Cancer and insulin-like growth factor-I

A potential mechanism linking the environment with cancer risk

Insulin-like growth factor-I acts as an important mediator between growth hormone and growth throughout fetal and childhood development. Its effects and those of the other insulin-like growth factors are modulated by at least six different binding proteins. The role of insulin-like growth factor-I in promoting cancer has been investigated for many years, but recently the quality and quantity of evidence has increased.[1] In particular, a number of prospective studies using stored blood collected up to 14 years before the onset of disease have shown associations between insulin-like growth factor-I and prostate cancer, premenopausal breast cancer, and colon cancer.[2–4]

The risk of cancer is higher among people with raised concentrations of insulin-like growth factor-I, and it is lower among those with high concentrations of insulin-like growth factor binding protein-3 (the main binding protein). The associations are similar when people whose blood samples were taken soon before diagnosis are excluded from analyses, suggesting that the observed relations are not due to the release of the growth factor by preclinical cancers.[2–4] The effects are sizeable and stronger than the effects seen in relation to most previously reported risk factors.[1] Weaker evidence from case-control studies suggests that the ratio of insulin-like growth factor-I to insulin-like growth factor binding protein-3 may also be related to the risk of childhood leukaemia and lung cancer.[5 6]

The increasing direct epidemiological evidence that relates insulin-like growth factor-I to the risk of cancer is consistent with more circumstantial evidence. Acromegaly, in which high concentrations of growth hormone stimulate production of high concentrations of insulin-like growth factor-I, has been associated with an increased risk of colorectal cancer and breast cancer in some studies and less consistently with prostate, thyroid, and haematological malignancies.[7] In many studies anthropometric markers of the activity of insulin-like growth factor-I, such as height and leg length, are associated with cancer incidence, particularly with the cancers for which risk increases with rising concentrations of insulin-like growth factor-I.[8] While adult height is not strongly associated with concentrations of insulin-like growth factor-I in cross sectional studies, it may be a marker for this growth factor during childhood growth,[9] and this may be the period

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during which it acts to increase the risk of cancer occurring in later life.[3] Additionally, animal studies have shown that high overall intake of energy in early postnatal life is associated with an increased cancer risk, and this association has recently been found in humans.[10] In animals, calorie restriction reduces the risk of cancer primarily by reducing the circulating concentrations of insulin-like growth factor-I.[11]

Support for the link between cancer and this growth factor comes from an understanding of the potential mechanisms. Concentrations of insulin-like growth factor-I could be a surrogate for the activity of sex steroid hormones, which in turn influence the risk of cancer. However, associations between insulin-like growth factor-I and cancers dependent on sex hormones are stronger than those between directly measured concentrations of sex hormones and these cancers. Insulin-like growth factor-I may increase cell turnover and the susceptibility of cells to malignant transformation both directly and by modulating the effects of sex steroids. The fact that the risk associated with increased concentrations of insulin-like growth factor-I is greater in people whose DNA is more susceptible to damage induced by mutagens supports this suggestion.[6] Alternatively, insulin-like growth factor-I might increase the risk of cancer through its anti-apoptotic activity.[1] In this case it prevents the programmed death of cells that have been transformed thus interrupting an important process which retards the development of cancer. Experiments using animal and cell cultures have shown that the anti-apoptotic activity of insulin-like growth factor-I is counterbalanced by the activity of insulin-like growth factor binding protein-3, which may have a direct and independent stimulatory action on apoptosis.

Given the increasing evidence of the risk of cancer, caution should be exercised in the exogenous use of either insulin-like growth factor-I or substances that increase concentrations of it. Despite supposedly being restricted to use only in licensed applications, growth hormone is easily available as an anti-ageing treatment and is surprisingly widely used by athletes and body builders, who also use insulin-like growth factor-I. Those who use these products are unlikely to be aware of their potentially harmful effects.

The final accounting on the balance sheet of growth hormone, insulin-like growth factor-I, and chronic disease is uncertain. The increasing evidence of a risk of cancer may be counterbalanced by a protective effect on the risk of cardiovascular disease. Growth hormone deficiency is associated with an adverse cardiovascular risk profile and increased risk of mortality from cardiovascular disease.[12] Low concentrations of insulin-like growth factor-I are also associated with cardiovascular morbidity in the elderly.[13] Furthermore, the same studies that have shown a positive association between height and cancer risk suggest that greater height is associated with decreases in cardiovascular and all cause mortality.[14]

The predictive value of insulin-like growth factor-I may be useful in screening for cancer. For example, the ratio of insulin-like growth factor-I to prostate specific antigen may be a better predictor of the development of prostate cancer than the antigen alone.[15] Growth hormone antagonists are being investigated as treatments for some cancers and chemotherapeutic agents are being developed to block the activity of insulin-like growth factor-I or to promote the activity of insulin-like growth factor binding protein-3; these agents may offer additional ways of stimulating apoptosis in malignantly transformed cells. Lastly, better knowledge of the factors that influence overall concentrations of insulin-like growth factor-I may help in devising strategies to prevent cancer at a population level.

Much recent attention has focused on the human genome project and its potential for unravelling the causes of cancer. The genes that have been identified as causing cancer so far account for only a small proportion of major cancers. The rapid and sizeable changes in the incidence of cancer that have been seen during times of economic development coupled with the findings from twin studies—which compare the concordance of cancer risk in identical and non-identical twins to determine the relative influence of genetic and environmental factors—both point to the importance of non-genomic factors.[16] The new epidemiological findings about insulin-like growth factor-I provide one potential mechanism through which an array of previously identified environmental risk factors may act.

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