The question of a link between insulin-like growth factor physiology and neoplasia

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Summary The results of both population and laboratory studies suggest that the physiology of insulin-like growth factors (IGFs) has important influences on cancer biology and cancer risk. This review highlights recent laboratory and epidemiological results in this rapidly evolving area of investigation. There is no direct evidence to suggest that growth hormone (GH) treatment of GH-deficient patients increases their risk of neoplasia, but recent research reinforces the need for careful surveillance. The monitoring of serum IGF-I levels may be advisable to help avoid inadvertent over-treatment, particularly in individuals undergoing long-term GH replacement therapy.

Key words: Cancer biology, cancer risk, epidemiology, growth hormone, insulin-like growth factor I.

INTRODUCTION

Converging data from population studies and laboratory studies suggest that the physiology of insulin-like growth factors (IGFs) has important influences on cancer biology and cancer risk. This review will highlight recent laboratory and epidemiological results in this rapidly evolving area of investigation.

CANCER RISK AND CARCINOGENESIS

Population studies are providing evidence for a relationship between circulating levels of both IGF-I and IGF-binding protein-3 (IGFBP-3) (but not IGF-II) and the risk of several common epithelial cancers, including those of the breast, prostate and colon[1–7]. Although this relationship needs to be confirmed and described in more detail, recent data suggest that IGF-I is positively related to risk and that IGFBP-3 is negatively related to risk, despite the well-known fact that there is a positive correlation between these two analytes. This finding:

- suggests that there is biological significance to inter-individual variability in IGF-I and IGFBP-3 levels,
- focuses attention on individuals who have unusual IGF-I:IGFBP-3 ratios (i.e. outliers on plots of IGF-I levels vs IGFBP-3 levels),
- motivates further research to better understand the genetic[8] and lifestyle[9–11] factors that modulate the relative concentrations of IGF-I and IGFBP-3 in serum,
- challenges us to understand the biology that links circulating peptide hormone levels to cancer risk[1–7].

Data on growth hormone (GH) and cancer risk also need to be reviewed in light of a prospective study that found a higher rate of mortality from cancer among Parisian policemen with high serum GH levels measured following a 75-g glucose load than among those with relatively low GH responses[12].

Overall, the magnitude of relative risk (RR) associated with high IGF-I levels or high IGF-I:IGFBP-3 ratios appears modest (approximately two- to four-fold) compared with the enormous RRs (greater than 10-fold) associated with the rare germ-line mutations that predispose to cancer. It has been pointed out, however, that the

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overall cancer burden attributable to risk factors that are modest in magnitude but are common may exceed the cancer burden attributable to factors associated with enormous risk but which are rare.

Although there is accumulating evidence that high IGF-I levels are related to an increased risk of cancer, advanced cancers are often associated with the very low IGF-I levels seen in malnourishment and/or cachexia. Thus, the need for prospective rather than retrospective studies in this area is clear.

Carcinogenesis does not take place in the circulation. Therefore, it seems clear that circulating IGF-I levels are not directly responsible for an increased risk of cancer but rather are surrogates for another biological variable that is a risk determinant. We hypothesize that circulating IGF-I may be positively related to tissue IGF bioactivity, that IGFBP-3 may be negatively related to tissue IGF bioactivity and that tissue IGF bioactivity may be a determinant of the turnover rate of epithelial cell populations. Thus, the excess cancer risk in individuals with higher IGF-I:IGFBP-3 ratios may be related to subtle differences in cell renewal kinetics[13] that result, over decades, in billions of extra divisions in the epithelial tissues of such people. Recent results suggest that serum levels of IGF-I may not be determinants of tissue bioactivity but rather may vary in parallel with autocrine or paracrine expression within tissues[14].

Although studies linking circulating peptide levels to epithelial cell renewal rate and cancer risk have just begun, the results to date are compatible with our hypothesis[15,16]. Our model would predict an interaction between IGF-related cancer risk and classic risk factors, including, for example, carcinogenic exposure and hereditary predisposition. Early data[17] are consistent with this prediction, and this area is of high priority for further research. Recent work describing relationships between IGF serum levels and mammographic density[18] raises the possibility that IGF biology may underlie certain previously described risk factors.

We further hypothesize that epithelial cell renewal dynamics may play yet another role in increasing the risk of cancer in individuals with higher IGF bioactivity. In the multistep process of the accumulation of somatic cell mutations leading to full transformation, the survival of partially transformed clones with one or a few mutational hits is a critical factor in carcinogenesis. Normal cells, and presumably most partially transformed cells, undergo apoptosis. Given the well-known anti-apoptotic actions of IGFs, the survival probability of such clones may be slightly higher in a host with slightly more IGF bioactivity, which would increase the pool of "target" cells available for second or subsequent hits.

CANCER PATHOPHYSIOLOGY AT THE CELLULAR LEVEL

In the previous section, we speculated regarding differences in "whole organism" physiology that may link circulating IGF-I and IGFBP-3 levels to an individual's cancer risk. IGFs may also, however, be involved in the cellular pathophysiology related to neoplastic progression. For example, the single most overexpressed gene in colorectal cancer, relative to normal colonic epithelial cells, is the gene encoding IGF-II[19]. Once this kind of derangement occurs, it is likely that variability between individuals with respect to IGF-I levels becomes completely irrelevant. Thus, it is conceivable that serum IGF-I levels may be related to cancer risk, but not to cancer behaviour or prognosis, which would depend more on the presence or absence of derangements of the cellular physiology of IGFs or other growth factors. Loss of the IGF-independent growth inhibitory actions of IGFBPs and/or IGFBP-related proteins may also contribute to neoplastic progression[20,21].

CANCER TREATMENT AND PREVENTION

It is interesting that many current and investigational cancer treatment and prevention strategies involve IGF physiology. Examples include anti-oestrogens[22–24], anti-androgens[25], castration[26–28] and vitamin D analogues[29,30], all of which up-regulate *IGFBP-3* and/or *IGFBP-5* gene expression in responding tissues. However, a cause-and-effect relationship between therapeutic action and these changes in gene expression has by no means been established.

Current therapeutic approaches being investigated include targeting the IGF-I receptor[31,32] and reducing GH output pharmacologically[33,34]. *In vivo* tumour model studies using relatively crude approaches, such as lowering IGF-I levels (but also IGFBP-3 levels) with somatostatin analogues or GH-releasing hormone (GHRH) antagonists, have produced encouraging results[34,35]. However, the results of initial controlled clinical trials in the treatment of advanced metastatic cancer have been disappointing[36]. Large ongoing trials are examining this approach in a different clinical setting—the post-surgical control of micrometastatic cancer.

If further data confirm a relationship between IGF-I levels and cancer risk, then it may prove worthwhile to evaluate the hypothesis that the risk of cancer will be decreased by interventions that reduce serum IGF-I concentrations (and perhaps tissue bioactivity) toward the lower end of the "normal" distribution. This hypothesis is now being studied in animal models. Although it seems unlikely that this kind of prevention strategy would be

applicable to unselected populations, it is conceivable that such strategies could deserve study in particular patient groups (e.g. those with the top decile of IGF-I levels, those with high IGF-I:IGFBP-3 ratios, or patients with either of these factors *plus* a history of carcinogen exposure or a family history of cancer). Potential agents in this regard include GH antagonists, somatostatin analogues and GHRH antagonists.

It will also be of interest to test the possibility that reduction in IGF-I serum levels may represent a useful "intermediate end point" in chemoprevention trials with compounds such as tamoxifen or retinoids[22,37]. Both tamoxifen and fenretinide reduce circulating IGF-I levels to varying degrees in different individuals, but it remains to be determined if this effect correlates with chemopreventative action.

GH THERAPY

Frank GH deficiency (GHD) is a clear indication for GH replacement therapy; however, despite considerable research, the use of GH in other non-GHD applications, including "somatopause", remains controversial[38]. Risk–benefit analysis is required[39]. Future studies in this area will have to be designed in a rigorous manner. Whereas GH therapy in older men in general may be hard to justify from a risk–benefit perspective, there may be important subsets of the elderly population (perhaps those with the lowest decile of IGF-I levels) who benefit objectively. For other patient subsets, "replacement" therapy might be without benefit or might even be hazardous.

There is no direct evidence to suggest that GH therapy in GHD increases the risk of neoplasia, but prudent practice suggests the need for careful surveillance. On theoretical grounds, prolonged treatment with GH (given over decades) that achieves IGF-I levels substantially higher than age-specific norms may elevate the risk of neoplasia. As no cohorts of patients have been followed for prolonged periods, such a long-term hazard cannot be ruled out at present. It should be noted, however, that GH therapy raises both IGF-I levels and IGFBP-3 levels, and in epidemiological studies, IGFBP-3 has been shown to attenuate risk to a certain extent. Nevertheless, it would seem prudent to avoid unnecessarily high GH doses and IGF-I levels in patients in whom GH therapy is indicated. The monitoring of serum IGF-I levels may be wise, particularly in individuals undergoing long-term replacement therapy. Whereas clinical end points may be important in selecting an optimum dose for a particular patient, the monitoring of IGF-I levels may help clinicians to avoid an inadvertent "over-correction" of GHD.

A retrospective study of patients with hypopituitarism diagnosed between 1956 and 1987 provides evidence of increased mortality related to cardiovascular disease yet decreased mortality related to cancer associated with the deficiency state[40]. These results, together with the biological issues reviewed above, indicate the need for rigour in defining indications, dosage and duration of GH therapy. Under-treatment must be avoided, but as in other areas of medicine, it is likely that over-treatment is not without risks.

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