Abstract

It has been difficult to identify factors that affect the risk of cancer, but we know that people are at higher risk as they get older, or if they have a strong family history of cancer. The potential influence of environmental and behavioral factors remains poorly understood. Early population-based and case–control studies suggested that higher serum levels of IGF1 could be associated with increased cancer risk. Since GH therapy increases IGF1 levels, concern has been raised regarding its potential role as a cancer initiation factor. Experimental evidence and some clinical studies showed that when GH/IGF1 secretion or action was inhibited, a decreased incidence and rate of progression of cancers occurred. However, human populations comprise a garden variety of genotypes that respond differently to the same kind of exposures. Human population studies frequently reveal only very small effects to these exposures. So, are GH and cancer guilty by association? After more than 20 years, leukemia, a major safety issue initially believed associated with GH treatment in children with GH deficiency (GHD), has not been confirmed but the risk of second malignancies in patients previously treated with irradiation has been detected or confirmed through the National Cooperative Growth Study. Overall, this large study confirmed the favorable overall safety profile of GH therapy in children with GHD, and also highlighted specific populations at potential risk. The risk of secondary malignancy following radiotherapy is surely related to radiotherapy more than GH therapy that may increase growth but is less likely to start the oncogenic process. In GH-deficient adults treated with GH, observational studies (KIMS, HypoCCS) have shown that when IGF1 levels were targeted within normal age-related reference ranges, the occurrence of malignancies was not higher than in the general population.

Introduction

It has been shown by experimental studies that growth hormone (GH) and insulin-like growth factors (IGFs) have mitogenic and proliferative properties (1, 2, 3, 4, 5, 6). Studies in the general population suggest that high-normal serum IGF1 levels may be associated with an increased risk of malignancies (7, 8). The question that then begs an answer is can GH replacement therapy in GH-deficient patients increase the risk of malignancy? Epidemiological studies have reported variable results of the incidence of malignancy in GH-deficient patients treated with GH, ranging from no increase in incidence to increased risk of malignancy in comparison with the risk in the general population (9, 10, 11). GH replacement therapy for adults with GH deficiency (GHD) was approved in 1995. The first observational studies have suggested that GH replacement therapy in GH-deficient adults is safe (12). In children, GH therapy was approved in 1985 with several hundred-thousand children receiving GH for growth purposes, and the overall safety remains favorable (13, 14, 15). There were no increases in new malignancies in GH-treated children without risk factors. However, studies in children with risk, that is, childhood cancer survivors, indicated a two- to threefold increased risk of second neoplasms in GH-treated children compared with that of non-GH-treated children (16, 17).

Experimental data on the role that the GH/IGF system plays in cancer

Available experimental data support the hypothesis that GH/IGF1 may influence neoplastic tissue growth. Malignant tumors have been induced in animals exposed to supraphysiological doses of GH, while hypophysectomy appears to protect animals from carcinogen-induced neoplasms (1, 2, 3, 4). GH and IGF1 receptors are found in multiple tumors, and these hormones have potent mitogenic and antiapoptotic activities (5, 6). IGF1 may be involved in angiogenesis, metastasis and resistance to...
chemotherapeutic agents (5, 6). The interpretation of association between circulating IGF1 levels and the risk of cancer is difficult and complex. In circulation, IGF1 is bound to IGF-binding proteins (IGFBPs) with higher affinity than to the IGF1 receptor. As a result, most of the circulating IGF1 is relatively unavailable for receptor activation. IGF1 activity at tissue level is not necessarily determined by the secretion rate of IGF1 nor by total IGF1 concentrations (18). IGFBPs not only restrict IGF1 activity but can also enhance activity at the cellular level by enhancing delivery of IGF1 to specific tissue compartments (19). The most abundant BP in the circulation is IGFBP3. Proteases capable of cleaving IGFBP3 are present in both the circulation and extravascular fluids. While in circulation protease inhibitors protect IGFBP3 from proteolysis, in extravascular interstitial fluids protease inhibitors are not present, which enables proteases to cleave IGFBP3, making IGF1 more available for cell receptors.

Based on experimental evidence in recent years, targeting the IGF system for anticancer therapy is a newly developing avenue (5). In general, when GH/IGF1 secretion or action is inhibited, a decreased incidence and rate of progression of cancers has been observed. Hypopituitary dwarf mice and GH receptor/BP (GHR/BP) knockout (KO) mice showed increased longevity (20, 21). These animals have a lower incidence and delayed occurrence of fatal neoplastic lesions compared with their wild-type littermates. Furthermore, lit/lit mice, characterized by a non-functioning GHRH receptor and thus very low GH and IGF1 levels, show almost complete inhibition of growth of transplanted human breast cancer cells (22).

Gene knock-out and knock-in experiments in laboratory animals reveal large effects. Animals with selective KO of the hepatic IGF1 gene (and marked reduction of IGF1 levels) show marked delay in the onset and development of chemically and genetically induced mammary and colonic tumors (23, 24). GH transgenic mice and IGF1 transgenic mice are two different phenotypes of hypersomatotropism in whom GH/IGF systems do not have the same role in individual tumor types. IGF1 transgenic animals do not show increased incidence of bowel cancer while GH transgenics do (25). Functional IGF1 receptors on the tumor cells, such as malignant breast epithelial cells, are needed for tumor formation and progression (26, 27).

There are limitations to these experimental studies. Experimental animals are single genetically homogeneous rodent colonies showing large knock-out and knock-in effects. All experiments are strictly controlled under standardized conditions and without environmental stimuli (18). By contrast, human population studies examine changes in the setting of heterogeneous genotype and reveal only very small effects. Furthermore, an important distinction is the high prevalence of occult preclinical neoplasias in elderly humans; in experimental studies most animals are young and growing (27).

In summary, while the evidence of initiation of the oncogenic process may not be ‘limited,’ there is good evidence for tumor growth and progression in transgenic models; therefore, it is biologically plausible that the GH/IGF system is involved in oncogenesis albeit in the setting of an artificial lab environment. Many aspects of human IGF pathophysiology can only be learned from studies in humans.

**Circulating IGF1 and cancer: data from the general population**

Early human population studies suggested that higher IGF1 levels could be associated with increased cancer risk (5, 7, 28). It was observed that patients with breast cancer had higher IGF1 levels than control subjects (29). Other studies confirmed an association between serum IGF1 levels in the upper quartile and the risk of prostate, breast, and colon cancer in the general population (30, 31, 32, 33, 34, 35). A systematic review and metaregression analysis of epidemiological studies analyzed the association between IGF1 and IGFBP3 with prostate, colorectal, premenopausal, and postmenopausal breast and lung cancer. High-normal IGF1 levels were associated with a twofold increased risk of prostate, colorectal, and premenopausal breast cancer but not postmenopausal breast cancer or lung cancer (7).

In a large case–control study in the UK, in which 100,000 men were offered prostate-specific antigen (PSA) testing, those who had elevated PSA levels underwent prostate biopsy and measurements of IGF1, IGF2, IGFBP2, and IGFBP3 did not find an association of IGF1 with PSA-detected prostate cancer (36). These authors concluded that reducing IGF1 might not prevent the initiation of prostate cancer but might prevent its progression. In the study of Stattin et al. (37), the patients with prostate cancer had significantly higher IGF1 levels than control subjects (mean IGF1 level: 229 vs 214 ng/ml respectively, P=0.02). The positive association between IGF1 level and prostate cancer risk was particularly strong in younger men (<59 years at the time of blood collection). These data suggest that circulating IGF1 may be specifically involved in the early pathogenesis of prostate cancer. In this study, adjustment for BMI did not alter the associations of IGF1 with prostate cancer risk.

Besides IGF1, IGFBPs also have growth-regulatory effects on cells through modulation of IGF bioactivity and other mechanisms. The most frequently studied IGFBP in relation to cancer was IGFBP3. In some studies an inverse association between serum IGFBP3 levels and risk for cancers has been demonstrated (32, 33, 38). Men in the highest quartile of IGF1 levels had a 2.6-fold higher prostate cancer risk, while men in the highest quartile of IGFBP3 levels had a 46% decreased risk compared with the lowest quartile (38). A similar result was observed for IGFBP1 in this study. The study of postmenopausal women showed an inverse association...
between IGFBP3 and risk of breast cancer, while other IGFBPs (IGFBP1, IGFBP4, and IGFBP6) were not significantly associated with breast cancer risk (39). There are also studies that reported no association between IGFBP3 and risk of cancer, or positive association between them (40, 41).

A recent meta-analysis (12 studies with 14,906 participants) analyzed the association between IGFBP3 and risk of cancer, or positive association between them. IGFBP3 was significantly associated with increased risk of breast cancer (42). This meta-analysis included 1411 hypopituitary adults without GH replacement therapy and 289 hypopituitary adults on long-term GH replacement and compared both with the normal population (11). In hypopituitary patients not treated with GH, the overall mortality was increased compared with the normal population and the causes were myocardial infarction, cerebrovascular events and malignancies. The mean age of the patients in whom a malignancy was diagnosed was 64.7 years.

Regarding congenital hypopituitarism, recent findings report prolonged life span in the ‘little people of Krč’ who survive to a very advanced age suggesting that when GH/IGF secretion or action is inhibited humans live longer (51). However, life span in patients suffering from congenital isolated GHD (IGHD) due to GH1 gene deletion (causing complete absence of GH) is reported to be shorter that the general population (males 56 years and females 46 years), with the main cause of death of these patients being heart and infectious diseases (52). Another large retrospective study measured longevity and compared mortality risk in 65 untreated patients with congenital IGHD (patients with a homozygous mutation in the GHRH receptor gene) with their 128 unaffected siblings from 34 families and the general population (53). These authors concluded that the risk of death of patients with congenital IGHD was not different from that of their siblings, and their life span was also not different from that of their siblings or the general population. A report of one confirmed cancer death in an individual with a homozygous mutation in the GHRH receptor gene and one confirmed cancer death observed by us in a 42-year-old female with familial congenital hypopituitarism (not yet reported) shows that the protection against cancer by GHD is not absolute (53).

In summary, cancer risk in hypopituitary patients either of childhood-onset GHD or adult-onset (AO) GHD is complex and may be explained by factors other than hypopituitarism.

Patients with congenital IGF1 deficiency

When discussing the causes of death in 222 congenital IGF1-deficient individuals, no cancer cases were
reported whereas a substantial percentage of family members had cancer, suggesting that the lack of IGF1 protects against cancer (54). In 90 Ecuadorian subjects with mutations in GHR leading to severe IGF1 deficiencies, only one nonlethal malignancy (a papillary serous epithelial tumor of the ovary) was reported in contrast to 17% cancer prevalence in the controls (55). Authors showed by in vitro studies that these GHR-deficient patients display a major reduction in pro-aging signaling. The sera from patients reduced DNA breaks, increased apoptosis in human mammary epithelial cells, and increased insulin sensitivity. These data from GHR-deficient patients are similar to those from GHR-deficient mice that display lower incidence (49%) and delayed occurrence of fatal neoplasms and increased insulin sensitivity (21).

In summary, patients with congenital IGF1 deficiency have a protective effect against developing cancer.

**Hypopituitary patients with GHD replaced with GH**

Quantifying the risk of cancer in relation to GH therapy in GH-deficient patients is even more complex (56). Most data on the safety of GH replacement therapy in humans have been collected in observational and randomized controlled studies. These surveillance studies include all patients that received GH replacement therapy in conditions of routine clinical practice and their follow-up has been long term (57). There are many limitations and pitfalls concerning these observational studies. A significant proportion of the data is from large pharmaceutical-sponsored post-marketing surveillance studies. Although these registries reflect the real-life clinical practice, each study is under the control of its sponsor. The disadvantages are that: they rely on physicians reporting on adverse events and physician evaluation as to whether this is a GH-related event big centers are mostly reporting there are pitfalls in. Other registries are in the methodology of IGF1 measurements, limited duration of follow up and the lack of control group. Nevertheless, the number of patients in these studies is large.

**Hypopituitary children with GHD replaced with GH**

The National Cooperative Growth Study (NCGS) analyzed 54,996 children treated with recombinant human GH and confirmed a favorable overall safety profile with specific populations at potential risk (15). After more than 20 years, leukemia, a major safety issue initially believed to be associated with GH, has not been confirmed. The authors reported no increase in new malignancies or recurrences of CNS tumors in GH-treated children without risk factors. The risk of second malignancies in patients previously treated with irradiation has been detected or confirmed through the NCGS (15). Second tumors were seen in 49 of the ~2500 patients enrolled in the NCGS who had a prior history of malignancy or ~4.6 cases per 1000 patient-years of GH exposure. The dominant risk factor appears to be a prior exposure to radiation. CNS tumors, followed by osteosarcoma, were the most frequently reported second neoplasms. The increased risk of developing second neoplasms in GH-treated childhood cancer survivors is now listed in US labeling for all rhGH products.

**Hypopituitary adults with GHD replaced with GH**

Patients with AO GHD have a decreased life expectancy due to increased mortality from cardiovascular diseases (44). In these patients important changes in cardiovascular risk factors (adverse lipid profile, increased BMI, and hypertension) are reported (58). Reports demonstrate that long-term GH replacement therapy in adults with GHD was not associated with an increase in mortality due to malignancies (11, 59, 60). Importantly, GH replacement therapy was not associated with a higher overall SMR than previously reported (60). Two big observational studies (KIMS and Hypopituitary Control and Complications Study (HypoCCS)) analyzed in particular the incidence of cancer in adults treated with GH therapy. The practice among pediatric and adult endocrinologists is to titrate the GH dose to achieve serum IGF1 concentrations that are perceived as both efficacious and safe: 14,752 patients received GH replacement and were enrolled in the Pfizer International Metabolic Database (KIMS) on March 16, 2010 (61). The majority of these adult patients (58.2%) had not received GH replacement before entry into KIMS. The mean follow-up time for all patients with an entry visit was 4.8 years. Malignant neoplasms have been reported as adverse events in 469 patients in KIMS (274 men and 195 women). The most frequently reported cancer types were skin cancers (including malignant melanoma), which were reported in 49 men and 38 women. The next most frequent cancer types were prostate cancer (77 men) and breast cancer (34 women). The interval between the start of GH therapy in KIMS and the diagnosis of a de novo neoplasm varied (range <1–175 months). A total of 41 patients were diagnosed with a malignant tumor within 6 months of enrolment in KIMS. In summary, this large database with long follow-up of GHD patients treated with GH or non-GH-treated patients showed no evidence of an increased risk of malignancy during GH replacement. In a sub-study from the same database on deaths among 1286 Swedish adult patients with hypopituitarism, all-cause and cause-specific mortality were prospectively monitored (period 1995–2009) and compared with the general population data in the Swedish National Cause of Death Registry (62). In this sub-study an excess mortality was found due to hypocortisolism during.
acute stress and de novo malignant brain tumors. These malignant brain tumors were reported in eight patients (six of which had had a benign pituitary lesion as a primary disease). Six of these eight patients were previously treated with radiotherapy.

In another sub-study from the KIMS database on the association between IGF1, IGFBP2, and IGFBP3 in GHD adults receiving GH therapy and the occurrence of de novo malignancies, no association between IGF1 SDSs and relative risk (RR) of malignancy was found (63). However, increasing IGFBP2 and IGFBP3 SDSs were associated with increasing RRs of malignancy. The authors concluded that IGF1 levels targeted to within normal age-related reference ranges during GH replacement therapy are not associated with the occurrence of malignancies (63). Clinicians target IGF1 to −1.5 to +1.5 IGF1 SDS. Findings regarding IGFBP2 and IGFBP3 levels require additional confirmation. The overall cancer mortality rate in GH-deficient patients treated with GH in a recent KIMS study was not different from that in the general population (60).

Out of 7780 adult hypopituitary patients evaluated in the HypoCCS database (64), 6840 patients were treated with GH and 940 patients were not treated with GH. The mean follow-up time was 3.7 years for GH-treated patients and 2.9 years for non-GH-treated patients. This prospective study reported 142 cancers in GH-treated patients, with an overall standardized incidence ratio of 0.88 (95% CI 0.74–1.04). The most common cancers in GH-treated patients were prostate cancer (n=24), breast cancer (n=16), malignant melanoma (n=15), colorectal cancer (n=11), lung cancer (n=11), thyroid cancer (n=9), and glioma (n=9). These data showed that the incidence of primary cancers in patients with GHD enrolled in HypoCCS who were treated with GH as adults appears similar to that of the general population. A recent published prospective study compared adverse events in 1988 GHD adults who were treated with GH with 443 GHD patients who were not treated with GH in the United States (65). After a mean follow-up time of 2.3 years, the authors did not find any difference in rates of death, cancer, intracranial tumor growth, or recurrence, diabetes, or cardiovascular events in GH-treated compared with untreated patients. The limitation of this study is that the follow-up duration was quite short (3–4 years) to see an effect of a treatment on cancer incidence. In summary, results from two large databases show that the incidence of primary cancers in adult patients with GHD who were treated with GH appears similar to the general population. It is reassuring that there is no association between IGF1 levels and cancer occurrence in adults with GHD treated with GH.

GH excess (acromegaly) and the risk for neoplasms (too much GH/IGF1)

Studies showed that overall mortality in acromegalic patients has increased (66, 67). Mortality is related to post-treatment GH levels in acromegals; as disease control improves mortality decreases. Reduction of GH to <1 μg/l or normalization of serum IGF1 reduces mortality to expected levels (66).

A recent comprehensive literature review of 12 years (1998–2010) confirmed that overall mortality in acromegaly has increased (67). Most deaths among acromegalic patients are attributable to cardiovascular and cerebrovascular diseases (60%), followed by respiratory causes (25%) (67). Cancer-related mortality in these patients did not increase. Cancer-related mortality in acromegaly varies widely amongst retrospective studies. In acromegaly, characterized by sustained elevation of GH and IGF1, some find increased cancer-related mortality while others do not. Orme et al. (68) reported a lower overall cancer incidence rate in 1362 acromegals compared with the general population. Only the colon cancer mortality rate was higher than expected with a standardized mortality ratio (SMR) OR 2.47 (CI 1.31–4.22). Subsequent studies in acromegalic patients suggested that elevated levels of GH/IGF1 may be associated with an increased risk of malignant disease, in particular, colorectal cancer (68, 69, 70, 71). However, a large epidemiological study failed to show higher prevalence of colonic neoplasia in acromegaly (72). Recent findings in acromegals who underwent colonoscopy show only 0.9% having colon cancer (73). Furthermore, newer studies show that colonic epithelial cell proliferation in acromegals correlates with IGF1 but IGF1 does not induce neoplasia (74). An observational study of colorectal cancer in groups of patients with hereditary predisposition (familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer) showed that the prevalence of colorectal cancer increases with age (75).

In a retrospective study we demonstrated an increased frequency of cancers not only in patients with acromegaly but also in patients with nonfunctional pituitary adenoma when compared with the general population, indicating that other factors besides GH/IGF1 might have a possible role in cancerogenesis (47). In summary, it has been proposed that both pituitary adenomas and cancer may have underlying genetic and/or epigenetic instability.

**Risk for pituitary adenoma when cancer was diagnosed in the family**

Other factors besides GH/IGF1 may have a possible role in cancerogenesis (11, 47). It has been proposed that both pituitary adenomas and cancer may share a unifying nonendocrine (genetic and/or epigenetic) etiology (76, 77). Analysis of data from the Swedish Family-Cancer Database (with data on 10.5 million individuals and comprising families with parents and offspring) showed that there is a significant association of pituitary adenomas and some cancers in the family (77).
The Swedish Family-Cancer Database from 1958 to 2002 included 3239 pituitary tumor patients. In this database pituitary adenomas are reported to have a low annual incidence (n = 100), while a total of 50,000 cancers are reported annually in the general population. The results from this study suggest an association of pituitary adenomas with nervous system hemangiopericytoma, breast and colorectal cancers, in addition to some other tumor types (lymphatic leukemia, kidney cancer, skin cancer, and Hodgkin disease) among parents and offspring. Even more interesting are findings reported in a Dutch study on brain magnetic resonance imaging in long-term survivors of breast cancer, in whom contrary to the commonly held opinion that an increased prevalence of meningiomas would be found, increased prevalence of pituitary adenomas was found (78). In summary, both pituitary adenomas and cancer may share a unifying nonendocrine etiology.

Modifiable cancer risk factors: obesity and insulin resistance

As already mentioned, the potential influence of environmental and behavioral factors remains poorly understood. However, recent studies on modifiable cancer risk factors besides smoking describe obesity being responsible for cancer (eating our way to cancer diagnosis). Many hypopituitary patients are obese and insulin resistant (due to obesity and possibly supraphysiological glucocorticoid replacement). GH therapy increases insulin resistance. Obesity and insulin resistance are found to be associated with an increased incidence of solid tissue cancers (colorectal, endometrium, kidney, pancreas, esophagus, postmenopausal breast cancer, and gall bladder) (79). It has been estimated that 15–20% of all cancer deaths in the United States can be attributed to overweight or obesity (80). Those with a BMI ≥ 40 had increased death rates from cancer (52% in men and 62% in women) compared with patients with normal weight. Epidemiological data suggest that obesity is associated with a 30–70% increased risk of colon cancer in men, whereas this association is less consistent in women (81). Obesity might be associated with worse cancer outcomes, such as recurrence of the primary cancer or mortality. Visceral fat (abdominal obesity) is of greater concern than subcutaneous fat (82).

The underlying mechanisms linking obesity to cancer are still not well defined. Hyperinsulinemia, elevated IGF1 level, increased production of estrogens by adipose tissue (due to increased aromatase activity in adipose tissue), decrease of sex steroid-binding globulin (due to reduction in the hepatic synthesis by hyperinsulinemia), altered circulating levels of adipokotines (TNF-α, IL6, IL1, VEGF, leptin, heparin-binding epidermal growth factor-like growth factor (HB-EGF), adiponectin), inflammation and oxidative stress are possibly involved (79).

Recently it has been postulated that increased dietary intake of cholesterol is associated with increased risk of cancer in postmenopausal women. It has been shown that a cholesterol metabolite, 27-hydroxycholesterol, is a potential regulator of estrogen receptor signaling (endogenous selective estrogen receptor modulator) that may act as a partial estrogen agonist in breast cancer cells and influence the pathology of breast cancer (83).

In summary, it is not known whether obesity and insulin resistance found in hypopituitarism are modifiable risk factors for cancer.

Conclusions

There are important distinctions between experimental models and clinical studies in humans when quantifying the risk of cancer in relation to GH. GH therapy has a long track record of efficacy and safety in GH-deficient patients. The risk for developing a malignant disease in adult hypopituitary patients undergoing GH replacement should be studied with longer follow-up periods and in particular in the elderly. For survivors of childhood cancer, some data indicate that GH could induce a slight increase in the risk of developing a second neoplasm in patients with prior radiotherapy (radiotherapy is the main risk factor for secondary neoplasm in GH-treated patients). In general, the results up-to-date are encouraging concerning the risk of cancer occurrence in GH deficient patients treated with GH.

Declarations of interest

V Popovic was on the advisory board of KIMS – Pfizer database and is currently a member of the International Board for Nordinet-Novol Nordisk.

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