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REVIEW ARTICLE

Does growth hormone cause cancer?

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Summary

The ability of GH, via its mediator peptide IGF-1, to influence regulation of cellular growth has been the focus of much interest in recent years. In this review, we will explore the association between GH and cancer. Available experimental data support the suggestion that GH/IGF-1 status may influence neoplastic tissue growth. Extensive epidemiological data exist that also support a link between GH/IGF-1 status and cancer risk. Epidemiological studies of patients with acromegaly indicate an increased risk of colorectal cancer, although risk of other cancers is unproven, and a long-term follow-up study of children deficient in GH treated with pituitary-derived GH has indicated an increased risk of colorectal cancer. Conversely, extensive studies of the outcome of GH replacement in childhood cancer survivors show no evidence of an excess of *de novo* cancers, and more recent surveillance of children and adults treated with GH has revealed no increase in observed cancer risk. However, given the experimental evidence that indicates GH/IGF-1 provides an anti-apoptotic environment that may favour survival of genetically damaged cells, longer-term surveillance is necessary; over many years, even a subtle alteration in the environmental milieu in this direction, although not inducing cancer, could result in acceleration of carcinogenesis. Finally, even if GH/IGF-1 therapy does result in a small increase in cancer risk compared to untreated patients with GH deficiency, it is likely that the eventual risk will be the same as the general population. Such a restoration to normality will need to be balanced against the known morbidity of untreated GH deficiency.

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Introduction

Since its identification, there have been unresolved concerns about the potential cancer-enhancing properties of GH. Circumstantial evidence in support comes from a number of sources: *in vitro* studies, animal studies, epidemiological observations within the general population and patients with GH excess and deficiency, and lastly from therapeutic manipulation of GH and IGF-1 actions. However, evidence supporting the ability of GH to induce cancer per se has been less convincing.

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The GH/IGF-1 axis

In addition to its classical endocrine actions, the GH/IGF-1 axis is increasingly recognized to have important effects at a paracrine and autocrine level.[1] Factors influencing the tissue-specific effects of IGF-1 include not only the density of the type 1 IGF-1 receptor, but also the presence of IGF-1/insulin receptor hybrids and the effects of the various IGF-binding proteins. In addition to regulating the amount of free IGF-1 available, a number of the binding proteins have IGF-1-independent actions of their own which may oppose the effects of IGF-1 itself. Complexity is further added to the system by the presence of various proteases that cleave the ligand from its binding protein. These include prostate-specific antigen (PSA), a protease for IGFBP-3, although it is uncertain whether its increased levels in the serum of patients with prostate carcinoma are causal or as a result of the cancer itself. Finally, local IGF-1 bioactivity is also influenced by tissue architecture and variations in proteoglycans, perhaps as a result of their varying affinities for the different binding proteins.

Actions of IGF-1 in relation to cancer

IGF-1 exerts powerful effects on each of the key stages of cancer development and behaviour: cellular proliferation and apoptosis, angiogenesis and metastasis, and more recently, development of resistance to chemotherapeutic agents.[2,3] It is a potent proliferative agent affecting almost every cell type, an effect predominantly, although not exclusively, mediated via the mitogen-activated protein (MAP) kinase signalling pathway. In addition to these proliferative actions, IGF-1 is also a powerful antiapoptotic agent influencing the apoptotic responses to a variety of agents of numerous cell types. These antiapoptotic actions tend to be mediated via the PI-3 kinase pathway, although this is again not exclusive, and there is considerable cross-talk between the two predominant signalling pathways.

The end results of these opposing effects of IGF-1 may be several-fold. First, there is increased proliferation and thus epithelial cell turnover within tissues. Second, the antiapoptotic effects cause an imbalance in the usual tight control between proliferation and

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cell death and result in hyperproliferation. This is the first stage in the development of many cancers and has been particularly well demonstrated in colorectal tumorigenesis in which it precedes the formation of colonic adenomas. Third, such an imbalance between cell proliferation and death would favour, even slightly, survival of stem cells that had undergone early genetic 'hits'.[4] This would increase the pool of damaged cells available for second and subsequent hits. Higher levels of IGF-1 would be expected to activate survival pathways that would make programmed cell death of damaged cells slightly less probable. When applied overall to a large number of 'at risk' cells over many years, even a small influence in favour of survival of such cells could accelerate carcinogenesis, although not initiate cancer development per se.

Animal studies

More compelling evidence comes from animal studies that have involved manipulation of the GH/IGF-1 axis. Transgenic mice for both human GH and agonists for the IGF-1 receptor show an increased incidence of breast tumour development.[5,6] In contrast, *lit/lit* mice, which are characterized by a nonfunctioning GHRH receptor and thus serum GH and IGF-1 levels approximately 10% that of normal, show almost complete inhibition of growth of transplanted human breast cancer cells.[7] In addition, serum from *lit/lit* mice was less mitogenic to breast cancer cells *in vitro* than control serum, a difference abolished by the addition of IGF-1 to the *lit/lit* serum. Antibodies against the IGF-1 receptor block the *in vivo* growth of subcutaneous breast cancers transplanted into nude mice,[8] and more recent studies have demonstrated mice transfected with the growth hormone receptor antagonist to have a significantly reduced incidence of mammary carcinogenesis.[9] Mechanisms for selective knockout of the hepatic IGF-1 gene, which results in a marked reduction of circulating IGF-1 levels, have recently been developed.[10,11] Not only do these animals provide an elegant model with which to explore the relative contributions of endocrine and paracrine/autocrine IGF-1 effects, but the reduction in circulating IGF-1 is associated with a marked delay in the onset of chemically and genetically induced mammary and colonic tumours.[10,11] It must be remembered, however, that all these models involve variations in IGF-1 levels that are large compared with the more subtle variations in IGF-1 physiology that exists between humans.

In addition to its proliferative and antiapoptotic actions, IGF-I exerts influential effects on the metastatic potential of cancers.[10,12] This is an area of considerable interest in the development of potential chemotherapeutic strategies, as it is the metastatic spread that is ultimately responsible for the mortality of most cancers. Powerful evidence in support of this role was recently demonstrated by Sachdev *et al.*, utilizing the LCC6 metastatic breast cancer cell line.[13] Cells were transfected with a truncated IGF-1 receptor that effectively silenced the expression of the endogenous IGF-1 receptor and thus inhibited IGF-1 mediated signalling. The transfected cells were transplanted into nude mice and subsequent metastatic spread assessed. After 2 months, multiple pulmonary metastases were present in animals transplanted with wild-type cells, whereas these were completely absent in those animals transplanted with the transfected cells.

Epidemiological studies

Childhood growth

Some evidence for a role of GH in carcinogenesis has emerged from normal childhood growth data predicting malignancy in later life. The Boyd–Orr study showed an SD of 1 inch height to be associated with a 42% (95% CI; 5–91%) higher risk of cancer mortality in later life in boys.[14] In this study, no association was found between childhood height and overall cancer mortality in girls. The UK 1946 birth cohort study demonstrated substantially higher risks of breast cancer among women who had been tall at 7 years of age.[15] Peak height velocity (PHV) is difficult to measure, requiring serial measurements of height made regularly over a 5–6-year period. No study has yet directly determined the relationship between PHV and risk of cancer in later life. However, estimated PHV using as a model a function of BMI at the age of 10, age at menarche and final height related to breast cancer risk has demonstrated a linear relationship between PHV and breast cancer.[16] Women who grew fast in adolescence had an approximately 30% increased risk of premenopausal breast cancer and 40% increased risk of postmenopausal breast cancer.

Epidemiological data derived from patterns of growth have also suggested a link with cancer. In a cohort of 117 415 Danish women, high birth weight (7%), high stature at 14 years (15%), low body mass index at 14 years (15%) and peak growth at an early age (9%) were independent risk factors for breast cancer. No effect of adjusting for age at menarche, age at first childbirth and parity was observed.[17]

Final height and cancer risk has been analysed in almost 300 case-control and cohort studies, which have investigated the associations between adult height and the risk of cancer.[18] The most consistent findings were increases in breast cancer by 22% with increased stature (> 175 cm *vs.* < 160 cm); prostate cancer by 20% (> 180 cm *vs.* < 170 cm), and colorectal cancer excess of 20–60% between these two height categories for men and women. Endometrial and haematopoietic cancers were also associated with taller heights but fewer published studies are available. A series of recent studies indicate that leg length is the component of height most strongly associated with cancer.[18]

Although an emerging body of evidence is suggestive of a link between greater height in childhood and adulthood and cancer risk, the putative mechanisms resulting in this association remain unclear and could include sex steroid exposure, increased calorie intake and increased total cellularity. Although these possibilities could all be mediated by IGF-1, it remains the case that no causal link between GH/IGF-1 status and cancer risk has been definitively demonstrated in these cohorts.

Cancer risk in children treated with GH

Is there an increased risk of tumour recurrence?

A specific group of patients at risk of GHD include the long-term survivors of childhood cancers who have received treatment with cranial irradiation either for primary brain tumours, nasopharyngeal carcinoma or acute lymphoblastic leukaemia, or total body irradiation in preparation for bone marrow transplantation.[19] Although

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newer treatment strategies have decreased mortality rates substantially such that the overall 5-year survival rate for childhood cancer is in excess of 70%, survivors are at risk of developing a variety of late complications that are directly attributable to their previous cancer treatment.

Brain tumour recurrence is a frequent cause of death in patients treated with GH,[20] but there is now a moderate amount of information on whether recurrence rates are greater after this treatment than in comparable untreated patients. A large study by Swerdlow and colleagues followed 180 children with brain tumours attending three large hospitals in the UK and treated with GH during 1965–1996, and 891 children with brain tumours who received radiotherapy but not GH in these hospitals.[21] Thirty-five first recurrences occurred in the GH-treated children and 434 in the untreated children. The relative risk of first recurrence in those treated with GH compared with untreated patients, adjusted for potentially confounding prognostic variables, was decreased (0·6; 95% confidence interval (CI), 0·4–0·9), as was the relative risk of mortality (0·5; 95% CI, 0·3–0·8). There was no significant trend in relative risk of recurrence with cumulative time over which GH treatment had been given or with time elapsed since this treatment started. The relative risk of mortality increased significantly with time from the first GH treatment. The results, based on much larger numbers than earlier studies on this subject, suggest that GH does not increase the risk of recurrence of childhood brain tumours. Data from the Childhood Cancer Survivor Study (CCSS) are also consistent with the finding that GH does not increase risk of disease recurrence for both primary brain tumours and acute leukaemias.[22]

However, despite these reassuring data, the rising trend in mortality relative risks with longer follow-up in the Swerdlow study indicates the need for continued surveillance. It is not possible to state with 100% confidence that GH therapy after cancer treatment is absolutely safe and so the need for ongoing surveillance programs continues.

Second malignant neoplasms

A retrospective cohort of 13 581 children, diagnosed with common cancers in 25 USA/Canadian institutes, before the age of 21 years and who had survived at least 5 years demonstrated a statistically significant excess of second malignant neoplasms (SMNs) following all childhood cancers.[23] The effect of GH treatment on incidence of SMNs in such individuals is therefore important to determine as they are a group already at increased risk of malignancy. In 2002, Sklar *et al.*, using a time-dependent Cox model, compared the risk of disease recurrence, SMNs and death in 361 cancer survivors treated with GH (including 172 brain tumour survivors) from among 13 539 survivors enrolled in the CCSS, with survivors who were not treated with GH.[22] The relative risk of disease recurrence was found to be 0·83 (95% CI, 0·37–1·86; $P = 0·65$) for survivors treated with GH. The relative risk of recurrence was not increased for any of the major cancer diagnoses. Subjects treated with GH were diagnosed with 15 SMNs, all solid tumours and no secondary leukaemias, for an overall relative risk of 3·21 (95% CI, 1·88–5·46; $P < 0·0001$). This was mainly caused by a small excess number of SMN observed in survivors of acute leukaemia treated with GH: osteogenic sarcoma in three of the leukaemias/lymphoma survivors treated with GH ($n = 122$) *vs* only two cases in more than 4500 non-GH-treated leukaemia/lymphoma survivors. The risk of death was not associated with GH use ($P = 0·43$). The authors concluded that GH therapy does not appear to increase the risk of disease recurrence or death in survivors of childhood cancer. The increased number of SMN, particularly in survivors of acute leukaemia, is of concern, but the data need to be interpreted with caution, given the small number of events.

Is there an increased risk of de novo cancer with GH therapy?

An initial early report of *de novo* leukaemia occurring in a child with possible Fanconi's anaemia after GH therapy[24] has not been substantiated by extensive long-term follow-up data, relating to GH replacement, from single centres and large multinational databases that have generally found no increase in the overall occurrence of *de novo* neoplasia or the rate of regrowth of primary pituitary tumours.[25–27]

In a study by Swerdlow *et al.*, 1848 patients treated in childhood/early adulthood from 1959 to 1985 with human pituitary GH were followed through for cancer incidence to December 1995 and for mortality through to December 2000[28] Risk of cancer was compared with that in the general population after controlling for age, sex and calendar period. The overall risk of cancer mortality was increased approximately threefold and from colorectal cancer and Hodgkin's disease (HD) approximately 11-fold. The incidence of colorectal cancer was increased approximately eightfold and both incidences and mortality of colorectal cancer, as well as that of HD, were increased even after excluding patients whose original diagnoses gave them higher risk of cancer. However, only two deaths each of colorectal cancer and HD were reported. The relatively small cohort and small number of cases argue for caution in the rush to judgement or conclusion, but again indicate the need for on-going long-term large surveillance programs.

The existing data available in paediatrics do not support the notion of an excess of malignancy after GH treatment. In the two largest international databases and surveillance studies, with a total of some 86 000 patients on GH, representing almost 250 000 GH treatment years, there is only one report of a gastrointestinal carcinoma – an adenocarcinoma in a 15-year-old girl initially treated by radiotherapy and chemotherapy for a brain tumour (astrocytoma). She developed gastrointestinal bleeding 3·5 years after the start of GH therapy when the tumour was diagnosed. There is also a report of spontaneous colon cancer in a girl with Turner's syndrome many years after discontinuation of GH therapy.[29] Similar reassuring data are available in adults with the largest database, showing no significant increase in cancer incidence in the approximately 8000 patients treated for a total of 27 000 patient years.[27] However, the average duration of follow-up on GH treatment is only 4 years and longer-term surveillance is clearly needed. Furthermore, none of the surveillance groups has an adequate control group of untreated patients. However, given that GH is administered, certainly in adults, as a replacement therapy, with the aim being restoration of GH and IGF-1 levels to within age-matched normal ranges, clarification is needed as to which reference population cancer risk is being compared. One can imagine that long-term surveillance studies might indicate cancer incidence to be increased in patients with GHD treated with GH, but that this is likely to be a similar risk level as the general population

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and thus overall cancer risk will not be increased. Any risk analysis needs to take into account the overall benefits of GH compared to the proven morbidity associated with untreated GHD. In contrast with the use of GH for replacement purposes, there is much more concern regarding the unlicensed usage of rGH in both the elderly and normal adults for its anabolic effects and as an 'elixir of youth'. In these subjects, IGF-1 levels are often elevated above the normal range with consequent distortion of normal physiology.

Epidemiological studies in the general population

Considerable epidemiological data have suggested a possible link between circulating GH and/or IGF-1 levels and the development of a variety of different cancers. More than 20 years ago, Emerman *et al.* observed that women with breast cancer had elevated serum GH levels[30] and subsequently it was noted that patients with breast and prostate cancer had increased circulating IGF-1 levels.[31] However, these studies were limited by the potential influence of the cancer itself on the GH/IGF-1 axis or by the possible secretion of IGF-1 by the cancer. The more recent results from a number of prospective studies would appear to overcome these limitations.[10,32–35] Serum had been stored from large cohorts of subjects and IGF-1 and IGFBP-3 levels measured many years later in those subjects who had developed a cancer, and comparison made with a control group of subjects. Many of these studies have suggested that subjects with serum IGF-1 levels that are in the higher centiles of the normal range have a significantly increased risk of developing a number of the most common cancers, such as colon, breast, prostate and possibly lung. Indeed, it has been suggested that serum IGF-1 levels have a stronger association than most other risk factors for these cancers.[36] However, not all studies have shown this association, with one study reporting increased levels of IGFBP-3 in patients with colorectal cancer.[37] Certainly, causality has not yet been established and elevated serum IGF-1 levels in patients with cancer may simply be a surrogate measure of some other process. In order to clarify this issue, Renehan *et al.* recently performed a systematic review and meta-regression analysis of epidemiological case-control studies, including studies nested in cohorts, to investigate the association between concentrations of IGF-1 and IGFBP-3 and prostate, colorectal, premenopausal and postmenopausal breast and lung cancer.[38] The studies included in this analysis had to be published as full article findings expressed as odds ratios with 95% CI and reported an association for at least three categories of peptide concentration. Methodological quality was assessed by the use of published criteria for observational studies. Of 139 relevant publications identified, 21 (26 data sets) had outcome data appropriate for meta-analysis that included 3609 cases and 7137 controls.

High normal concentrations of IGF-1 were associated with a two-fold increased risk of prostate cancer ($P = 0{\cdot}009$), colorectal cancer ($P = 0{\cdot}09$) and premenopausal breast cancer ($P = 0{\cdot}007$) but not postmenopausal breast cancer or lung cancer. IGFBP-3 was associated positively with an increased risk of premenopausal breast cancer ($P = 0{\cdot}05$). Mutual adjustment for IGF-1 and IGFBP-3 did not appear to affect results. The data confirm an undisputed link between IGF-1 and cancer. Whereas it is appreciated that IGFBP-3 influences IGF-1 bioactivity both by endocrine and by paracrine actions, and it also exerts IGF-independent effects on cell proliferation and apoptosis,[39,40] the link between IGFBP-3 levels and cancer risk is less clear cut.

Acromegaly

One of the more controversial issues in the GH and cancer debate is that which relates to cancer risk in patients with acromegaly. Several retrospective studies have reported a variety of cancers in these patients (reviewed in reference 41), although others suggest the risk is actually lower than would be expected within the general population.[42,43] However, older reviews are limited by the use of mortality data from more than 50 years ago and will not reflect the current morbidity of patients with acromegaly that have been subjected to modern therapeutic strategies. Regardless, there appears to be general consensus that these patients are at increased risk of colorectal cancer, although there is on-going debate as to the exact extent of this risk. A summary of 14 prospective colonoscopic screening studies, involving more than 800 patients, suggests a 7·6-fold increased risk of colorectal cancer, compared to matched control subjects.[41] Other workers suggest the risk is considerably lower at approximately twofold.[42]

The risk of premalignant colonic adenomas is also controversial. The majority of clinical observations demonstrate an increased prevalence and suggest that these colonic adenomas behave more aggressively with an increased tendency for malignant progression,[44] but Renehan *et al.*, using other control groups, made a case that adenoma prevalence rates were not increased.[45] Importantly, the relation of this neoplasia to IGF-1 was clarified by a prospective study involving a second colonoscopic evaluation of more than 100 patients at intervals after the original screening examination, when all visible polyps had been removed.[46] The occurrence of new adenomas was significantly related to both serum GH and IGF-1 levels and patients who had IGF-1 levels above the normal range had a 4·5-fold increased risk of developing a new adenoma compared to patients in whom disease activity was controlled. Previous work has also shown the colonic epithelium of patients with acromegaly to be characterized by increased proliferation, which is proportional to serum IGF-1 levels.[47]

Whether the prevalence of other cancers in acromegaly is increased remains unproven. Orme *et al.* reported the mortality from breast cancer to be increased, although this did not reach statistical significance[48] and an early retrospective review suggested the incidence but not mortality from this disease was increased fourfold.[49] The rarity of this condition and the consequent small number of patients in these studies makes it difficult to determine the true incidence of cancer in acromegaly.

Therapeutic manipulation of the GH/IGF-1 axis

Given the evidence to support an important role for GH and/or IGF-1 in the development and behaviour of cancers, there is increasing interest in the manipulation of this axis as a therapeutic manoeuvre. Several strategies are currently being employed to inhibit IGF-1 signalling: monoclonal antibodies against the IGF-1R inhibit breast cancer proliferation *in vitro* and block the mitogenic effects of exogeneous IGF-I.[8] This blockade also inhibits the *in vivo* growth of oestrogen-independent breast cancer cells.[8] Dominant negative mutants

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of the IGF-1 receptor suppress adhesion and invasion of breast cancer cell lines.[50] Antisense RNA directed against the IGF-1R inhibits colon cancer growth *in vivo*.[51] Selective inhibitors of the IGF-1R also inhibit proliferation and enhance apoptosis by increasing the response of tumour cells to ionizing radiation.[52] However, there remains concern as to how these peptides might function in the clinical setting in terms of cross-reactivity with the insulin receptor. The availability of pegvisomant, the growth hormone receptor antagonist, has given further impetus to this novel chemotherapeutic avenue.[53,54] In animal models of metastatic colon cancer, pegvisomant, in combination with conventional chemotherapy, virtually abolishes metastatic disease.[54]

Conclusions

Convincing experimental data suggest that the GH/IGF-1 axis plays an important role in cancer development and behaviour. Epidemiological studies have supported an association with cancer, but not with tumour induction per se, although this is a distinction that is important mechanistically but not clinically. Acromegaly is associated with an increased risk of colorectal cancer; the magnitude of the risk is controversial but appears linked to elevated GH/IGF-1 levels. The relevance to physiological replacement in patients with GHD is uncertain. Extensive study of cancer survivors treated with GH has failed to demonstrate an increase in tumour recurrence and *de novo* cancers but a small increase in second malignant neoplasms. One long-term follow-up study of children treated with human pituitary GH suggested an increase in colorectal cancer and lymphoma,[31] but surveillance data from many thousands of children and adults treated with GH have not shown any increase in cancer risk.[32] However, it is prudent for further long-term surveillance to continue. Existing experimental data have shown the proliferative and anti-apoptotic effects of IGF-1, which would provide an environment that favours survival of genetically damaged cells. Even if such an environment had only a small influence on survival of such damaged cells, exposure to a large number of 'at risk' cells over many years, although not inducing cancer, could serve to accelerate carcinogenesis.

Finally, even if GH/IGF-1 therapy does result in a small increase in cancer risk compared with untreated patients with GH deficiency, it is likely that the eventual risk will be the same as the general population. Such a restoration to normality will need to be balanced against the known increased morbidity of untreated GH deficiency. However, these *in vitro* effects countenance strongly against the use of rGH or rhIGF-I as an 'elixir of youth' in adults with an intact GH/IGF-I axis.

Conflict of Interest

PJJ and SMS have received unconditional research support from pharmaceutical companies that manufacture rGH. The views expressed in this review are, entirely and without reservation, those of the authors and are not influenced by any funding support.

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