Growth Hormone Treatment in Children is not Associated with an Increase in the Incidence of Cancer: Experience from KIGS (Pfizer International Growth Database)

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Objective To assess the incidence of cancer in patients treated with growth hormone (GH) in KIGS—the Pfizer International Growth Database—without cancer or any other condition in medical history known to increase the risk of cancer.

Study design Data were analyzed from patients with growth disorders enrolled in an observational survey KIGS who had no known increased risk of developing cancer before starting recombinant human GH treatment. The incidence of cancer in this patient cohort (overall, site-specific, and according to etiology of growth disorder) was compared with the incidence in the general population by using the standardized incidence ratio (ie, relating the observed to expected number of cases with stratification for age, sex, and country).

Results A total of 32 new malignant neoplasms were reported in 58 603 patients, versus the 25.3 expected (incidence, 16.4 per 100 000 patient-years; standardized incidence ratio, 1.26; 95% confidence interval, 0.86-1.78). No category of growth disorder showed a statistically significant difference in observed compared with the expected number of cases.

Conclusion There is no evidence in this series that GH treatment in young patients with growth disorders results in an increased risk of developing cancer relative to that expected in the normal population. However, surveillance for an extended time should continue to allow further assessment. *(J Pediatr 2010;157:265-70)*.

Treatment of short children with recombinant human growth hormone (GH) is associated with significant improvements in linear growth, leading to attainment of normal or near-normal final height.[1,2] Treatment also has a beneficial impact on body composition.[3] In addition, GH is considered to be well tolerated, with few reported adverse reactions.[4] The possibility of an increased risk of cancer in patients receiving GH treatment, however, has been discussed since the first report of leukemia in GH-deficient children undergoing GH replacement therapy in 1988.[5] The role of the GH–insulin-like growth factor I (IGF-I) axis in tumori-genesis has been studied extensively. Although it is known that IGF-I is a mitogen, animal models suggest permissive rather than causative roles for both IGF-I and GH in tumor-genesis.[6] The identification of 2 cases of colorectal cancer in a long-term cohort study of children and adolescents treated with pituitary-derived GH prompted the authors to suggest that the risk of developing cancer increases after GH treatment.[7] There are also data suggesting an increased risk of malignancy in GH-treated survivors of childhood cancer[8] and in GH-treated patients with other conditions associated with an increased risk of cancer.[9] The aim of this study was to assess the incidence of cancer in patients treated with GH in the Pfizer International Growth Database (KIGS) without cancer or any other condition in medical history known to increase the risk of cancer.

Methods

KIGS is a large international pharmacoepidemiological database that was established in 1987 to monitor long-term clinical and safety outcomes in children with growth disorders who are receiving recombinant human GH (Genotropin; Pfizer, New York, New York). Any patient who is taking or will be treated with GH is eligible to be included in KIGS. The study is conducted in compliance with and is consistent with the Declaration of Helsinki. All applicable local regulatory requirements in the countries involved are adhered to. Relevant independent ethics committees

GH	Growth hormone
GHD	Growth hormone deficiency
IARC	International Agency for Research on Cancer
IGF-I	Insulin-like growth factor I
KIGS	Pfizer International Growth Database
NCGS	National Cooperative Growth Study
SGA	Small for gestational age
SIR	Standardized incidence ratio

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in each participating country approved the study. Patients were enrolled after informed consent. The database protocol requires that physicians report all adverse events in patients followed in KIGS, regardless of whether they are associated with GH treatment. As of August 2008, KIGS contained data from 58 603 patients with no history of neoplasm or any other medical condition presumed to increase the risk of cancer (eg, neurofibromatosis, Langerhans cell histiocytosis, renal transplantation with subsequent immunosuppressive therapy, Fanconi anemia, and Down syndrome). Patients with Turner syndrome were included despite evidence that there is an increased risk of certain types of cancers associated with this chromosomal disorder.[10-14]

A total of 197 173 patient-years of follow-up were available for analysis. A total of 98.5% of patient-years were accumulated during the first 10 years of follow-up. The mean duration of follow-up was 3.6 years. The mean patient age (plus or minus SD) at enrollment in KIGS was 10.3 (± 4.0) years. Fifty-eight percent of patients were male. The mean dose of recombinant human GH at start was 0.24 mg/kg/week, and for the entire duration of treatment, it was 0.25 (± 0.10) mg/kg/week. In >95% of patients, GH treatment was administered.

For each patient, follow-up time in patient-years was calculated from the date of enrollment in KIGS or GH treatment start, when this was later than entry into KIGS, until either the date of the last documented visit, the date of exit from the register (for patients with an exit date), the date of a reported malignant neoplasm, or the date of death, whichever was earliest. Patient-years were stratified by country, sex, and attained age at follow-up. Thirty-one percent of the patients had received GH before enrollment in KIGS, representing 43 080 patient-years (mean, 2.4 years) not included in the risk analysis.

Growth disturbance was the result of idiopathic growth hormone deficiency (GHD) in 54% of patients, Turner syndrome in 11% of patients, congenital GHD in 5% of patients, being born small for gestational age (SGA) in 7% of patients, and acquired GHD in 3% of patients. A number of other conditions, including chronic renal insufficiency and Prader–Willi syndrome, were responsible for short stature in the remaining patients.

The development of a neoplasm in a patient in KIGS is recorded as a serious adverse event. In our analysis, we included all malignant neoplasms reported during the time at risk, defined as aforementioned. The incidence of cancer in KIGS (overall, site-specific and according to etiology of growth disorder) was calculated in relative terms by using the standardized incidence ratio (SIR), a statistical measure that quantifies the relationship between the observed and expected number of new cancers. The latter number was calculated overall or for each cancer site by using the age-, sex-, and country-specific cancer incidence rate from the general population published by the International Agency for Research on Cancer (IARC) in *Cancer Incidence in 5 Continents*, volume IX,[15] multiplied with the correspondingly stratified number of patient-years in KIGS. These stratum-specific expected values were summed over strata to get the total expected value. "Attained age" was stratified in 5-year bands, "sex" in male and female patients, and "country" in 50 countries. Forthy-three of these countries, contributing with 98.5% of all patient-years in this study, had reference incidence rates published in IARC. For the 7 countries (contributing with 1.5% or 2956 patient-years) without reference rates in IARC, IARC incidence rates from a neighboring country was used as a proxy. Results were similar when excluding these 7 countries without direct representation in IARC.

In a separate analysis, the temporal pattern of SIR was assessed. Time was classified into 0 to <2 years, 2 to <5 years, and 5 to <10 years since GH start within KIGS. The interval >10 years included a limited number of patient-years (3019 patient-years) and no cases and was therefore excluded from this time-trend analysis.

In a third analysis in patients not treated with GH before entry into KIGS ("GH-naïve"), data from the first year after the start of GH treatment were omitted to avoid the potential inclusion of cancer cases that were present but undiagnosed before KIGS entry.

The observed number of cancers was assumed to follow a Poisson distribution. 95% confidence intervals (CIs) were calculated by using Byar's approximation formula.[16]

Results

Between January 1987 and August 2008, new malignant neoplasms were reported in 32 patients in KIGS who had no known factors conveying an a priori increased risk. Twelve neoplasms were reported in male patients, and 20 neoplasms were reported in female patients (7 in girls with Turner syndrome). **Table I** shows information on GH treatment, the etiology of the growth disorders, and the specific malignancy for each patient in whom a malignant neoplasm developed. Cancer was diagnosed at a mean age of 11.9 years (range, 5.0-17.6 years). The mean duration of GH therapy in KIGS before the diagnosis of cancer was 3.6 years (range, 0.08-9.70 years). Eight of 32 patients with a new cancer were treated with GH before enrollment in KIGS for a median of 0.7 years (range, 0.06-4.5 years). A total of 7626 patients were observed in KIGS after GH was discontinued. In 6 of these patients, a malignant neoplasm was reported for as long as 3.1 years after stopping GH. The mean dose of GH in patients in whom a neoplasm developed was 0.26 (± 0.08) mg/kg/week (range, 0.12-0.48). Serum IGF-I levels measured 1 to 12 months before the onset of a neoplasm were only available for 7 patients. Three patients had IGF-I SD scores >0 (range, 0.6-1.7), whereas 4 patients had IGF SD scores between –0.6 and –1.9.

The overall incidence of cancer in this patient cohort was similar to that in the general population, with 32 cases reported in KIGS versus the 25.3 expected (**Table II**). This corresponds to an SIR of 1.26 (95% CI, 0.86-1.78). Seventeen cases were reported within the first 2 years in

Table I. Characteristics of tumor cases in KIGS in patients with no known factors conveying an a priori increased risk of cancer in whom a new malignant neoplasm was diagnosed during treatment with growth hormone

Etiology of growth disorder	Type of neoplasm	Age at diagnosis (years)	Sex	Mean GH dose (mg/kg/wk)	Time after GH start (years)
Idiopathic GHD	Germinoma	15.5	F	0.29	3.1
Idiopathic GHD	Germinoma	17.2	F	0.36	2.7
Idiopathic GHD	Glioma	12.2	M	0.32	5.4
Idiopathic GHD	Primitive neuroectodermal tumor	16.7	M	0.33	1.8
Idiopathic GHD	Astrocytoma	6.7	M	0.22	1.6*
Idiopathic GHD	Brain tumor	17.6	M	0.20	9.7
Idiopathic GHD	Brain stem tumor	6.3	F	0.30	1.2
Idiopathic GHD	Non-Hodgkin lymphoma	10.8	M	0.14	3.8
Idiopathic GHD	Non-Hodgkin lymphoma	12.9	F	0.12	0.3
Idiopathic GHD	Acute myeloid leukemia	8.0	F	0.20	0.4
Idiopathic GHD	Seminoma	15.8	M	0.14	5.4*
Idiopathic GHD	Rhabdomyosarcoma	9.3	F	0.27	1.0
Idiopathic GHD	Papillary kidney carcinoma	5.6	M	0.13	2.9
Idiopathic GHD	Fibromyxoid sarcoma	16.3	F	0.30	1.6*
Congenital GHD	Hodgkin lymphoma	9.9	M	0.16	3.2
GHD post encephalitis	Acute lymphoid leukemia	7.7	F	0.17	2.6
GHD and ADH deficiency	Infiltration mass, hypothalamic area	10.5	F	0.29	1.1
Craniopharyngioma	Neuroblastoma	5.0	M	0.23	0.3
Craniopharyngioma	Osteoid sarcoma	12.2	M	0.17	0.8
ISS	Malignant melanoma grade 1	12.0	F	0.48	2.2
ISS	Mixed germ cell teratocarcinoma	13.7	M	0.32	9.3
ISS	Testicular teratocarcinoma	14.8	M	0.20	3.9
Turner syndrome	Papillary thyroid carcinoma	11.8	F	0.32	6.2
Turner syndrome	Lung carcinoma	16.0	F	0.24	3.4
Turner syndrome	Malignant melanoma	14.8	F	0.26	6.5*
Turner syndrome	Diffuse gliomatosis	12.7	F	0.33	0.5
Turner syndrome	Non-Hodgkin lymphoma	12.4	F	0.31	0.4
Turner syndrome	Adrenal cortical carcinoma	8.5	F	0.34	3.9
Turner syndrome	Papillary mesothelioma	14.8	F	0.31	1.4*,†
SGA	Acute myeloid leukemia	8.3	F	0.21	4.6
SGA	Nephroblastoma	6.4	F	0.22	6.4
Nephrotic syndrome	Ovarian small-cell carcinoma	17.5	F	0.33	4.7*

F, Female; *ISS*, idiopathic short stature; *M*, male.
*GH had been discontinued when the neoplasm was diagnosed.
†Exited KIGS.

KIGS, 11 cases between 2 and 5 years, and the remaining 4 cases between 5 and 10 years. The corresponding SIRs for these 3 intervals were 1.45, 1.19, and 1.03, respectively. Thus, there was no trend for SIR to increase with time (P = .32). There was no statistical difference in temporal pattern in SIR between patients treated with GH (non-naïve) and patients not treated with GH (naïve) before KIGS enrollment (P = .70). Specifically, in the group of GH-naïve patients, 24 neoplasms were reported when 18.3 were expected, corresponding to an SIR of 1.31 (95% CI, 0.84-1.95). When data from the first 12 months in KIGS were excluded from the assessment of this group, 19 cases were observed, compared with 13.7 expected (SIR, 1.39; 95% CI, 0.83-2.17).

More than 1 malignancy was reported for 7 different tumor sites (**Table II**). For the most common site of neoplasm in children, the central nervous system, there were 9 observed cases, compared with 4.0 expected. Three cancers were likely present at enrollment in KIGS. Two cases of germinomas in girls classified as having idiopathic GHD may have been the cause of GHD rather than a de novo tumor during GH treatment. The third case was reported in a girl with GHD and diabetes insipidus, with an enlarged infundibulum on magnetic resonance imaging that was classified as "autoimmune inflammation." An infiltration mass in the pituitary/hypothalamic area was found on magnetic resonance imaging after 13 months of receiving GH. This case could be interpreted as Langerhans cell histiocytosis developing more extensive granulomatosis with time rather than a de novo cranial tumor. Excluding these 3 uncertain cases, an SIR of 1.49 (95% CI, 0.55-3.25) was found, in contrast to 2.24 (95% CI, 1.02-4.25) when the assessment included all 9 cases.

For the next most common type of childhood neoplasm, leukemia, 3 cases were reported, compared with the 6.24 expected, corresponding to an SIR of 0.48 (95% CI, 0.10-1.41). There were 3 cases of non-Hodgkin lymphoma versus 2.1 expected. Three cases of testicular cancer were reported, compared with the 1.2 cases expected. Two cases were histological different testicular embryonal carcinomas. These occurred in pubertal boys, one of whom had a medical history of an undescended testis. The third case was a seminoma diagnosed in a 15.8-year-old boy with idiopathic GHD who was born SGA and had a history of undescended testis. He had received GH replacement for 5.4 years.

Table II. Observed and expected number of tumor cases, estimated standardized incidence ratio with 95% CI by site of malignant neoplasm in 58 603 patients treated with growth hormone in KIGS with no known factors conveying an a priori increased risk of cancer

Site of malignant neoplasm (*ICD-10* classification)	Number of observed cases	Number of expected cases	SIR (95% CI)
Any primary cancer (C00–C97, except C44*)	32	25.3	1.26 (0.86-1.78)
Brain/ CNS (C70–C72)	9	4.0	2.24 (1.02-4.25)
Testis (C62)	3	1.2	2.55 (0.51-7.46)
Non-Hodgkin lymphoma (C82–C85, C96)	3	2.1	1.41 (0. 28-4.11)
Leukemia (C91–C94)	3	6.2	0.48 (0.10-1.41)
Adrenal gland (C74)	2	0.25	7.93 (0.89-28.6)
Malignant melanoma (C43)	2	0.8	2.57 (0.29-9.27)
Kidney (C64)	2	0.7	2.98 (0.33-10.8)
Trachea and lung (C33+C34)	1	0.1	9.98 (0.13-55.5)
Bone (C40–C41)	1	2.05	0.49 (0.01-2.71)
Mesothelioma (C45)	1	0.05	22.0 (0.29-123)
Peripheral nerves , connective and soft tissue (C47, C49)	1	1.2	0.85 (0.01-4.72)
Ovary (C56)	1	0.7	1.36 (0.02-7.57)
Thyroid (C73)	1	0.75	1.33 (0.02-7.40)
Hodgkin lymphoma (C81)	1	2.5	0.40 (0.01-2.24)
Other and unspecified (C26, C39, C48, C76, C80)	1	0.3	3.43 (0.04-19.1)
All other cancer sites excluding non-melanoma skin tumors	0	2.4	Not applicable

ICD-10, International Statistical Classification of Diseases, 10th Revision.
*Other malignant neoplasm of skin (eg, basal cell carcinoma).

Estimates of cancer risk according to etiology of growth disorder are displayed in Table III. The greatest number of reported cancer cases was in patients with idiopathic GHD (the most common etiology of growth disorders in KIGS). There were 14 observed cases, including the 2 cases of germinoma aforementioned, compared with 13.8 expected. Types of neoplasm reported in patients with idiopathic GHD included cranial tumors (n = 7), non-Hodgkin lymphoma (n = 2), acute myeloid leukemia (n = 1), seminoma (n = 1), rhabdomyosarcoma (n = 1), papillary kidney cancer (n = 1), and fibromyxoid sarcoma (n = 1).

Discussion

This study excludes a large increase of the cancer incidence in patients treated with GH in KIGS with no known risk factors for cancer development compared with the overall cancer rate in the general population after accounting for age, sex, and country. This finding is in line with other studies that have assessed the risk of cancer in patients treated with GH, "high-risk" patients excluded.[17,18] Results published in 2000 from the National Cooperative Growth Study (NCGS), which used the same methodology as our study and also had a similar duration of follow-up, showed that the incidence of cancer in patients treated with GH who were "not at high-risk" was similar to that in the general population.[18] The estimated cancer incidence in the NCGS was 5.8 per 100 000 patient-years. In our study, the estimated incidence was 16.4 per 100 000 patient-years. The difference between the studies can be mainly attributed to the more restrictive definition of cancer cases in the NCGS, which included only extra-cranial malignancies and excluded leukemia. In this study, we included cranial tumors, despite the challenges in assessing whether the tumors diagnosed and reported as adverse events (eg, germinoma) were truly de novo tumors or rather the cause of GHD and thus present at start of treatment.

Three cases of testicular cancer were reported in KIGS, but only 1.2 cases were expected. Two of the patients had a medical history of cryptorchidism, a well-known risk factor for testicular cancer,[19] and 1 patient was also born SGA, which has similarly been described to increase the risk of testicular cancer.[20] The latter case has been reported previously.[21] Three cases of leukemia (1 acute lymphoblastic leukemia, 2 acute myeloblastic leukemia) were reported in KIGS, a number not significantly different from what would be expected in the general population. This result is in accordance with findings from studies in North America and Japan showing that the incidence of leukemia in patients treated with GH without known risk factors for cancer is no greater than the incidence in the general population.[22,23]

Swerdlow et al reported an increased incidence of colon cancer in patients treated with pituitary-derived GH in the United Kingdom.[7] No cases of colon cancer were reported in KIGS. However, although this analysis included a greater number of patients and patient-years (58 603 and 197 173, respectively) than the UK cohort (1848 patients, 29 817 patient-years), the follow-up time in KIGS (mean, 3.6 years) was limited compared with the UK study (mean, 16.1 years). This precludes a comprehensive evaluation of cancer risk in this analysis, particularly for cancers such as colon cancer that have a very low expected incidence in children, teenagers, and young adults in the general population.

Table III. Number of patients, patient-years, observed cases, expected cases, and overall standardized incidence ratio of malignant neoplasms by etiology of growth disorder in 58 603 patients treated with growth hormone patients in KIGS with no known factors conveying an a priori increased risk of cancer

Etiology of growth disorder	Number of patients	Number of patient-years	Number of observed cases	Number of expected cases	SIR (95% CI)
Idiopathic GHD	31 690	106 284	14	13.8	1.01 (0.55-1.70)
Turner syndrome	6510	26 370	7	3.2	2.21 (0.89-4.56)
Other causes of short stature	8806	28 097	3	3.5	0.87 (0. 17-2.54)
Craniopharyngioma	1151	4628	2	0.6	3.24 (0.36-11.7)
Other acquired GHD	446	1703	2	0.2	8.52 (0.96-30.7)
SGA	4215	9603	2	1.2	1.61 (0.18–5.82)
Chronic renal failure	1319	3918	1	0.5	1.84 (0.02-10.2)
Congenital GHD	2785	11479	1	1.6	0.65 (0.01-3.59)
Prader–Willi syndrome	1532	4556	0	0.6	0.0 (0.0-5.65)

Patients with Turner syndrome were included in this analysis, despite the possibility that this condition is associated with an increased risk of certain malignant neoplasms. An extensive epidemiological study including all patients diagnosed with Turner syndrome in Denmark did not find a general increase in the risk of malignant tumors in these patients, but did find an increase in colon cancer.[13] A recent study from the United Kingdom suggested an increased risk of some types of malignancy (colorectal cancer, bladder and urethra cancer, corpus uteri cancer, and neural crest-derived tumors such as neuroblastoma) associated with Turner syndrome.[14] Other studies have suggested an increased risk of gonadoblastoma.[10,12] In this study, no cases of any of these tumors were reported in patients with Turner syndrome, and the risk of developing malignant neoplasms was not significantly increased compared with that in the general population. This is in accordance with the findings in the NCGS in the United States.[24]

If there were an association between GH therapy and cancer, it is likely that the development of the tumor would take some time. There was no evidence that tumor incidence increased with time in this analysis. The highest SIR was found in the first 2 years of follow-up in KIGS. One possible explanation could be that some neoplasms diagnosed during GH treatment already existed before enrollment. We also compared 2 approaches to the classification of tumor onset in GH-naive patients with no known cancer-associated risk factors. The first approach involved the inclusion of all tumors reported and patient-years accumulated since the start of follow-up in KIGS, and the second involved the exclusion of tumors and patient-years occurring within 1 year of the start in KIGS. Both approaches resulted in similar SIRs and comparable risk estimates for all patients.

Various potential limitations of this study merit consideration. The study compared incidence rates in the study population with those in the general population. This methodological approach has been used in most studies evaluating the relationship between GH treatment and cancer.[7,9,17,18,22,23] However, the ideal reference population would be a cohort of patients who are affected by a similar range of growth disorders to the study population, but who have never received GH treatment. To our knowledge, such a cohort is not available. Consequently, the IARC database that contains reports on cancer incidence for the period 1998 to 2002 in most of the countries with patients in KIGS provided the information to enable us to stratify the KIGS data according to country, attained age at follow-up, and sex.

A comprehensive assessment of cancer risk associated with GH treatment would require follow-up of patients after the cessation of treatment. However, there is no systematic monitoring of patients who have exited the database (irrespective of whether they continue or cease GH therapy). Another limitation of this analysis is that the average follow-up period was only 3.6 years, with 84% of the patient-years being accumulated in the first 5 years after the initiation of treatment within KIGS. These 2 factors make it difficult to draw firm, general conclusions about the long-term risk of cancer associated with GH treatment.

It has been suggested previously that physicians may not report complete data to pharmacoepidemiological databases such as KIGS. However, we believe that because of concerns of the scientific community about the potential increase in cancer risk associated with GH treatment, the probability of under-reporting of cancer is low as long as the patients are participating in KIGS. Because a decision to stop GH treatment may have been motivated by suspicion of the development of cancer, we also included neoplasms when they were reported after exiting KIGS. There was only 1 such case reported, and it occurred 70 days after the patient's file had been closed. However, no formal follow-up occurs after the patients exit.

In conclusion, the incidence of cancer in young patients treated with GH who have no known risk factors for cancer was similar to the incidence in the general population. However, surveillance should continue to allow further assessment. ■

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References

1. Reiter EO, Price DA, Wilton P, Albertsson-Wikland K, Ranke MB. Effect of growth hormone (GH) treatment on the near-final height of 1258 patients with idiopathic GH deficiency: analysis of a large international database. J Clin Endocrinol Metab 2006;91: 2047-54.
2. Baxter L, Bryant J, Cave CB, Milne R. Recombinant growth hormone for children and adolescents with Turner syndrome. Cochrane Database Syst Rev 2007:CD003887.
3. Saenger P, Czernichow P, Hughes I, Reiter EO. Small for gestational age: short stature and beyond. Endocr Rev 2007;28:219-51.
4. Critical evaluation of the safety of recombinant human growth hormone administration: statement from the Growth Hormone Research Society. J Clin Endocrinol Metab 2001;86:1868-70.
5. Watanabe S, Tsunematsu Y, Fujimoto J, Komiyami A, Delemaare-van deWaal HA, Odink RJH, et al. Leukemia in patients treated with growth hormone. Lancet 1988;331:1159-60.
6. Perry JK, Emerald BS, Mertani HC, Lobie PE. The oncogenic potential of growth hormone. Growth Horm IGF Res 2006;16:277-89.
7. Swerdlow AJ, Higgins CD, Adlard P, Preece MA. Risk of cancer in patients treated with human pituitary growth hormone in the UK, 1959-85: a cohort study. Lancet 2002;360:273-7.
8. Ergun-Longmire B, Mertens AC, Mitby P, Qin J, Heller G, Shi W, et al. Growth hormone treatment and risk of second neoplasms in the childhood cancer survivor. J Clin Endocrinol Metab 2006;91: 3494-8.
9. Fradkin JE, Mills JL, Schonberger LB, Wysowski DK, Thomson R, Durako SJ, et al. Risk of leukemia after treatment with pituitary growth hormone. JAMA 1993;270:2829-32.
10. Teter J, Boczkowski K. Occurrence of tumors in dysgenetic gonads. Cancer 1967;20:1301-10.
11. Wertelecki W, Fraumeni J, Mulvihill J. Nongonadal neoplasia in Turners syndrome. Cancer 1970;26:485-8.
12. Hasle H, Olsen JH, Nielsen J, Hansen J, Friedrich U, Tommerup N. Occurrence of cancer in women with Turner syndrome. Br J Cancer 1996; 73:1156-9.
13. Gravholt CH, Juul S, Naeraa RW, Hansen J. Morbidity in Turner syndrome. J Clin Epidemiol 1998;51:147-58.
14. Schoemaker MJ, Swerdlow AJ, Higgins CD, Wright AF, Jacobs PA. Cancer incidence in women with Turner syndrome in Great Britain: a national cohort study. Lancet Oncol 2008;9:239-46.
15. Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Henaue, et al., editors. Cancer incidence in five continents. vol IX. Lyon: 2007.
16. Breslow D. The design and analysis of cohort studies. Statistical methods in cancer research. Lyon: IARC Scientific Publications; 1987. p. 69.
17. Tuffli G, Johanson A, Rundle A, Allen D. Lack of increased risk for extracranial, nonleukemic neoplasms in recipients of recombinant deoxyribonucleic acid growth hormone. J Clin Endocrinol Metab 1995;80:1416-22.
18. Maneatis T, Baptista J, Connelly K, Blethen S. Growth hormone safety update from the National Cooperative Growth Study. J Pediatr Endocrinol Metab 2000;13(Suppl. 2):1035-44.
19. Moller H, Skakkebaek NE. Testicular cancer and cryptorchidism in relation to prenatal factors: case-control studies in Denmark. Cancer Causes Control 1997;8:904-12.
20. Michos A, Xue F, Michels KB. Birth weight and the risk of testicular cancer: a meta-analysis. Int J Cancer 2007;121:1123-31.
21. Sakai Y, Tachibana N, Abo W, Tsukui A. Testicular neoplasm in patient treated with growth hormone. Lancet 1996;348:832.
22. 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:S32-6.
23. Nishi Y, Tanaka T, Takano K, Fujieda K, Igarashi Y, Hanew K, et al. Recent status in the occurrence of leukemia in growth hormone-treated patients in Japan. GH Treatment Study Committee of the Foundation for Growth Science, Japan. J Clin Endocrinol Metab 1999;84:1961-5.
24. Bolar K, Hoffman A, Maneatis T, Lippe B. Long-tem safety of recombinant human growth hormone in Turner syndrome. J.Clin Endocrinol Metab 2008;93:344-51.