Risk of cancer after growth-hormone treatment

In this issue of *The Lancet*, Anthony Swerdlow and colleagues report findings on cancer risk in a cohort of 1848 patients who were deficient in growth hormone and treated with human-pituitary growth hormone at young ages between 1959 and 1985. These individuals were followed up for cancer incidence to December, 1995, and for mortality to December, 2000. Compared with cancer rates in the general population, rates in treated patients showed significantly increased risks of mortality from cancer overall, particularly from colorectal cancer and Hodgkin's disease.

The investigators are rightly cautious in their interpretations of the findings. Several points, mostly

discussed by the investigators, are worth emphasising. Most importantly, the cases are few in number. It would be unwise to draw firm conclusions from two cases of colorectal cancer, even though only 0·25 were expected in such a young population and even though the results are statistically significant. Because of the small numbers, the confidence intervals for colon cancer mortality include relative rates that range from 1·3-fold to more than 30-fold increases over control. Most of the patients followed up were under the age of 45. The incidence of most cancers increases logarithmically with age, and the individuals in the cohort are just beginning to enter the age groups when cancer incidence starts to rise precipitously. Continued follow-up of these individuals is imperative, as there are precedents for exposures at critical periods early in life that can influence life-long cancer risk.[1]

Although the latest findings are not definitive, they are provocative and somewhat worrisome. Moreover, the results are consistent with an increasing body of literature which suggests that patients with acromegaly,[2] adults with circulating concentrations of insulin-like growth factor I (IGF-I) at the high end of the normal range,[3–9] and taller individuals[10,11] are at increased risk of epithelial cancers, especially colorectal cancers.[2,4,6–8] Of particular interest in this context is a recent report that a common polymorphism in the human growth-hormone gene that is associated with reduced concentrations of growth hormone and IGF-I is inversely associated with colorectal cancer risk.[12]

The results could have major implications because more than 100 000 patients worldwide are estimated to have received growth-hormone treatments.[13] This figure may be a conservative estimate in view of the increasing use of growth hormone for various off-label indications. However, the relevance of the findings to current therapy with recombinant growth hormone is unclear. In the cohort studied by Swerdlow and colleagues, the preparations and doses of growth hormone were not equivalent to current therapy with recombinant growth hormone, and were given two or three times per week. Recombinant growth hormone is typically given daily at lower doses.

Any increased cancer risk in people treated with growth hormone is plausibly related to the effects of treatments on concentrations of IGF-I and IGF-binding proteins. It was not possible to compare these concentrations in the population studied with those achieved with more modern replacement regimens for growth hormone. Nevertheless, the results do provide indirect support for the view that the dosage of growth hormone used in the treatment of growth hormone deficiency should be individualised, with a target of achieving IGF-I concentrations in the normal range for the age of the patient.[14,15] This view contrasts with more casual approaches to dosage, such as titrating dose against growth rate, or choosing an arbitrary dose based on the patient's age or weight.

It must be emphasised that the treatment of growth hormone deficiency has established health benefits, and that there is no evidence that physiological growth-hormone replacement increases cancer risk.[13] While the data reported by Swerdlow and colleagues should not discourage appropriate treatment of growth hormone deficiency, they should provoke reassessment of the risks and benefits of growth hormone therapy for more controversial indications that are unrelated to growth hormone deficiency, particularly if such treatment is prescribed for long periods. One example of potential concern is the long-term use of growth hormone administration as an "anti-ageing" regimen in healthy middle-aged individuals who show the expected decline of circulating IGF-I concentration with age. After a 6-month study that suggested benefits for such therapy,[16] the use of growth hormone has increased substantially, but the potential long-term hazards of maintaining peripubertal concentrations of IGF-1 for decades have not been studied in detail. Although further research is required to find definitive answers, sufficient suggestive data exist to warrant caution rather than a cavalier attitude in the use of growth hormone. Furthermore, several pharmacological strategies[17,18] are available to target growth hormone, and, conceivably, future data may provide a basis for investigation of the possibility that reduction of IGF-I concentrations from the high to the low end of the normal range may reduce cancer risk for certain individuals.

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