Insulin-like growth factor-I and new opportunities for cancer prevention

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The growth hormone (GH) and insulin-like growth factor-I (IGF-I) axis plays a large part in regulating fetal and childhood somatic growth, and there is substantial evidence that it also could be critical in maintaining neoplastic growth. It may also be an important determinant of cancer incidence, as suggested by the report in today's *Lancet* of a strong association between circulating IGF-I concentrations and the relative risk of breast cancer in premenopausal women. A similar association has been reported for prostate cancer.[1] The value of the studies identifying these associations derives from their prospective nature. The GH/IGF-I axis is known to be perturbed in patients with cancer, but the changes are most likely to be a consequence of the cancer. That circulating IGF-I, measured long before presentation, is so strongly associated with the risk of breast and prostate cancers, raises important questions about the cause of these diseases and strategies for risk assessment and reduction.

The development of biosynthetic GH enabled the hormone to be given therapeutically. Prescription was initially restricted to children with GH deficiency, with treatment being given for a few years to improve longitudinal growth. After studies indicating benefits for some adults with GH deficiency[2] and the recommendation that therapy be extended throughout adult life, the market for GH expanded greatly. Administration of GH for more general indications has also been advocated, either for its systemic effects in catabolic disorders, or for local effects, such as in chronic heart failure.[3] In addition to licensed applications, abuse of both GH and IGF-I by athletes and body-builders is widespread.

Endocrinologists have argued that raising GH concentrations is safe because acromegaly carries no increased risk of other cancers. A recent large survey of patients with acromegaly has, however, revealed significant increases in the incidence of colorectal and breast cancers.[4] The reports linking IGF-I with breast and prostate cancers indicate that the association between cancer risk and IGF-I concentrations is strengthened if these concentrations are adjusted for the amount of its main carrier protein (IGFBP-3). Patients with high IGF-I and low IGFBP-3 concentrations incur the greatest risk. In many adults with GH deficiency, circulating IGF-I concentrations are not low and may be raised to the higher end of the normal range or beyond by GH administration,[2] but in these patients and in acromegalic patients there are also increases in IGFBP-3 concentrations. IGFBP-3 may have a protective effect and account for the relatively lower incidence of breast and prostate cancers in patients with acromegaly; furthermore, it may imply that the risk of these cancers from GH therapy is limited. At this stage there are, however, new unanswered questions, and more work is required to establish the extent of any risk. Extensive world-wide experience of GH use in children indicates no increase in cancers; but prostate and breast cancers do not normally present until after puberty and much longer follow-up may be required than hitherto foreseen.

Actions of IGF-I

- Promotes
  - local tissue and somatic growth
  - cell metabolism
  - cell survival (anti-apoptotic effect)
- Amplifies local actions of trophic hormones (eg, amplifies actions of gonadotropins)

What could be the biological mechanism behind such strong associations? Both breast and prostate are sex-steroid-dependent tissues. IGF-I is a powerful amplifier of gonadotropin action, enhancing the production of gonadal steroids. In addition, gonadal steroids modulate the GH/IGF-I axis at several points. The association could therefore be due to overall sex-steroid activity as reflected by IGF-I concentrations. Estimates of the relative risk of cancer associated with marked perturbations in sex-steroid status—for example, the relative risk of breast cancer (1·0–2·0) associated with contraceptive use or hormone-replacement therapy—have, however, been much lower than those reported for circulating IGF-I and breast (7·28) and prostate cancers (4·3). These differences suggest that IGF-I is not merely reflecting sex-steroid status. The proliferative effects of sex-steroids on the breast and prostate are now thought to be mediated by local growth factors: additional IGF-I from the circulation could potentiate these effects. Hyperplasia of the breast after GH or IGF-I administration to primates,[5] and of the prostate in young men with acromegaly,[6] have been described. Greater cell turnover in these tissues could increase disposition to neoplastic transformation. Although these potential mechanisms are plausible, a more powerful argument has arisen from work showing that IGF-I is critical for cell survival and for maintenance of transformed cells.[7]

Most human tumours develop by a multistep process in which cells acquire growth advantage by genetic damage involving an accumulation of mutations. Frequent gene mutations undoubtedly occur spontaneously throughout life, and such events increase with exogenous mutagens. The body, however, has sophisticated defence mechanisms to delete such damaged cells. Genetic damage is detected by internal checks that direct the cell to "commit suicide" in an ordered manner, a process called apoptosis. Apoptosis can be prevented by external "survival" signals, of which IGF-I seems to be the most abundant and the most potent for many cell types.[8] Its main carrier protein, IGFBP-3, is not only important for determining IGF-I availability, but recent evidence indicates that it also has intrinsic IGF-independent apoptosis-promoting actions on prostate[9] and breast[10] epithelial cells. Complexes of IGF-I and IGFBP-3 are abundant throughout the body, and the balance between their survival and death signals may establish a "defence" threshold that determines the extent to which damaged cells may survive to accumulate mutations and develop into a tumour. Tamoxifen has several effects on the IGF system that are consistent with a shift in the balance between IGF-I and IGFBP-3 that results in a reduction in this survival threshold.[11] Preliminary data from the prophylactic intervention trial of tamoxifen in the USA indicate that the drug might reduce breast-cancer incidence by 45%. The level at which such defences are set may therefore be as, if not more, critical than the initial mutations for the incidence of cancers. The implication is that measurement of IGF-I may be of value for identifying individuals at high risk

of cancer so that they can be given new prophylactic measures against cancer.

Other than smoking-related cancers and familial cancers, which account for a very small proportion of breast and prostate tumours, the recent prospective epidemiological studies suggest that circulating IGF-I concentrations are associated with greater relative risk for major common cancers than any other factor yet described. Other epidemiological findings link birthweight[12] and early childhood nutrition[13] with cancer risk later in life. Nutritional intake is a strong determinant of IGF-I concentration, which then controls somatic growth. Nutrition in early life may therefore have a "programming" effect, via IGF-I, that influences cancer risk later in life. Perhaps new strategies of nutritional intervention might reduce cancer incidence.

The main thrust of cancer research over the second half of this century has focused on unravelling the mechanisms whereby genetic damage initiates cancer; breakthroughs in understanding of cell biology together with the new epidemiology may justify more emphasis being placed on investigation of the body's natural defence mechanisms and how these may be influenced to avoid cancer.

Jeff Holly
University Division of Surgery, Bristol Royal Infirmary, Bristol BS2 8HW, UK

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