Articles

Risk of cancer in patients treated with human pituitary growth hormone in the UK, 1959–85: a cohort study

A J Swerdlow, C D Higgins, P Adlard, M A Preece

Summary

Background Growth hormone raises serum concentrations of insulin-like growth factor IGF-I, which is mitogenic and antiapoptotic. There is evidence that raised endogenous levels of growth hormone and IGF-I might be associated with increased risk of certain solid cancers, but there have been no data on long-term risks of solid cancers after growth hormone treatment.

Methods We did a cohort study to investigate cancer incidence and mortality in 1848 patients in the UK who were treated during childhood and early adulthood with human pituitary growth hormone during the period from 1959 to 1985. Patients were followed up for cancer incidence to December, 1995 and for mortality to December, 2000. Risk of cancer in the cohort was compared with that in the general population, controlling for age, sex, and calendar period.

Findings Patients treated with human pituitary growth hormone had significantly raised risks of mortality from cancer overall (standardised mortality ratio 2·8, 95% CI 1·3–5·1; ten cases), colorectal cancer (10·8, 1·3–38·8; two cases), and Hodgkin's disease (11·4, 1·4–41·3; two cases). Incidence of colorectal cancer was also greatly raised (7·9, 1·0–28·7). After exclusion of patients whose original diagnosis rendered them at high risk of cancer, the significance and size of the risks of colorectal cancer incidence and mortality, and of Hodgkin's disease mortality were increased.

Interpretation Although based on small numbers, the risk of colorectal cancer is of some concern and further investigation in other cohorts is needed. We have no evidence as to whether growth hormone in modern dosage regimens is associated with an increased risk of colorectal cancer.

Lancet 2002; **360:** 273–77
See Commentary page 268

Section of Epidemiology, Institute of Cancer Research, Sutton SM2 5NG, UK (Prof A J Swerdlow DM, C D Higgins MSc)**; Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK** (C D Higgins MSc)**; and Biochemistry, Endocrinology and Metabolism Unit, Institute of Child Health, London, UK** (P Adlard MD, Prof M A Preece MD)

Correspondence to: Prof A J Swerdlow
(e-mail: a.swerdlow@icr.ac.uk)

Introduction

Treatment of patients with growth hormone was initially used to remedy short stature in childhood.[1] However, as experience with, and availability of, the treatment improved, the range of indications and the number of patients for which growth hormone was prescribed increased greatly. This increase was especially noticeable after synthetic growth hormone became available in 1985. The role of growth hormone in carcinogenesis is unclear, but it raises serum concentrations of insulin-like growth factor (IGF)-I, which is mitogenic and antiapoptotic, and results from in-vitro and animal studies suggest that growth hormone might raise the risk of hyperplasia and malignancy.[2,3] Furthermore, there is epidemiological evidence that the growth hormone/IGF-I axis might affect cancer risk in human beings. Results of cohort studies suggest,[4–8] although not entirely consistently,[9] that raised concentrations of IGF-I in serum predict a greater risk of certain cancers, and there is evidence that the risk of colonic polyps and colon cancer are increased in patients with acromegaly,[10–13] a disorder attributable to endogenous excess of growth hormone.

Direct evidence about cancer risk in patients treated with growth hormone is very limited. Studies of leukaemia after childhood growth hormone treatment[14–17] have found a raised risk in patients overall.[14,16,17] However, several cases were in patients with an underlying high risk (eg, Fanconi's anaemia) and after exclusion of these high risk conditions, risk does not seem to be substantially raised, if at all. There are no reported data on long-term risks of solid malignancies; the only analyses have been after an average of 4 years since first treatment.[18] We therefore examined risk of malignant neoplasms in patients in the UK who were treated with human pituitary growth hormone before its use was discontinued in May, 1985, and for whom there is now up to 40 years of follow-up.

Methods

Treatment with human pituitary growth hormone in the UK started in 1959 as a Medical Research Council clinical trial, and when this trial ended in 1977, treatment was continued as a health service activity administered by a central committee. Treatment of each new patient had to be authorised centrally, and the end of treatment reported to the central authority, whereon supplies of growth hormone for the patient were stopped.

After approval from the Great Ormond Street Hospital and Institute of Child Health ethics committee, we used many sources of information to compile a list of all patients who received growth hormone treatment as part of the national scheme, during the period from 1959 to May, 1985, and extracted data on all of the treatments every patient had received. Sources of this information included the records of the national co-ordinating centre, local listings at each of the 21 endocrinology centres in the UK where patients were treated, endocrinology case-notes

held at these centres, research records for auxological studies related to growth hormone, records from the central distribution centre, local pharmacies, and the Medical Research Council and Department of Health central steering committees when they authorised patients to be treated, notifications to these committees when patients finished treatment, and listings compiled to enable discontinuation of treatment nationally in May, 1985, when the risk of Creutzfeldt-Jakob disease transmission was identified. We excluded patients treated in the UK who were resident abroad because we could not achieve full follow up. We also excluded patients treated solely with commercially prepared growth hormone (there were about 40 of these in the UK)[19] because they were not treated via the national scheme and there is no way to identify them systematically.

Identifying information about all treated patients in the cohort was sent to the UK National Health Service (NHS) Central Registers for England and Wales and for Scotland, and to the Central Services Agency (CSA) for Northern Ireland, which are national population registers, to obtain follow-up information on occurrence of cancer, death, and emigration. Follow-up data were also provided by clinical sources, and information from death certificates was coded to the revision of the International Classification of Diseases in use at the time of death.[20]

We calculated person-years at risk of death from cancer in cohort members by sex and 5-year age-group starting from the date of first treatment with growth hormone and ending at Dec 31, 2000, death, or other loss to follow-up, whichever was earliest. For analyses of cancer incidence, risk was calculated from the date of first treatment or Jan 1, 1971 (cancers incident from this date onwards were entered in the NHS Central Registers), whichever was later, and ended at the date of cancer incidence, death, other loss to follow-up, or Dec 31, 1995, whichever was earliest. The curtailment of follow-up at the end of 1995 was because recent data on cancer incidence were not complete on the NHS Central Registers. For the data on cancer incidence, but not mortality, Northern Ireland patients were excluded from analysis because the population register there does not record cancer incidence.

We calculated the expected numbers of cancers and cancer deaths in the study group overall and in subdivisions by analytical variables, by multiplying the person-years at risk in these groups specific by age, sex, and calendar year, by British national cancer incidence and mortality rates for the same age, sex, and calendar year categories, compiled from data from the Office for National Statistics and the Information Services Division and General Register Office for Scotland. Standardised incidence ratios (SIRs) and standardised mortality ratios (SMRs) were then calculated by the division of the observed number of cancers and cancer deaths by the number expected. The Poisson distribution was used to obtain exact confidence intervals and exact p values and, where appropriate, we did trend and heterogeneity tests.[21] In all analyses we excluded non-melanoma skin cancer, because national cancer registration is particularly incomplete for these tumours.[22] We also excluded cancers of the nervous system, because many of the initial diagnoses were either nervous system tumours or diagnostic categories such as idiopathic growth hormone deficiency that might have included undiagnosed nervous system tumours. We also excluded from the mortality analyses, deaths from other cancers that were the reason for the start of growth hormone therapy.

Role of the funding source
The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We identified 1849 UK residents who had been treated with human growth hormone as part of the national scheme between 1959 and 1985. Because this scheme was centrally administered and controlled, and also because data from many different sources were used, we are confident that we have identified all patients treated under the national scheme. We were able to ascertain the commencement date of growth hormone treatment for all patients, and definite end dates of treatment for all but ten patients, whose treatment we regarded as ended when the last known batches supplied to them were used. All but one of the patients were traced for follow-up at the NHS Central Registers and CSA; the individual who could not be traced was excluded from analysis.

There were 1209 men and 639 women in the cohort, almost all younger than 10 years (39%) or 10–19 years (60%) at first treatment. Growth-hormone deficiency was of idiopathic origin in 53% of patients and attributable to intracranial neoplasia in 26%. Many other disorders affected the remaining 21% of patients, including 22 cases of leukaemia or lymphoma, four of chromosome fragility syndromes, and two of glycogen storage disease. During follow-up to Dec 31, 2000, 241 patients died and 28 (1·5%) were lost to follow-up. Certified cause of death was ascertained for all but four deaths. In total, there were 29 817 years of follow-up in the cancer incidence analyses (average 16·1 years per patient), and 39 178 person-years of follow-up in the mortality analyses (average 21·2 years per patient). Most of the follow-up (76% of the person-years for the cancer incidence analyses, 81% for the mortality analyses) was at ages of 15 years and older, but few patients had yet reached older adulthood—only 0·6% of person-years were at ages 45 years or greater. 12 cancers, other than of the nervous system or non-melanoma skin cancer, were noted in the cohort by the end of 1995, and 10 deaths attributable to such cancers by Dec 31, 2000. All but one of the cancers, and all of the cancer deaths, happened at age 15 years or older and all cancers occurred after human growth hormone treatment had ceased.

The overall risk of cancer incidence in the cohort was greater, but not significantly so, than that of the general population (table). Among cancer sites of interest from the previous literature on growth hormone and IGF-I, there were no cases of breast cancer (expected=0·62), prostate cancer (expected=0·01), or leukaemia (expected=0·69). Three cancers occurred in patients with a previous tumour, one of which (a bone cancer) might well have been caused by radiotherapy for the initial tumour. One cancer (of the cervix) was reported in a patient with Bloom's syndrome, and a liver cancer occurred in a patient with type I glycogen-storage disease. We reanalysed data excluding 496 patients whose initial diagnoses could have put them at high risk of subsequent cancer—ie, patients with neoplasia (including intracranial tumours; either pituitary or non-pituitary, benign or malignant), who might have received cranial radiation and chemotherapy, and those with chromosome fragility or glycogen-storage disease. After these exclusions, we calculated an SIR for cancer in total that was less raised than that for the cohort overall, and an SIR for colorectal cancer that was greater than that for the whole cohort, and significantly raised compared with the general population (table).

	Entire cohort				Cohort excluding high-risk groups*			
	Number of cancers	Number expected	SIR/SMR (95% CI)	p	Number of cancers	Number expected	SIR/SMR (95% CI)	p
Incidence								
Colon and rectum†	2	0·25	7·9 (1·0–28·7)	0·05	2	0·18	11·1 (1·3–39·9)	0·03
Bone	2	0·27	7·3 (0·9–26·4)	0·06	0	0·21	0 (0–17·7)	1·00
Hodgkin's disease	2	0·85	2·3 (0·3–8·5)	0·42	2	0·64	3·1 (0·4 -11·3)	0·27
All sites‡	12	7·14	1·7 (0·9–2·9)	0·11	7	5·16	1·4 (0·5–2·8)	0·52
Mortality								
Colon and rectum†	2	0·19	10·8 (1·3–38·8)	0·03	2	0·13	14·9 (1·8–53·9)	0·02
Bone	1	0·19	5·2 (0·1–28·7)	0·35	0	0·15	0 (0–24·8)	1·00
Hodgkin's disease	2	0·18	11·4 (1·4–41·3)	0·03	2	0·13	15·3 (1·9–55·2)	0·02
All sites‡	10	3·58	2·8 (1·3–5·1)	0·01	6	2·60	2·3 (0·8–5·0)	0·10

SIR=Standardised incidence ratio. SMR=Standardised mortality ratio. *Excluding patients treated with human pituitary growth hormone after a malignant neoplasm, chromosomal fragility syndrome, or glycogen storage disease. †Both were cancers of the colon. SIRs for colon cancer are 12·0 (1·5–43·3), and 16·7 (2·0–60·2) for entire cohort and after exclusion of high-risk groups, respectively; SMRs are 16·4 (2·0–59·2) and 22·9 (2·8–83·0). ‡All sites except nervous system and non-melanoma skin cancer. In addition to sites shown in table, there were single cases of cancers of the mouth, liver, bile duct, cervix, ovary and testis, and there were deaths from these cancers except for testicular cancer.

Risks of cancer incidence and mortality after treatment with human pituitary growth hormone

Cancer mortality was significantly raised in the cohort (table), with significantly increased risks of death from cancer of the colon and rectum, and Hodgkin's disease. The two deaths from colon cancer were at young ages (23 years and 37 years) in patients whose original diagnosis was idiopathic growth hormone deficiency (IGHD); the Hodgkin's disease deaths occurred at ages 22 years and 32 years in patients whose original diagnosis was IGHD also; these cases were all histologically confirmed. None of the patients with colorectal cancer or Hodgkin's disease had a family history of the same or a related cancer. There was an unclear possibility of polyposis coli in one of the patients with colorectal cancer. No deaths from breast cancer (expected=0·32), prostate cancer (expected=0·01), or leukaemia (expected=0·64) were reported. Reanalysis of the cancer mortality risks excluding high-risk patients left significantly raised risks of cancers of the colon and rectum and of Hodgkin's disease. Cancer mortality overall was greater, but not significantly so, than for the general population (table).

Examination of risks of overall cancer incidence by sex, age at first treatment, diagnosis that led to treatment, and duration of treatment, showed no substantial patterns of risk (data not shown). There were too few cases of any one site to conduct such analyses site-specifically. For mortality, similar analyses did not show significant results. When cohort members with an existing high risk of cancer were excluded, reanalyses showed that all cases occurred at least 10 years after first treatment, but again there were no significant patterns (data not shown).

Discussion

Concern about cancer in patients treated with growth hormone has focused primarily on risk of leukaemia, perhaps because available data have largely been for children, in whom leukaemia is the most common cancer. No leukaemias occurred after treatment in our cohort; we calculated an expected incidence of 0·71. Our finding adds to evidence from other cohort studies[14,16,17] which suggest that leukaemia risk is not substantially raised if high-risk groups such as those with chromosomal fragility are excluded.

There has been much less research on other cancer risks, and our findings in this area were not reassuring. There was significantly raised mortality from cancer overall, colon and rectal cancer, and Hodgkin's disease, and risk of incidence was also raised for all of these categories, although not significantly. When high-risk groups were excluded from the cohort, overall cancer mortality was less raised and not significant, but the risks of colon and rectum cancer and of Hodgkin's disease were further increased. The exclusion of high-risk groups is not straightforward to interpret because the general population, from whom expected rates were gained, also includes high-risk groups whose deaths we cannot exclude, and hence the relative risks we calculated could be underestimates. On the other hand, one of the colorectal cancer patients might have had familial polyposis. At the young ages examined in the study, an appreciable proportion of the colorectal cancer patients in the general population used to calculate expected numbers would have had such a family history.

One should not overinterpret risks based on such small numbers; our results should be considered cautiously, and we emphasise the need for more data from other sources. Another minor caveat is that, although we went to great effort to ensure that the data on human growth hormone treatment were as complete as possible, we have no information on treatment with synthetic (recombinant) growth hormone after May, 1985, when the national scheme was discontinued. This lack of information will not have affected most of the analyses, which were based on ever-treatment or first treatment, but will have introduced misclassification into the analyses by duration of treatment. Therefore if there is truly a duration-response effect, it might not have been apparent in our analyses because of misclassification. The expected rates of cancer in the analyses were taken from national general population rates. We have no evidence on whether there were differences in social background between the cohort and the general population, but if so they would not plausibly explain the magnitude of the risks we report. The ideal comparison group for this study would have been comparable growth hormone-deficient patients who had not received growth hormone treatment. We have no such cohort from the same period but, on the basis of results from studies of such cohorts,[23,24] our results would be unlikely to be much different if such a comparison were possible.

Despite these limitations, the high incidence of cancer, and in particular of colon cancer, is worrying. That growth hormone might increase the risk of colorectal cancer is plausible for several reasons. Growth hormone causes raised serum IGF-I and to a lesser extent IGF binding protein-3 (IGFBP-3), and consequently causes a raised ratio of IGF-I to IGFBP-3, with this ratio being greater as growth hormone concentrations increase.[25–27] IGF-I receptors have been identified on human colorectal cells, mRNAs for IGF-I have been detected in colorectal tumours, IGF-I is a potent stimulator of

colorectal-cancer-cell proliferation in vitro, and blockade of IGF-I receptors inhibits growth of human colorectal cancer cells.[28] Patients with acromegaly have raised colonic epithelial cell proliferation, and this proliferation rises with greater growth hormone and IGF-I concentrations,[29] although the same has not been found in adults treated with growth hormone.[30] There is evidence from cohort studies that patients with acromegaly have a higher risk of colon cancer than the general population,[10–12] and colonoscopy has suggested a high rate of colonic polyps in such patients,[13] although calculation of appropriate expected numbers is difficult and controversial.[31] Raised serum IGF-I concentrations have been noted in patients with high-risk colorectal adenomas,[32] and three cohort studies in Western populations report a raised risk of colon cancer in relation to raised serum IGF-I concentrations[6–8] (and in two instances decreased concentrations of IGFBP-3) several years earlier.[6,7] A study in Shanghai, China did not find this result.[9] The only previous data on solid-cancer risks in growth hormone-treated patients are from a commercial database reliant on physician reports on cancer, which had a short follow-up (maximum 8 years, average 4 years).[18] No colon or rectal cancers were reported, nor was a raised rate of extracranial non-leukaemic tumours noted overall. However, completeness of reporting is unclear, especially after patients left paediatric care, and person-years in the analysis do not seem to have been censored at death or loss to follow-up, which would dilute risks.

It is possible that growth hormone-deficient patients might be intrinsically at high risk of colorectal cancer, and this predisposition rather than growth hormone treatment, might be responsible for the raised incidence in our study. Intuitively, this possibility seems unlikely, because deficiency of a mitogenic hormone would be expected, if anything, to diminish cancer risk. Also, in cohort studies, growth-hormone-deficient patients who did not receive growth hormone have had cancer risks the same as[23] or below[24] those in the general population, and had no indication of raised colorectal cancer risk.

Information on serum IGF-I and IGFBP-3 concentrations in the cohort would have been valuable in explaining the raised risk, but such data are not available; satisfactory immunological assays did not exist for most of the period when human growth hormone was used. Our results are therefore epidemiological observations of an association, and do not give evidence on mechanisms. However, data exist that show that growth hormone treatment of young patients with growth hormone deficiency raises their IGF-I and IGFBP-3 concentrations, and their IGF-I/IGFBP-3 ratio.[25] Although IGF-I would be expected to increase the risk of cancer, IGFBP-3 would be expected to diminish it; however, a raised IGF-I to IGFBP-3 ratio would be expected to increase free IGF-I and hence to favour its action. The dosage regimen used for human growth hormone would be expected to result in supraphysiological peaks of serum growth hormone, especially because it was only given two to three times per week in doses of up to 10 IU. Growth hormone concentrations would have been especially high in younger children, because the same dose was given to all ages of patient, irrespective of their body size.

Whether our results can be generalised to patients treated presently is uncertain, and our caution about small numbers of colorectal cancers should be remembered. Also the young age of these patients at treatment should be taken into account, because applicability to treatment at older ages is uncertain.

Furthermore, there are differences between the human growth hormone treatment given in the study period and the synthetic growth hormone treatment given afterwards. Although there is no reason to believe that there would be an intrinsic difference in carcinogenicity between human pituitary and synthetic growth hormone, human pituitary growth hormone was usually given two or three times per week, whereas the synthetic version has been given daily. Therefore peaks of serum growth hormone will have been substantially greater for the regimen with human pituitary growth hormone than for that with the synthetic hormone. Also, the dosage of synthetic growth hormone is titrated by body size, whereas all patients who received human pituitary growth hormone were given the same dose, which effectively resulted in a much larger dose for young children. There is no evidence on whether growth hormone in modern dosage regimens is associated with colorectal-cancer risk. There is a need for large-scale follow-up data on this topic, especially as such studies could potentially overcome a weakness in our investigation by including measured serum growth hormone, IGF-I, and IGFBP-3 concentrations.

Cancers of the breast[4] and prostate[5] have also been associated with raised IGF-I concentrations in cohort studies, although in each instance data are available from only one study. No cases of these tumours were reported in our cohort, but because the cohort members are young, expected numbers of cancers incident were small, especially for prostate cancer. Therefore if treatment has an effect on the frequency of these cancers, it might not yet be apparent.

The risk of death due to Hodgkin's disease was significantly raised in the cohort, based on two cases; the increase in incidence was less pronounced. We know of no evidence that Hodgkin's disease incidence or survival are affected by endogenous growth hormone or IGF-I concentrations. Three cases of Hodgkin's disease have been reported in US cohorts of growth hormone-treated patients, without calculation of expected numbers for this tumour.[14,18] Analyses of relative risks of incidence and mortality based on larger numbers than the present study are desirable.

In conclusion, we found a significantly raised frequency of colon cancer mortality after growth hormone treatment which, although based on small numbers, is of concern because it concurs with raised risks found in patients with acromegaly and in individuals with previously increased concentrations of IGF-I. Two cases are too few to allow firm conclusions to be drawn, but there are no previous data to help in evaluation. In view of the large relative risk and supporting evidence, there is an urgent need to gain further data. An association between human pituitary growth hormone treatment and raised frequencies of certain malignant disease in patients from our cohort cannot necessarily be generalised to patients treated with synthetic hormones in regimens which are intended to produce hormone concentrations that are closer to physiological. There are an estimated 100 000 patients worldwide who have received growth hormone treatment.[33] Our data do not show conclusively whether cancer incidence is increased by growth hormone treatment, but they do suggest the need for increased awareness of the possibility of cancer risks, and for surveillance of growth hormone-treated patients.

Contributors

A J Swerdlow contributed to study design, organisation, and writing of the report. C D Higgins contributed to data collection and analysis. P Adlard and M A Preece initiated and maintained the surveillance programme from 1985. All authors worked on interpretation.

Conflict of interest statement

M A Preece has advised the growth hormone industry on scientific issues and received honoraria.

Acknowledgments

We thank past and present paediatric endocrinologists in the UK, and their staff for providing data about the cohort in this study. We thank B Peachey for her tireless dedication in organising the data for this study; Z Qiao for extensive computing work; M Snigorska for secretarial help; and the NHS Central Registers, CSA, and Thames Cancer Registry for follow-up information. We thank the Medical Research Council and the Department of Health for funding.

References

1 Raben MS. Treatment of a pituitary dwarf with human growth hormone. *J Clin Endocrinol Metab* 1958; **18:** 901–03.
2 Ogilvy-Stuart AL. Safety of growth hormone after treatment of a childhood malignancy. *Horm Res* 1995; **44** (suppl 3)**:** 73–79.
3 Ng ST, Zhou J, Adesanya OO, Wang J, LeRoith D, Bondy CA. Growth hormone treatment induces mammary gland hyperplasia in aging primates. *Nat Med* 1997; **3:** 1141–44.
4 Hankinson SE, Willett WC, Colditz GA, et al. Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. *Lancet* 1998; **351:** 1393–96.
5 Chan JM, Stampfer MJ, Giovannucci E, et al. Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. *Science* 1998; **279:** 563–66.
6 Ma J, Pollak MN, Giovannucci E, et al. Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-1 and IGF-binding protein-3. *J Natl Cancer Inst* 1999; **91:** 620–25.
7 Giovannucci E, Pollak MN, Platz EA, et al. A prospective study of plasma insulin-like growth factor-1 and binding protein-3 and risk of colorectal neoplasia in women. *Cancer Epidemiol Biomarkers Prev* 2000; **9:** 345–49.
8 Kaaks R, Toniolo P, Akhmedkhanov A, et al. Serum C-peptide, insulin-like growth factor (IGF)-I, IGF-binding proteins, and colorectal cancer risk in women. *J Natl Cancer Inst* 2000; **92:** 1592–600.
9 Probst-Hensch NM, Yuan J-M, Stanczyk FZ, Gao Y-T, Ross RK, Yu MC. IGF-1, IGF-2 and IGFBP-3 in prediagnostic serum: association with colorectal cancer in a cohort of Chinese men in Shanghai. *Br J Cancer* 2001; **85:** 1695–99.
10 Pines A, Rozen P, Ron E, Gilat T. Gastrointestinal tumors in acromegalic patients. *Am J Gastroenterol* 1985; **80:** 266-69.
11 Ron E, Gridley G, Hrubec Z, Page W, Arora S, Fraumeni JF Jr. Acromegaly and gastrointestinal cancer. *Cancer* 1991; **68:** 1673–77.
12 Orme SM, McNally RJQ, Cartwright RA, Belchetz PE, for the United Kingdom Acromegaly Study Group. Mortality and cancer incidence in acromegaly: a retrospective cohort study. *J Clin Endocrinol Metab* 1998; **83:** 2730-34.
13 Jenkins PJ, Fairclough PD, Richards T, et al. Acromegaly, colonic polyps and carcinoma. *Clin Endocrinol (Oxf)* 1997; **47:** 17–22.
14 Fradkin JE, Mills JL, Schonberger LB, et al. Risk of leukemia after treatment with pituitary growth hormone. *JAMA* 1993; **270:** 2829–32.
15 Blethen SL, Allen DB, Graves D, et al. Safety of recombinant deoxyribonucleic acid-derived growth hormone: the National Cooperative Growth Study Experience. *J Clin Endocrinol Metab* 1996; **81:** 1704–10.
16 Allen DB, Rundle AC, Graves DA, Blethen SL. Risk of leukemia in children treated with human growth hormone: review and reanalysis. *J Pediatr* 1997; **131:** S32–36.
17 Nishi, Y, Tanaka, T, Takano, K, et al . Recent status in the occurrence of leukemia in growth hormone-treated patients in Japan. *J Clin Endocrinol Metab* 1999; **84:** 1961–65.
18 Tuffli GA, Johanson A, Rundle AC, Allen DB. Lack of increased risk for extracranial, nonleukemic neoplasms in recipients of recombinant deoxyribonucleic acid growth hormone. *J Clin Endocrinol Metab* 1995; **80:** 1416–22.
19 Buchanan CR, Preece MA, Milner RDG. Mortality, neoplasia, and Creutzfeldt-Jakob disease in patients treated with human pituitary growth hormone in the United Kingdom. *BMJ* 1991; **302:** 824–28.
20 World Health Organization. Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death. Geneva: World Health Organization, 1977.
21 Breslow NE, Day NE. Statistical methods in cancer research. volume II - the design and analysis of cohort studies. IARC Scientific Publication number 82. Lyon: International Agency for Research on Cancer, 1987.
22 Swerdlow A, dos Santos Silva I, Doll R. Cancer incidence and mortality in England and Wales: trends and risk factors. Oxford: Oxford University Press, 2001.
23 Tomlinson JW, Holden N, Hills RK, et al. Association between premature mortality and hypopituitarism. *Lancet* 2001; **357:** 425–31.
24 Rosén T, Bengtsson B-Å. Premature mortality due to cardiovascular disease in hypopituitarism. *Lancet* 1990; **336:** 285–88.
25 Juul A, Pedersen SA, Sorensen S, et al. Growth hormone (GH) treatment increases serum insulin-like growth factor binding protein-3, bone isoenzyme alkaline phosphatase and forearm bone mineral content in adults with GH-deficiency of childhood onset. *Eur J Endocrinol* 1994; **131:** 41–49.
26 Juul A, Main K, Blum WF, Lindholm J, Ranke MB, Skakkebaek NE. The ratio between serum levels of insulin-like growth factor (IGF)-I and the IGF binding proteins (IGFBP-1, 2 and 3) decreases with age in healthy adults and is increased in acromegalic patients. *Clin Endocrinol (Oxf)* 1994; **41:** 85–93.
27 Ghigo E, Aimaretti G, Maccario M, et al. Dose-response study of GH effects on circulating IGF-I and IGFB-3 levels in healthy young men and women. *Am J Physiol* 1999; **276:** E1009–13.
28 Lahm H, Amstad P, Wyniger J, et al. Blockade of the insulin-like growth-factor-I receptor inhibits growth of human colorectal cancer cells: evidence of a functional IGF-II-mediated autocrine loop. *Int J Cancer* 1994; **58:** 452–59.
29 Cats A, Dullaart RPF, Kleibeuker JH, et al. Increased epithelial cell proliferation in the colon of patients with acromegaly. *Cancer Res* 1996; **56:** 523–26.
30 Beentjes JAM, van Gorkom BAP, Sluiter WJ, de Vriest EGE, Kleibeuker JH, Dullaart RPF. One year growth hormone replacement therapy does not alter colonic epithelial cell proliferation in growth hormone deficient adults. *Clin Endocrinol (Oxf)* 2000; **52:** 457–62.
31 Renehan AG, O'Dwyer ST, Shalet SM. Colorectal neoplasia in acromegaly: the reported increased prevalence is overestimated. *Gut* 2000; **46:** 440.
32 Renehan AG, Painter JE, Atkin WS, Potten CS, Shalet SM, O'Dwyer ST. High-risk colorectal adenomas and serum insulin-like growth factors. *Br J Surg* 2001; **88:** 107–13.
33 Growth Hormone Research Society. Critical evaluation of the safety of recombinant human growth hormone administration: Statement. *J Clin Endocrinol Metab* 2001; **86:** 1868–70.