primary pituitary tumors [91]. A recent analysis from the Hypopituitary Control and Complication Study (HypoCCS) showed that GH treatment in 3668 patients with pituitary adenoma history and 956 GH treated patients with craniopharyngioma history did not increase the risk of primary tumor recurrences [100]. Other studies confirmed that the rate of NFPA recurrence or progression was similar in GH treated and untreated patients [101]. Recently published large study on tumor recurrence or regrowth in GHD adults with NFPA treated with rhGH reported tumor progression in 12.1% of the patients after a median time of 2.2 years (range 0.1–14.9 years) [102]. Prior radiotherapy decreased tumor progression risk compared to no radiotherapy [102].

In conclusion, rhGH replacement therapy does not appear to cause pituitary tumor re-growth and recurrences compared to similar patients without GH treatment. However, follow-up time is still relatively short. We need long-term randomized controlled trials to fortify the conclusion that rhGH is safe in GHD patients.

Risk of secondary neoplasms in childhood cancer survivors

Growth hormone deficiency (GHD) is the most common late complication observed in childhood cancer survivors (CCS) previously treated with cranial radiotherapy (CRT) either for primary brain tumor, nasopharyngeal carcinoma, acute lymphoblastic leukemia or total body irradiation in preparation for bone marrow transplantation [103,104]. The risk of GHD in CCS treated with CRT is known to increase in a time- and dose-dependent manner [103,105]. Recently published retrospective study of CCS with 748 participants treated with CRT observed for a mean of 27.3 years (range, 10.8–47.7 years) showed that 99.7% of patients developed GHD [104].

The association between rhGH therapy and risk of secondary neoplasms is controversial. GH treatment of pediatric cancer survivors does not appear to increase the risk of recurrence but may increase the risk for subsequent neoplasms [99,106–108]. A large retrospective analysis of prospective cohort study on CCS (Genetics and Neuroendocrinology of Short Stature International Study-GeNeSIS) reported that 3.8% of CCS treated with GH developed a secondary neoplasm, with the estimated cumulative incidence of SN at 5 years of follow-up of 6.2% [109]. Common secondary neoplasms in CCS include nonmelanoma skin cancer, breast and thyroid carcinoma, bone tumors and benign CNS tumors like meningiomas [110–113]. Risk factors associated with secondary neoplasms in CCS are: female sex, young age at primary cancer diagnosis, radiation exposure, chemotherapeutic agents–alkylating agents, topoisomerase inhibitors, hematopoietic stem cell transplantation, genetic background (cancer predisposition syndromes), family history of cancer, primary diagnosis of sarcoma or Hodgkin's lymphoma [107,112]. Many studies confirmed that radiation exposure is one of the most important risk factors for secondary neoplasms in CCS [110,113–115].

There are also studies with opposite results, which do not confirm the association between GH replacement therapy and secondary neoplasms in CCS [113,116]. Patterson et al. analyzed data from the CCSS including 12.098 pediatric cancer survivors diagnosed with cancer prior to age 21 years, of whom

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338 were treated with rhGH [116]. The authors concluded that there was no statistically significant increase in risk of secondary brain tumors associated with GH exposure.

In conclusion, childhood cancer survivor (CCS) patients may be at increased risk for secondary neoplasms compared with the general population. In GH-deficient CCS, provided that they are in remission, GH therapy should be used cautiously particularly in the presence of other risk factors (previous chemotherapy, radiation therapy, genetic predisposition, family history of malignancy).

Monitoring of GH therapy and cancer surveillance

Practice among pediatric and adult endocrinologists involves titrating GH dosage to achieve serum IGF-I concentrations that are perceived as both efficacious and safe i.e. to restore normality. Measurement of IGF-1 concentration is mandatory during the rhGH therapy. It is important to establish the population specific IGF-1 reference values and to individualize decision on the length of treatment and on the target IGF-1 value (mid-normal or low-normal when concerned with risk factors). When deciding on the initial dose, it is important to take into account age, gender and in females oral estrogen replacement status.

The authors of the recently published position statement paper on safety of rhGH concluded that GH continues to have a good safety record when used for approved indications and at recommended doses [2]. In practice GH therapy may be commenced usually 2 years after completion of cancer treatment and with approval from patient's oncologist. Close tumor screening during therapy is mandatory [63]. It is important to consider baseline and 12–18 months follow-up MRI scans in patients suspected for intracranial expansive lesions [63].

Conclusions

Quantifying the risk of cancer in relation to GH therapy in adult GH deficient patients is complex. In humans infinitely varied genotypes respond in many different ways to many environmental insults. Replacement therapy with rhGH for GH deficiency is generally safe but caution is advisable when an individual had a history of cancer or has a strong family history of cancer and is aged. We believe that the benefits of GH therapy against the morbidity of untreated GH deficiency outweigh the cancer risk in that population.

Practice points

- benefits of GH therapy in GH deficiency outweigh the theoretical cancer risk
- overall GH replacement therapy is safe and available data do not indicate increased cancer risk
- theoretical evidence linking GH to cancer occurrence or promotion is progressively weaker when moving from *in vitro* studies to *in vivo* animal studies to epidemiological studies and finally to studies on GH treated patients
- proper dosing and monitoring of GH therapy with diligent cancer surveillance is essential
- addressing modifiable risk factors for cancer in GHD patients is important: such as obesity, insulin resistance, sedentary behavior, circadian rhythm disruption, chronic low grade inflammation and concomitant sex hormone replacement
- overall the risk of *de novo* cancers is not increased in GH-treated patients with safety issues reported from observational studies which have methodological limitations
- insufficient data are available in patients with history of cancer, in patients with strong family history of cancer and patients with advancing age
- childhood cancer survivors may be at increased risk for secondary neoplasms and GH therapy should be offered to them cautiously and with respect to other risk factors

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Future research agenda

- long-term randomized prospective clinical trials are needed to generate conclusive evidence on the safety of GH treated population in comparison with the untreated population
- longer follow-ups of larger patient cohorts are needed to elucidate cancer risk in GH excess i.e. acromegaly
- dedicated guidelines are needed for monitoring of GH therapy and cancer surveillance in GHD subgroups with increased cancer risk
- population-specific IGF-1 reference values are needed for monitoring of GH therapy and there is a need in future studies to show the value of IGF-1 monitoring for safety in particular in children
- further studies on therapeutic manipulation of GH/IGF-1 axis in cancer patients are needed

Acknowledgment

This study was supported by a grant from the Ministry of Science of Republic of Serbia (Project 175033).

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