0021-972X/06/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 91(9):3494–3498
Copyright © 2006 by The Endocrine Society
doi: 10.1210/jc.2006-0656

BRIEF REPORT

Growth Hormone Treatment and Risk of Second Neoplasms in the Childhood Cancer Survivor

Berrin Ergun-Longmire, Ann C. Mertens, Pauline Mitby, Jing Qin, Glenn Heller, Weiji Shi, Yutaka Yasui, Leslie L. Robison, and Charles A. Sklar

Department of Pediatrics (B.E.-L.), New York Presbyterian Hospital, Weill Medical College of Cornell, New York, New York 10021; Department of Pediatrics (A.C.M., P.M.), University of Minnesota School of Medicine, Minneapolis, Minnesota 55455; Departments of Epidemiology and Biostatistics (J.Q., G.H., W.S.), Memorial Sloan-Kettering Cancer Center, New York, New York 10021; Department of Public Health Sciences (Y.Y.), University of Alberta, Edmonton, Alberta, Canada, T6G 2G3; Department of Epidemiology and Cancer Control (L.L.R.), St. Jude Children's Research Hospital, Memphis, Tennessee 38105; and Department of Pediatrics (C.A.S.), Memorial Sloan-Kettering Cancer Center, New York, New York 10021

Context: GH deficiency is common in childhood cancer survivors. In a previous report, although we did not find an increase in the risk of disease recurrence in survivors treated with GH, GH-treated survivors did have an increased risk of developing a second neoplasm (SN) (rate ratio, 3.21).

Objective: In this analysis, we have reassessed the risk of GH-treated survivors developing an SN after an additional 32 months of follow-up.

Design and Setting: We conducted a retrospective cohort multicenter study.

Patients: Among a total of 14,108 survivors who were enrolled in the Childhood Cancer Survivor Study, a retrospective cohort of 5-yr survivors of childhood cancer, we identified 361 who were treated with GH.

Main Outcome: We assessed the risk of developing an SN.

Results: During the extended follow-up, five new SN developed in survivors treated with GH, for a total of 20 SN, all solid tumors. Using a time-dependent Cox model, the rate ratio of GH-treated survivors developing an SN, compared with non-GH-treated survivors, was 2.15 (95% confidence interval, 1.3–3.5; $P < 0.002$). Meningiomas were the most common SN (n = 9) among the GH-treated group.

Conclusion: Although cancer survivors treated with GH appear to have an increased risk of developing SN compared with survivors not so treated, the elevation of risk due to GH use appears to diminish with increasing length of follow-up. Continued surveillance is essential. **(*J Clin Endocrinol Metab* 91: 3494–3498, 2006)**

GH DEFICIENCY IS one of the most common endocrinopathies that develop in childhood cancer survivors (1, 2). GH, which has been used for more than 25 yr, appears to improve final height of childhood cancer survivors (3, 4). However, there have been safety concerns about the use of GH because of the mutagenic and carcinogenic properties of GH and IGF-I (5, 6).

To date, multiple reports, including our previous study, have not shown an increased risk of disease recurrence in childhood cancer survivors treated with GH (7–10), although potential selection bias makes the results of these studies difficult to interpret. However, our previous report indicated that cancer survivors treated with GH had a 3-fold increased risk of developing a second neoplasm (SN) compared with survivors not so treated (9).

In this study we have reassessed the risk of our initial cohort of GH-treated survivors developing an SN after an additional 32 months of follow-up.

First Published Online July 5, 1006

Abbreviations: CCSS, Childhood Cancer Survivor Study; CI, confidence interval; CNS, central nervous system; RR, rate ratio; SN, second neoplasm(s).

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

Subjects and Methods

Childhood Cancer Survivor Study (CCSS)

The details of the conduct and characteristics of the CCSS, also known to study participants as the Long-Term Follow-Up Study, have been published previously (11). In brief, the CCSS is a retrospective cohort of 5-yr survivors of childhood cancer diagnosed before age 21 yr, between the years 1970 and 1986, and treated at one of 26 contributing centers in the United States or Canada. Subjects with benign tumors, including craniopharyngioma, were excluded from the study. The study was approved by the institutional review board at each participating center, and each participant or parent, if participant was less than 18 yr of age, signed informed consent before participation.

Participation in the Long-Term Follow-Up Study consisted of completion of a 24-page questionnaire (complete questionnaire available at http://www.cancer.umn.edu/ccss), consent for release of medical records, and consent to be contacted in the future to update health history and to consider participation in ancillary research projects. The baseline questionnaire contained questions regarding a broad spectrum of topics, including demographics, medical conditions diagnosed by a doctor, prescription medications taken during the past 2 yr, and development of subsequent neoplasms. For individuals who indicated that they had been diagnosed with a subsequent neoplasm, verification of the diagnosis was made by requesting copies of the pathology report from the treating institution. All submitted material was reviewed by a single

pathologist (Sue Hammond, M.D., Children's Hospital, Columbus, OH). In the current analysis, subjects with SN do not include the occurrence of nonmelanoma skin cancers.

Detailed medical information was abstracted from the medical record of each participant (copy of abstraction forms available at http://www.cancer.umn.edu/ccss). Data collected included all treatments for the primary diagnosis, including the initial treatment, treatment for any relapse, and preparatory regimens for bone marrow transplant. Information about cancer treatment included qualitative information on 42 chemotherapeutic agents, quantitative information on 22 selected chemotherapeutic agents, surgeries performed from the time of diagnosis, and quantitative radiation data on field size, site, and dose.

The CCSS cohort consists of 14,352 survivors. Two hundred forty-four survivors were excluded from this analysis: 204 because of missing data regarding their exposure to GH treatment; 38 for diagnosis of a second tumor 5 yr or less from their primary cancer diagnosis; and two because of missing data on time of diagnosis of a second tumor. Thus, 14,108 survivors were eligible for this analysis, including 361 individuals previously documented to have been treated with GH (9). Details of their exposure to GH including start and stop date of GH, dose of GH, and height data were obtained from their physicians. All but two of the 361 survivors who were treated with GH began treatment before age 18 yr. A total of 3946 survivors (28%) were either lost to follow-up or refused participation in the current extended follow-up; this included 76 survivors treated with GH (21%) and 3870 survivors not treated with GH (28%; $P < 0.003$). An additional 60 survivors reported that they had started GH therapy during this 32-month extended follow-up. The data from these individuals were omitted from this analysis because of lack of detailed information on their GH exposure.

Statistical analysis

The relationship between GH therapy and the time to development of an SN, and death, were examined using a time-dependent Cox model (12). An adjustment for potential confounding factors such as age, sex, chemotherapy, alkylating agent score, and radiation were incorporated into the model. A test of association between the GH administration and SN is based on the score test derived from the partial likelihood of the model. The test examines whether $\beta = 0$, a result that implies that GH use does not alter the risk of SN. SN experienced within 5 yr of diagnosis were excluded from the analysis because of the CCSS eligibility criterion of survival of at least 5 yr after the original cancer diagnosis.

Results

The clinical characteristics of survivors, those both treated and not treated with GH, are summarized in Table 1. During this 32-month extended follow-up, five additional solid SN were reported for a total of 20 SN (Table 2). Among the survivors of central nervous system (CNS) tumors, there were three additional cases of meningioma and one new case of thyroid carcinoma. One of the neuroblastoma survivors developed an astroglial CNS tumor. There were no secondary leukemias found in this updated analysis, as was the case in our previous report (9). No new SN were reported among survivors of acute leukemia. A total of 555 SN were reported in the survivors not treated with GH, including 211 that occurred during this 32-month extended follow-up.

The risk factors associated with the development of an SN, in both the univariate and multivariate models, are shown in Table 3. The time-dependent Cox model revealed that after adjusting for potential cofounders such as age at diagnosis, sex, radiation, and alkylating agent effects, the rate ratio (RR) of GH-treated survivors developing an SN was 2.15 [95% confidence interval (CI), 1.33–3.47; $P = 0.002$] compared with survivors not treated with GH. The number of SN in GH-treated survivors compared with the number of SN in survivors who were not treated with GH is illustrated in Fig. 1. When the survivors were stratified by original cancer diagnosis, the differences between survivors who did and did not receive GH did not reach statistical significance for any of the diagnostic groups; the RR of developing an SN for survivors of leukemia was 2.3 (95% CI, 0.9–5.8; $P = 0.07$) and for CNS tumor survivors was 1.42 (95% CI, 0.67–3.02; $P = 0.35$). There was no association between dose and duration of GH therapy and the risk of developing an SN ($P = 0.1$ and $P = 0.8$, respectively).

In the GH-treated survivors, meningiomas were the most

TABLE 1. Patient characteristics

Variable	GH-treated (n = 361)	Non-GH-treated (n = 13,747)
Sex (male/female)	237/124	7317/6430
Age at cancer diagnosis (yr), median (range)	3.5 (0–17.2)	7.1 (0–21)
Diagnoses		
Tumors of the CNS	172	1601
Medulloblastoma[a]	71	265
Astroglial	66	1040
Ependymoma	15	116
Germ cell	14	36
Miscellaneous	6	144
Acute leukemia[b]	119	4825
Soft tissue sarcoma	43	772
Rhabdomyosarcoma	39	646
Neuroblastoma	17	698
Other	10	5851
Age at start of GH (yr), median (range)	11 (1–20.8)	
Duration of GH therapy (yr), median (range)	4.6 (0.1–14)[c]	
GH preparation		
Human pituitary only	43	
Recombinant only	279	
Both	27	
Unknown	12	

[a] Includes cases diagnosed with primitive neuroectodermal tumors.
[b] Includes cases diagnosed with non-Hodgkin's lymphoma.
[c] As of initial contact.

TABLE 2. Patients with SN after GH therapy

Patient no.	Sex	Primary malignancy					SN		
		Age at diagnosis (yr)	Diagnosis	Treatment			Diagnosis and site	Time after first diagnosis (yr)	Time after start of GH (yr)
				RT (site)	Chemo	AA			
1	M	5.2	ALL	Yes (B+TBI)	Yes	Yes	Osteosarcoma, LE	12.7	3.7
2	M	3	ALL	Yes (B+TBI)	Yes	Yes	Osteosarcoma, bone	10	2.5
3	M	2.5	ALL	Yes (B+S)	Yes	Yes	Astrocytoma, brain	10.1	2.7
4	F	7.2	ALL	Yes (B+S)	Yes	Yes	Glioma, brain	7.9	2.5
5	F	8.8	NHL	Yes (B+S)	Yes	Yes	Meningioma	15.5	11.7
6	F	5.8	NHL	Yes (F)	Yes	Yes	Osteosarcoma, F	12.5	6.5
7	F	1.5	Medulloblastoma	Yes (B+S)	Yes	Yes	Meningioma	9	4.5
8	F	7.9	Medulloblastoma	Yes (B+S)	Yes	Yes	Mucoepidemoid carcinoma, parotid	11.6	4.7
9	M	1	Medulloblastoma	Yes (B+S)	Yes	Yes	Meningioma	8.1	3.8
10	M	2	Medulloblastoma	Yes (B+S)	Yes	Yes	Meningioma	5.6	2.1
11	M	10.8	PNET	Yes (B+S)	Yes	Yes	Meningioma	12.7	9.4
12	M	4.8	Glioma	Yes (B)	No	No	Adenocarcinoma, colon	8.5	5.2
13	M	7.4	Germ cell tumor	Yes (B+S)	Yes	Yes	Meningioma	10.1	6.5
14	F	6.6	Rhabdomyosarcoma, nspx	Yes (F+N)	Yes	Yes	Spindle cell sarcoma, N	17	2.8
15	M	4.6	Rhabdomyosarcoma, nspx	Yes (F+N)	Yes	Yes	Sarcoma, tongue	16.1	6.9
16[a]	M	6.8	PNET	Yes (B+S)	No	No	Meningioma	14	11
17[a]	F	4.8	Astrocytoma	Yes (B)	No	No	Papillary carcinoma, thyroid	15	8.9
18[a]	F	6.6	Astrocytoma	Yes (B)	No	No	Meningioma	22	17
19[a]	F	3.2	Cerebral sarcoma	Yes (B)	Yes	Yes	Meningioma	13	2.7
20[a]	F	1.5	Neuroblastoma	Yes (B+S)	No	No	Glioma, B	18	11

AA, Alkylating agent; ALL, acute lymphoblastic leukemia; B, brain; Chemo, chemotherapy; F, face; LE, lower extremity; NHL, non-Hodgkin's lymphoma; nspx, nasopharynx; PNET, primitive neuroectodermal tumor; RT, radiation therapy; S, spine; M, male; F, female; N, neck; TBI, total body irradiation.

[a] New cases.

common SN (nine of 20). In the survivors who were not treated with GH, there were a total of 62 cases that developed a meningioma. All GH-treated survivors who developed a meningioma had received radiation to the brain/head. The latency period for developing a meningioma in the GH-treated group was 12.2 yr, compared with 19 yr in the survivors not treated with GH ($P < 0.01$). In the GH-treated group, six survivors were diagnosed with a meningioma after completing their GH treatment, and three survivors developed a meningioma while they were still receiving GH treatment.

TABLE 3. Risk factors for occurrence of SN

Covariate	RR (95% CI)	*P*
Univariate model		
Sex		<0.0001
Female	1.00	
Male	0.53 (0.44–0.62)	
Age at primary diagnosis (risk/yr)	1.08 (1.06–1.09)	<0.0001
Alkylating agent		0.0002
No	1.00	
Yes	1.41 (1.18–1.69)	
Radiation		<0.0001
No	1.00	
Yes	3.00 (2.32–3.87)	
Chemotherapy		0.67
No	1.00	
Yes	0.96 (0.78–1.17)	
GH		0.004
No	1.00	
Yes	1.92 (1.22–2.99)	
Multivariate model		
Sex		<0.0001
Female	1.00	
Male	0.52 (0.43–0.63)	
Age at diagnosis (risk/yr)	1.07 (1.06–1.09)	<0.0001
Alkylating agent		0.004
No	1.00	
Yes	1.30 (1.09–1.56)	
Radiation		<0.0001
No	1.00	
Yes	2.88 (2.20–3.78)	
GH		0.002
No	1.00	
Yes	2.15 (1.33–3.47)	

A total of 1570 survivors have died, including 33 of the 361 GH-treated survivors and 1537 survivors not treated with GH. The percentage of deaths due to an SN was similar for survivors treated with GH compared with survivors not so treated (25 *vs.* 13%; $P = 0.16$). After adjusting for the covariate effects of age at diagnosis, sex, radiation, and chemotherapy

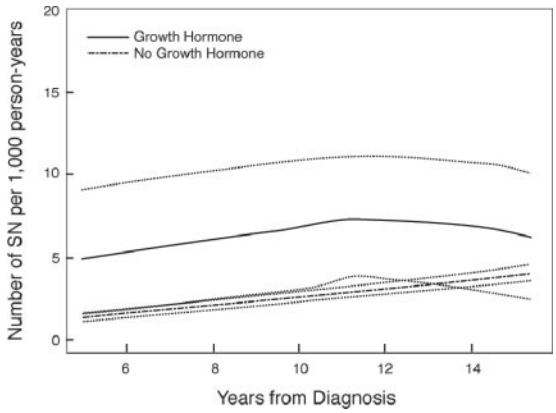

FIG. 1. Comparison of the number of SN estimated per 1000 person-years for survivors who did and did not receive treatment with GH, plotted against time from diagnosis. The plot includes 95% CIs.

in the multivariate model, the RR of death for GH-treated patients compared with those not treated with GH was 1.20 (95% CI, 0.81–1.79; $P = 0.36$).

Discussion

In this updated analysis that includes an additional 32 months of follow-up of our initial cohort, we have shown that the risk of developing an SN in childhood cancer survivors treated with GH remains elevated compared with the risk seen in survivors not treated with GH. Although this finding is in agreement with our previous report (9), our current findings suggest that the risk appears to diminish with increasing length of follow-up (*i.e.* RR 2.15 *vs.* RR 3.21).

Of the SN noted among our survivors treated with GH, we found that meningiomas were the most common. In the current study, all GH-treated survivors who developed a meningioma had received some radiation to the brain as part of the treatment for their primary cancer. Meningiomas are known to develop after radiation to the head for benign and malignant conditions (13–15). For survivors of CNS tumors, meningiomas are among the most common SN observed after therapeutic radiation to the brain (16–18).

Because meningiomas may remain asymptomatic for prolonged periods of time (19, 20), the possibility of surveillance/detection bias needs to be considered when interpreting our results. Thus, if survivors treated with GH had been subjected to more consistent and frequent medical surveillance (*e.g.* magnetic resonance imaging of the head) compared with survivors not treated with GH, our results could have overestimated the risk (21). We did observe a shorter latency period between radiation and the diagnosis of meningiomas in the GH-treated group compared with the group not so treated. Although this could represent differences in how the two groups were followed and scrutinized, we cannot exclude a true biological effect of GH on the development and progression of the meningiomas (5). In the current study, we did not have sufficient data to determine whether surveillance bias played a role in our findings; this can be determined best through a long-term prospective study.

In our previous study, we noted no cases of secondary leukemia but an excess number of secondary osteogenic sarcomas among leukemia survivors treated with GH. In this extended follow-up study, we also failed to detect any cases of secondary leukemia among the survivors treated with GH. No additional cases of osteogenic sarcoma or any other SN were found in leukemia survivors treated with GH in this extended follow-up, which is reassuring. Although the lost-to-follow-up/refusal rates were lower for the GH-treated survivors compared with survivors not so treated, it is unlikely that this difference (21 *vs.* 28%) has resulted in an appreciable bias in our estimates of RR of SN.

In conclusion, this updated analysis confirms our previous report that childhood cancer survivors treated with GH appear to have an elevated risk of developing a secondary solid tumor compared with survivors not so treated. However, the elevation of risk resulting from GH use appears to decrease with increasing length of follow-up, and the overall risk remains small. This risk should be weighed against the potential benefits of GH therapy in cancer survivors. Our findings indicate a need for continued surveillance of childhood cancer survivors treated with GH.

Acknowledgments

The following is the list of CCSS institutions and investigators: University of California-San Francisco, San Francisco, CA: Robert Goldsby, M.D.,[a] and Arthur Ablin, M.D.[b]; University of Alabama, Birmingham, AL: Roger Berkow, M.D.[a]; International Epidemiology Institute, Rockville, MD: John Boice, Sc.D.[c]; University of Washington, Seattle, WA; Norman Breslow, Ph.D.[c]; University of Texas-Southwestern Medical Center at Dallas, Dallas TX: Gail Tomlinson, M.D.,[a] and George R. Buchanan, M.D.[b]; Cincinnati Children's Hospital Medical Center, Cincinnati, OH: Stella Davies, M.D., Ph.D.[c]; Dana-Farber Cancer Institute, Boston, MA: Lisa Diller, M.D.,[a] Holcombe Grier, M.D.,[b] and Frederick Li, M.D.[c]; Texas Children's Center, Houston, TX: Zoann Dreyer, M.D.[a]; Children's Hospital and Medical Center, Seattle, WA: Debra Friedman, M.D., M.P.H.,[a] and Thomas Pendergrass, M.D.[b]; Roswell Park Cancer Institute, Buffalo, NY: Daniel M. Green, M.D.[a,c]; Hospital for Sick Children, Toronto, Ontario, Canada; Mark Greenberg, M.B., Ch.B.[a]; St. Louis Children's Hospital, St. Louis, MO: Robert Hayashi, M.D.,[a] and Teresa Vietti, M.D.[b]; St. Jude Children's Research Hospital, Memphis, TN: Leslie L. Robison, Ph.D.,[a,c] and Melissa Hudson, M.D.[a,c]; University of Michigan, Ann Arbor, MI: Raymond Hutchinson, M.D.[a]; Stanford University School of Medicine, Stanford, CA: Neyssa Marina, M.D.,[a] Michael P. Link, M.D.,[b] and Sarah S. Donaldson, M.D.[c]; Emory University, Atlanta, GA: Lillian Meacham, M.D.[a]; Children's Hospital of Philadelphia, PA: Anna Meadows, M.D.,[a,c] and Bobbie Bayton[c]; Children's Hospital, Oklahoma City, OK: John Mulvihill, M.D.[c]; Children's Hospital, Denver, CO: Brian Greffe, M.D.,[a] and Lorrie Odom, M.D.[b]; Children's Hospitals and Clinics of Minnesota: Joanna Perkins, M.D.,[a] and Maura O'Leary, M.D.[b]; Columbus Children's Hospital, Columbus, OH: Amanda Termuhlen, M.D.,[a] Frederick Ruymann, M.D.,[b] and Stephen Qualman, M.D.[c]; Children's National Medical Center, Washington, DC: Gregory Reaman, M.D.,[a] and Roger Packer, M.D.[c]; Children's Hospital of Pittsburgh, Pittsburgh, PA: A. Kim Ritchey, M.D.,[a] and Julie Blatt, M.D.[b]; University of Minnesota, Minneapolis, MN: Ann Mertens, Ph.D.,[a,c] Joseph Neglia, M.D., M.P.H.,[c] and Mark Nesbit, M.D.[c]; Children's Hospital Los Angeles, Los Angeles, CA: Kathy Ruccione, R.N., M.P.H.[a]; Memorial Sloan-Kettering Cancer Center, New York, NY: Charles Sklar, M.D.,[a,c] and Kevin Oeffinger, M.D.[c]; National Cancer Institute, Bethesda, MD: Barry Anderson, M.D.,[c] and Peter Inskip, Sc.D.[c]; Mayo Clinic, Rochester, MN: Vilmarie Rodriguez, M.D.,[a] W. Anthony Smithson, M.D., and Gerald Gilchrist, M.D.[b]; University of Texas M.D. Anderson Cancer Center, Houston, TX: Louise Strong, M.D.,[a,c] and Marilyn Stovall, Ph.D.[c]; Riley Hospital for Children, Indianapolis, IN: Terry A. Vik, M.D.,[a] and Robert Weetman, M.D.[b]; Fred Hutchinson Cancer Research Center, Seattle, WA: Wendy Leisenring, Sc.D.,[a,c] and John Potter, M.D., Ph.D.[b,c]; University of Alberta, Edmonton, Alberta, Canada: Yutaka Yasui, Ph.D.[b,c]; and University of California-Los Angeles, Los Angeles, CA: Lonnie Zeltzer, M.D.[a,c] ([a] Institutional Principal Investigator; [b] Former Institutional Principal Investigator; [c] Member CCSS Steering Committee).

Received March 24, 2006. Accepted June 23, 2006.

Address all correspondence and requests for reprints to: Charles A. Sklar, M.D., Department of Pediatrics, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, New York, 10021. E-mail: sklarc@mskcc.org.

This work was supported by grants from the National Institutes of Health (U24-CA-55727 to L.L.R., Principal Investigator) and the Genentech Foundation for Growth and Development (awarded to C.A.S.). This research used the CCSS, a resource supported by the National Cancer Institute to promote and facilitate research on long-term survivors of cancer diagnosed in childhood and adolescence. Investigators may apply to use the CCSS by proposing an analysis of existing data or proposing new initiatives that would use the cohort. Interested investigators are encouraged to visit the CCSS website at www.cancer.umn.edu/ccss to learn more about this unique resource.

Disclosure summary: B.E.-L., A.C.M., P.M., J.Q., G.H., W.S., and Y.Y. have nothing to declare. L.L.R. is on the advisory board of Eli Lilly & Co.

C.A.S. was on the advisory board of Novo Nordisk and has received lecture fees from Genentech, Novo Nordisk, and Pfizer.

References

1. **Clayton PE, Shalet SM** 1991 Dose dependency of time of onset of radiation-induced growth hormone deficiency. J Pediatr 118:226–282
2. **Sklar CA, Constine LS** 1995 Chronic neuroendocrinological sequelae of radiation therapy. Int J Radiat Oncol Biol Phys 31:1113–1121
3. **Gleeson HK, Stoeter R, Ogilvy-Stuart AL, Gattamaneni HR, Brennan BM, Shalet SM** 2003 Improvements in final height over 25 years in growth hormone (GH)-deficient childhood survivors of brain tumors receiving GH replacement. J Clin Endocrinol Metab 88:3682–3689
4. **Brownstein CM, Mertens AC, Mitby PA, Stovall M, Qin J, Heller G, Robison LL, Sklar CA** 2004 Factors that affect final height and change in height standard deviation scores in survivors of childhood cancer treated with growth hormone: a report from the childhood cancer survivor study. J Clin Endocrinol Metab 89:4422–4427
5. **Khandwala HM, McCutcheon IE, Flyvbjerg A, Friend KE** 2000 The effects of insulin-like growth factors on tumorigenesis and neoplastic growth. Endocr Rev 21:215–244
6. **Sklar CA** 2004 Growth hormone treatment: cancer risk. Horm Res 62 (Suppl 3):30–34
7. **Moshang Jr T, Rundle AC, Graves DA, Nickas J, Johanson A, Meadows A** 1996 Brain tumor recurrence in children treated with growth hormone: the National Cooperative Growth Study experience. J Pediatr 128:S4–S7
8. **Swerdlow AJ, Reddingius RE, Higgins CD, Spoudeas HA, Phipps K, Qiao Z, Ryder WD, Brada M, Hayward RD, Brook CG, Hindmarsh PC, Shalet SM** 2000 Growth hormone treatment of children with brain tumors and risk of tumor recurrence. J Clin Endocrinol Metab 85:4444–4449
9. **Sklar CA, Mertens AC, Mitby P, Occhiogrosso G, Qin J, Heller G, Yasui Y, Robison LL** 2002 Risk of disease recurrence and second neoplasms in survivors of childhood cancer treated with growth hormone: a report from the Childhood Cancer Survivor Study. J Clin Endocrinol Metab 87:3136–3141
10. **Leung W, Rose SR, Zhou Y, Hancock ML, Burstein S, Schriock EA, Lustig R, Danish RK, Evans WE, Hudson MM, Pui CH** 2002 Outcomes of growth hormone replacement therapy in survivors of childhood acute lymphoblastic leukemia. J Clin Oncol 20:2959–2964
11. **Robison LL, Mertens AC, Boice JD, Breslow NE, Donaldson SS, Green DM, Li FP, Meadows AT, Mulvihill JJ, Neglia JP, Nesbit ME, Packer RJ, Potter JD, Sklar CA, Smith MA, Stovall M, Strong LC, Yasui Y, Zeltzer LK** 2002 Study design and cohort characteristics of the Childhood Cancer Survivor Study: a multi-institutional collaborative project. Med Pediatr Oncol 38:229–239
12. **Andersen P, Borgan O, Gill R, Keiding N** 1991 Statistical methods based on counting processes, 1st ed. Berlin: Springer
13. **Mann I, Yates PC, Ainslie JP** 1953 Unusual case of double primary orbital tumour. Br J Ophthalmol 37:758–762
14. **Neglia JP, Meadows AT, Robison LL, Kim TH, Newton WA, Ruymann FB, Sather HN, Hammond GD** 1991 Second neoplasms after acute lymphoblastic leukemia in childhood. N Engl J Med 325:1330–1336
15. **Pollak L, Walach N, Gur R, Schiffer J** 1998 Meningiomas after radiotherapy for tinea capitis–still no history. Tumori 84:65–68
16. **Strojan P, Popovic M, Jereb B** 2000 Secondary intracranial meningiomas after high-dose cranial irradiation: report of five cases and review of the literature. Int J Radiat Oncol Biol Phys 48:65–73
17. **Al-Mefty O, Topsakal C, Pravdenkova S, Sawyer JR, Harrison MJ** 2004 Radiation-induced meningiomas: clinical, pathological, cytokinetic, and cytogenetic characteristics. J Neurosurg 100:1002–1013
18. **Jostel A, Mukherjee A, Hulse PA, Shalet SM** 2005 Adult growth hormone replacement therapy and neuroimaging surveillance in brain tumour survivors. Clin Endocrinol (Oxf) 62:698–705
19. **Kamiguchi H, Shiobara R, Toya S** 1996 Accidentally detected brain tumors: clinical analysis of a series of 110 patients. Clin Neurol Neurosurg 98:171–175
20. **Kuratsu J, Kochi M, Ushio Y** 2000 Incidence and clinical features of asymptomatic meningiomas. J Neurosurg 92:766–770
21. **Pottern LM, Kaplan MM, Larsen PR, Silva JE, Koenig RJ, Lubin JH, Stovall M, Boice Jr JD** 1990 Thyroid nodularity after childhood irradiation for lymphoid hyperplasia: a comparison of questionnaire and clinical findings. J Clin Epidemiol 43:449–460.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.