



Insulin-like growth factor physiology and cancer risk

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Abstract

In the past few years, both laboratory investigations and population studies have provided strong circumstantial evidence that insulin-like growth factor (IGF) physiology influences cancer risk. In contrast to the influence of germ line mutations that are rare but are associated with very high risks, the impact of inter-individual variability in IGF physiology on risk appears to be modest but to effect a relatively high percentage of the population. Although this field of investigation is young, attention is already being given to the possibility that it may be relevant to clinical assessment of risk and/or to the identification of novel prevention strategies and intermediate endpoints. This review summarises key results in this field and provides a hypothesis concerning the mechanism by which IGF physiology influences risk of common epithelial cancers including those of breast, prostate, lung and colon. © 2000 Published by Elsevier Science Ltd. All rights reserved.

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1. Introduction

Insulin-like growth factors (IGFs) are potent mitogenic and anti-apoptotic molecules involved in the regulation of cell proliferation in renewing epithelial cell populations of organs including breast, prostate, colon and lung. Unlike many other regulatory peptides, IGFs have characteristics of both classic ‘endocrine’ hormones and also characteristics of tissue growth factors. IGF physiology has been the subject of several recent reviews [1,2]. Circulating levels are subject to complex physiological regulation. The vast majority of circulating IGFs are bound to high affinity IGF binding proteins (IGFBPs), with >90% bound to a high molecular weight complex comprised of IGF binding protein 3 (IGFBP-3) and a separate protein known as the acid-labile subunit. However, IGF bioactivity in tissues is not merely a function of circulating levels: local expression of genes encoding IGFs, IGFBPs and proteases that digest IGFBPs are at least as important as circulating levels in determining the IGF bioactivity in a given tissue. Whilst IGFBP-3 functions as a carrier

protein in the circulation, this molecule as well as other IGFBPs are also found in the extra-vascular tissue compartment, where they appear to have separate roles, generally as growth inhibitors [2].

It is important to recognise that there is considerable heterogeneity between normal individuals with respect to IGF-I and IGFBP-3 levels. In the past, endocrinologists defined the relatively rare disease states of hypopituitarism (associated with IGF-I deficiency) and acromegaly (associated with IGF-I excess), but did not investigate in depth the possibility of physiological significance of variability between individuals within the broad ‘normal’ range between these extremes. More recent studies have confirmed the inter-individual variation, and have begun to investigate the genetic and non-genetic determinants of IGF-I and IGFBP-3 plasma levels [3–5].

Converging data from recent population studies and laboratory studies (see below) suggest that IGF physiology has important influences on cancer biology, cancer risk and carcinogenesis. This convergence of data from different disciplines has generated considerable interest. However, it must be emphasised that this is a relatively novel topic in the IGF field, and in many cases additional studies are needed to confirm initial observations and determine their significance.

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2. Population studies

Population studies are providing evidence for a relationship between circulating levels of both insulin-like growth factor (IGF)-I and IGF binding protein 3 (IGFBP-3) (but not IGF-II) and the risk of several common cancers, including premenopausal breast cancer, colon cancer, prostate cancer and lung cancer [6–13]. In general, the data to date suggest that plasma IGF-I is positively related to risk, and plasma IGFBP-3 is negatively related to risk. Overall, the magnitude of risk associated with high IGF-I levels or high IGF-I/IGFBP-3 ratios appears modest (RR ~2 to 4-fold) compared with the enormous relative risks associated with the rare germ line mutations that predispose to cancer. However, it has been pointed out that the overall cancer burden attributable to risk factors that are modest in magnitude but common in the population may exceed that attributable to factors that are associated with enormous risk, but are rare.

The evidence that cancer risk is positively correlated with IGF-I level and negatively correlated with IGFBP-3 level is somewhat peculiar, as it is well known that there is a positive correlation between these two analytes. This, (1) suggests that there may be a biological significance to the heterogeneity between individuals with respect to IGF-I and IGFBP-3 levels within the broad ‘normal’ ranges between acromegaly and growth hormone deficiency, (2) focuses attention on individuals who have unusual IGF-I to IGFBP-3 ratios (outliers on plots of IGF-I versus IGFBP-3), (3) motivates further research to better understand the genetic [3] and lifestyle [5,14,15] factors that influence the relative concentrations of IGF-I and IGFBP-3 in serum and (4) challenges us to understand the biology linking circulating peptide hormone levels to the risk of several common epithelial cancers, including breast, prostate, lung and colon [6–13]. Data for growth hormone (GH) and cancer risk also need review in light of a prospective study showing a higher cancer mortality in Parisian policemen with high serum GH following a 75 g glucose load [16].

While there is accumulating evidence that high IGF-I levels are related to increased risk, advanced cancers are often associated with very low IGF-I levels that have long been recognised to be associated with malnourishment and/or cachexia. The hypothesis supported by recent studies [6–13] is that individuals with higher IGF-I levels (or higher IGF-I/IGFBP-3 ratios) have a modestly elevated predisposition to cancer relative to individuals with low levels. Nevertheless, after a diagnosis of cancer, and particularly in the setting of advanced disease with poor nutrition, circulating levels of IGF-I generally fall. Thus, the need for prospective studies in this field of research is clear.

3. Hypothesised mechanism underlying IGF-related risk

Carcinogenesis does not take place in the circulation, so it seems clear that circulating levels are not directly responsible for risk, but rather are surrogates for another biological variable that is a risk determinant. We hypothesise 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 [17,18] that result, over decades, in billions of extra divisions in epithelial tissues of those people with higher ratios. Recent results suggest that serum levels may not be determinants of tissue bioactivity but rather may vary in parallel with autocrine or paracrine expression within tissues [19]. Although studies linking circulating peptide levels to epithelial cell renewal rate and cancer risk have just begun, results are compatible with our hypothesis [20,21]. Our model would predict an interaction between IGF-related risk and classic risk factors, including carcinogenic exposure, germ line mutations predisposing to cancer (e.g. *BRC1*), etc. Early data [22] are consistent with this prediction and this is a high priority area for further research. Recent work describing relationships between IGF serum levels and mammographic density [23] raises the possibility that IGF biology may underlie certain previously described risk factors.

We further hypothesise that individuals with a higher IGF bioactivity may be at increased risk for another reason related to epithelial cell renewal dynamics. In the multistep process of an accumulation of ‘hits’ leading to full transformation, survival of partially transformed clones with one or a few hits is critical for carcinogenesis to proceed. 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. This would increase the pool of ‘target’ cells available for second or subsequent hits.

One prediction of the above hypothesis is that controlling for confounding factors, individuals with neoplasms would have a higher turnover rate of epithelial cells in their normal tissues than individuals without cancers. Data compatible with this prediction have been reported for colon cancer. Several studies [24–28] have shown a significantly higher turnover rate in the normal colonic mucosa (at a distance from resected cancers) of individuals with colon cancer than in the normal colonic mucosa of individuals without colon cancer. IGF levels were not measured in these studies (which were motivated,

in part, by hypotheses related to the influences of bile acids on proliferation and risk), but ongoing research is being undertaken to determine if circulating and/or tissue IGF-I levels can be related to turnover rate in colonic mucosa. One important study [29] involving patients with acromegaly did document a correlation between colonic mucosa labelling index and serum IGF-I levels.

The inhibitory effect of starvation on experimental rodent carcinogenesis is well known. Starvation is associated with reduced IGF-I levels, and some have speculated that this may be an adaptive physiological response to minimise nutrient consumption related to cell turnover. A recent study [14] provides support for the hypothesis that the inhibitory effect of starvation on experimental rodent carcinogenesis is in fact mediated by the starvation-related IGF-I suppression, as carcinogenesis was restored in diet-restricted rodents who received IGF-I supplementation.

Cancer pathophysiology at the cellular level represents an entirely different 'playing field'. Above, we speculated regarding differences between individuals in 'whole organism' physiology that may link circulating IGF-I and IGFBP-3 levels to cancer risk. IGFs may also 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 *IGF-II* [30]. Once this kind of derangement occurs, it is likely that variability between individuals with respect to IGF-I levels becomes completely irrelevant. It is thus, 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 disruptions in the cellular physiology of IGFs or other growth factors. Loss of IGF-independent growth inhibitory actions of IGFBPs and/or IGFBP related proteins may contribute to neoplastic progression [31,32].

4. Cancer treatment and prevention

It is interesting that many current and investigational cancer treatment and prevention strategies impact IGF physiology. Examples include anti-oestrogens [33,34], antiandrogens [35], castration [36–38] and vitamin D analogues [39,40]. These all upregulate IGF binding protein expression in responding tissues, but a cause-and-effect relationship between therapeutic action and these changes in gene expression has by no means been established. Current therapeutic approaches that are being investigated include targeting the IGF-I receptor [41,42], and reducing growth hormone output pharmacologically [43,44]. *In vivo* tumour model studies using relatively crude approaches such as lowering IGF-I levels (but also IGFBP-3 levels) with somatostatin analogues or growth hormone-releasing hormone (GHRH)

antagonists were encouraging [44,45]. However, initial controlled clinical trials in advanced metastatic cancer have been disappointing [46]. 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, the hypothesis that interventions that reduce serum concentrations (and perhaps tissue bioactivity) towards the lower end of the 'normal' distribution will reduce risk may deserve evaluation. This is now being studied in animal models. Whilst it seems unlikely that this kind of prevention strategy would be applicable to unselected populations, it is conceivable that it could deserve study for particular groups (e.g. those in the top decile of IGF-I or with high IGF-I/IGFBP-3 ratios, or with these plus a history of carcinogen exposure or a family history of cancer).

It will be of interest to examine the possibility that the reduction of IGF-I serum levels represents a useful 'intermediate endpoint' in chemoprevention trials with compounds such as tamoxifen [47]. It is intriguing that anti-oestrogens, which reduce or at least delay breast cancer [48], reduce IGF-I levels [47] and upregulate IGFBP-3 [33], particularly in the context of data that IGF-I levels have been positively correlated with breast cancer risk [6]. IGF-I levels have also been reported to be positively related to high mammographic density, which is known to be related to increased risk [23]. Furthermore, retinoids, which may have preventative activity for premenopausal breast cancer [49], also downregulate IGF-I levels and upregulate IGFBP-3 levels [50]. A recent study provides evidence that lower expression of transforming growth factor (TGF) beta in the breast is associated with increased breast cancer risk [51]. In this context, it is intriguing that IGF-I has been shown to suppress TGF beta expression in the mammary gland of experimental animals [52].

Taken together, recent results provide interesting circumstantial evidence that IGF physiology plays a role in determining cancer risk, and justify ongoing multidisciplinary research in this area. It remains possible that regulatory molecules in the IGF regulatory system will be found to be important molecular targets for novel cancer prevention strategies.

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