0013-7227/02/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 87(7):3136–3141

Risk of Disease Recurrence and Second Neoplasms in Survivors of Childhood Cancer Treated with Growth Hormone: A Report from the Childhood Cancer Survivor Study

CHARLES A. SKLAR, ANN C. MERTENS, PAULINE MITBY, GLENN OCCHIOGROSSO, JING QIN, GLENN HELLER, YUTAKA YASUI, AND LESLIE L. ROBISON

Departments of Pediatrics (C.A.S., G.O.) and Epidemiology and Biostatistics (J.Q., G.H.), Memorial Sloan-Kettering Cancer Center, New York, New York 10021; Department of Pediatrics, University of Minnesota School of Medicine (A.C.M., P.M., L.L.R.), Minneapolis, Minnesota 55455; and Cancer Prevention Research Program, Fred Hutchinson Cancer Research Center (Y.Y.), Seattle, Washington 98104

GH deficiency is common in survivors of childhood cancer, especially in those treated with radiation to the brain. The impact of GH therapy on disease recurrence has been studied in survivors of pediatric brain tumors, but few data are available on the risk of disease recurrence in survivors of other tumor types who are treated with GH. Likewise, the risk of second neoplasms (SN) associated with GH use has not been systematically evaluated.

We studied 361 GH-treated cancer survivors (including 172 brain tumor survivors) from among 13,539 survivors enrolled in the Childhood Cancer Survivor Study, a cohort of 5-yr survivors of childhood cancer. Using a time-dependent Cox model, we compared risk of recurrence, risk of SN, and risk of death between survivors who did and did not receive treatment with GH.

The relative risk of disease recurrence was 0.83 (95% confidence interval, 0.37–1.86; $P = 0.65$) for GH-treated survivors. The relative risk of recurrence was not increased for any of the major cancer diagnoses. GH-treated subjects were diagnosed with 15 SN, all solid tumors and no secondary leukemias, for an overall relative risk of 3.21 (95% confidence interval, 1.88–5.46; $P < 0.0001$). This was mainly due to a small excess number of SN observed in GH-treated survivors of acute leukemia. The risk of death was not associated with GH use ($P = 0.43$).

We conclude that GH therapy does not appear to increase the risk of disease recurrence or death in survivors of childhood cancer. The increased number of SN, particularly in survivors of acute leukemia, is of concern, but the data need to be interpreted with caution given the small number of events. (*J Clin Endocrinol Metab* 87: 3136–3141, 2002)

THE SURVIVAL rates for children and adolescents with cancer have improved steadily over the past 25–30 yr, largely due to improvements in therapy. Currently, the overall 5-yr survival rate for childhood cancer is in excess of 70% (1). Although newer treatment strategies have decreased mortality rates substantially, survivors are at risk of developing a variety of late complications that are directly attributable to their previous cancer treatment. The most prevalent late effects of cancer therapy are endocrine disorders, which can be demonstrated in some 40% of childhood cancer survivors (2).

GH deficiency is among the most common endocrinopathies noted in this population. It is found in survivors treated for tumors that arise in the region of the hypothalamus and pituitary (3) or, more commonly, after irradiation of the hypothalamic-pituitary unit (4). As GH has mitogenic and proliferating properties, there has been concern that treating cancer survivors with GH might increase their risk of either disease recurrence or the development of second neoplasms (SN). These concerns have been fueled by a variety of clinical studies, including those demonstrating an increased risk of colon cancer in subjects with acromegaly (5), a possible increased incidence of leukemias occurring in pediatric subjects treated with GH (6, 7), and the recent epidemiological data suggesting that higher circulating levels of IGF-I within the normal range, in particular if associated with low IGF-binding protein-3 levels within the normal range, are associated with an increased risk for the common malignancies of adulthood (8, 9).

A number of investigators have now addressed the issue of GH replacement therapy and the risk of disease recurrence, with largely negative findings (10–14). However, as these studies have been confined, almost exclusively, to survivors of central nervous system (CNS) tumors, there remains uncertainty about the risk of disease recurrence when GH is administered to survivors of pediatric cancers other than CNS tumors. Similarly, there is only limited information on the risk of SN in childhood cancer survivors treated with GH (15). In the current study we have attempted to address these deficiencies by assessing the risk of disease recurrence and SN in a large cohort of childhood cancer survivors, including a sizable number of survivors of cancers other than brain tumors, who have been treated with GH replacement therapy.

Abbreviations: CCSS, Childhood Cancer Survivor Study; CI, confidence interval; CNS, central nervous system; RR, relative risk; SN, second neoplasms.

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 (16, 17). In brief, the CCSS is a retrospective cohort of 5-yr survivors of childhood cancer diagnosed before age 21 yr, between the years of 1970–1986, and treated at 1 of 25 contributing centers located 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 relating to 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).

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.

Survivors treated with GH

The baseline questionnaires of all 13,539 participants in the CCSS available at the time of this study were scanned, and 684 participants were identified as having indicated "yes" or "not sure" to the query, "Have you ever received injections of GH?" and/or included GH on the list of prescription medications. We attempted to contact each of the 684 survivors, or their parents if they were either under age 18 yr or known to be deceased, to obtain the name and contact information of the physician(s) who had prescribed GH. For cases who were lost to follow-up or unreachable, we asked the data manager at the treating institution to search the medical records for this information.

Once a physician was identified, we sent them a form requesting specific and detailed information about the GH exposure of the individual survivor. In addition, we requested copies of important laboratory studies (*e.g.* GH stimulation tests) and all available growth records. Completed forms were returned for 469 of 684 (69%) survivors. We were able to verify that 361 of the 469 had been or were currently being treated with GH, whereas 108 had never received GH therapy. For the remaining 215 survivors (31%), GH treatment status was unknown: 30 patients refused to participate in this study; for 149 cases no forms were returned despite multiple attempts to obtain information from the physicians' offices; and for 36 cases data forms were returned, but the information provided was deemed to be insufficient. The patients with complete data were similar to those for whom we had no or insufficient data in terms of cancer diagnoses, cancer treatment exposures, and survival status, but the survivors lacking adequate GH information had been diagnosed and treated for cancer during an earlier time period ($P < 0.005$).

Statistical analysis

This was an observational study intended to determine whether there is a relationship between GH and 1) time to recurrence of the primary malignancy and 2) time to an SN. To demonstrate the association between GH administration and the time to recurrence, the Kaplan-Meier estimate was modified to incorporate the postbaseline GH treatment. Each patient receiving GH was compared with a randomly selected group of 39 patients who never received GH. The time of GH administration for the single patient became the starting time for all 40 patients, effectively equalizing the follow-up period. This technique simulated the situation where follow-up began at the time of GH administration. As the time to GH administration varied significantly between patients, no single landmark time was deemed appropriate to start the follow-up time in the Kaplan-Meier estimate; hence, this methodology was chosen.

The influence of GH administration on the risk of an SN was examined through the hazard rate. A kernel smoothed hazard function integrated over a 1-yr period was used to estimate the number of SN in the following year per 1000 people (18). The estimate of T years after diagnosis was computed for the group who received GH by time T and separately for the group who did not. Once GH was administered, the estimate for that subject shifts from the no GH incidence curve to the GH incidence curve.

The relationship between GH therapy and the clinical events, time to recurrence, and SN was also examined using a time-dependent Cox model (18). The time-dependent GH indicator was defined as:

$$g(t) = \begin{cases} 1 & \text{if GH was administered by time t} \\ 0 & \text{otherwise} \end{cases}$$

An adjustment for potential confounding factors, such as age, sex, chemotherapy, alkylating agent score (19), and radiation, was incorporated into the model.

The time-dependent Cox model can be written as

$$RR(t) = \exp\left[\beta\, g(t) + \sum_j \gamma_j z_j\right]$$

where RR(t) is the relative risk of recurrence or SN at time t, β is the log relative risk parameter associated with the GH covariate, and $\{z_j\}$, $\{\gamma_j\}$ represent the sets of possible confounding factors and their parameters, respectively. A test of association between GH administration and clinical outcome is based on the score test derived from the partial likelihood of this model. The test examines whether $\beta = 0$, a result that implies that GH use does not alter the risk of clinical outcome. Recurrences and 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 the 361 GH-treated survivors are summarized in Table 1. Patients were followed for a median of 6.2 (0.4–20.6) years after initiation of GH.

Risk of recurrence

Complete data on first recurrence were available for 12,039 patients, including 297 who were treated with GH. Survivors treated with GH experienced 9 first recurrences, 6 of which occurred after starting GH replacement therapy. Five recurrences were noted during GH therapy and 1 after therapy was completed. A total of 502 first recurrences were recorded in the survivors who had not been treated with GH.

The risk factors associated with disease recurrence for both the univariate and multivariate models are listed in Table 2. In the univariate analysis we found no association between GH administration and risk of recurrence ($P = 0.52$; see Fig. 1). The time-dependent Cox model revealed that after adjusting for age at diagnosis, radiation, and chemotherapy effects, the RR of a first recurrence was 0.83 [95% confidence interval (CI), 0.37–1.86; $P = 0.65$] for GH-treated survivors compared with those not treated with GH.

We calculated RR estimates for disease recurrence for GH-treated survivors stratified by initial cancer diagnosis (Table

TABLE 1. Characteristics of survivors

Variable	GH treated (n = 361)	Non-GH treated (n = 12,963)
Sex: M:F	237:124	6,874:6,089
Age at cancer diagnosis (yr) median (range)	3.5 (0–17.2)	7.2 (0–21)
Diagnoses		
Tumors of the CNS	172	1,489
Medulloblastoma[a]	73	245
Astroglial	68	979
Ependymoma	15	104
Germ cell	14	34
Miscellaneous	2	127
Acute leukemia[b]	122	4,545
Soft tissue sarcoma	43	731
Rhabdomyosarcoma	39	608
Neuroblastoma	17	659
Other	7	5,539
Age at start of GH (yr) median (range)	10 (3.1–20.8)	
Duration of GH therapy (yr) median (range)	4.6 (0.1–14)	
GH preparations		
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.

TABLE 2. Risk factors for disease recurrence

Covariate	RR (95% CI)	*P*
Univariate model		
Radiation		<0.0001
No	1.00	
Yes	2.12 (1.66–2.70)	
Age at tumor diagnosis (risk/yr)	1.04 (1.02–1.05)	<0.0001
Chemotherapy		0.0048
No	1.00	
Yes	1.46 (1.12–1.90)	
Sex		0.48
Female	1.00	
Male	1.09 (0.92–1.30)	
GH		0.48
No	1.00	
Yes	0.75 (0.34–1.68)	
Multivariate model		
Radiation		<0.0001
No	1.00	
Yes	2.01 (1.57–2.57)	
Age at diagnosis (risk/yr)	1.03 (1.01–1.05)	0.0004
Chemotherapy		0.0022
No	1.00	
Yes	1.52 (1.16–1.98)	
GH		0.65
No	1.00	
Yes	0.83 (0.37–1.86)	

3). For all diagnoses the risk of disease recurrence was not greater for GH-treated survivors compared with survivors who were not treated with GH. For CNS tumor survivors as a group as well as for medulloblastoma survivors, the risk of disease recurrence was actually significantly reduced for cases treated with GH compared with survivors not treated with GH (Table 3).

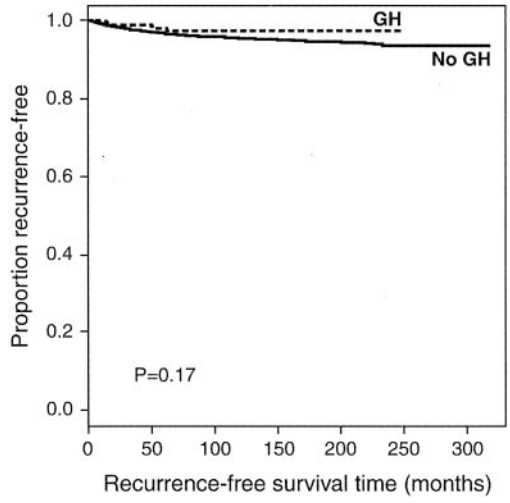

FIG. 1. The proportion of survivors who did not experience a recurrence of their primary cancer. Survivors treated with GH are compared with survivors who never received GH treatment.

TABLE 3. Multivariate analysis of risk of disease recurrence in patients treated with GH by initial diagnosis

Diagnosis	RR (95% CI)	*P*
CNS Tumors	0.31 (0.13–0.77)	0.01
Medulloblastoma	0.13 (0.02–0.94)	0.04
Astroglial	0.98 (0.35–2.75)	0.96
Ependymoma	0 (0–13)[a]	0.41
Germ cell	[b]	
Acute leukemia	0.85 (0.12–6.14)	0.87
Rhabdomyosarcoma	0 (0–4)[a]	0.31
Neuroblastoma	0 (0–35)[a]	0.73

[a] No recurrences occurred after GH therapy in patients in these diagnostic groups and, thus, the RR estimate is 0. The 95% CIs are calculated using the offset method in the time-dependent Cox model.
[b] No recurrences occurred in either the GH- or non-GH-treated groups, therefore, the RR cannot be determined.

Risk of SN

Complete information on SN was available for 13,222 patients, including 354 who were treated with GH. Survivors treated with GH had been diagnosed with 16 SN, 15 of which occurred after the start of GH therapy. Seven SN occurred during GH therapy and 8 after its completion. All 15 post-GH SN were solid tumors; no secondary leukemias were found (Table 4). All but 1 (case 12, Table 4) of the 14 evaluable SN arose at a site previously exposed to external radiation and in a patient exposed to alkylating agents during his/her initial cancer therapy. A total of 344 SN were recorded in the cases never treated with GH.

The risk factors associated with the occurrence of SN in both the univariate and multivariate models are shown in Table 5. The time-dependent Cox model revealed that after adjusting for age at diagnosis, sex, radiation, and alkylating agent effects, the RR of an SN for GH-treated survivors compared with those not treated with GH was 3.21 (95% CI, 1.88–5.46; $P < 0.0001$).

The risk of developing an SN for GH-treated survivors, grouped by original cancer diagnosis, is shown in Table 6. The overall increased RR noted for patients treated with GH would appear to be accounted for primarily by the excess

TABLE 4. Patients with second neoplasms after GH

Patient no.	Sex	Primary malignancy					Second neoplasm		
		Age at diagnosis (yr)	Diagnosis	Treatment			Diagnosis	Time after first diagnosis (yr)	Time after start of GH (yr)
				RT (site)	Chemo	AA			
1	M	5.2	ALL	Y (B, TBI)	Y	Y	Osteogenic sarcoma, LE	12.7	3.7
2	M	3.0	ALL	Y (B, TBI)	Y	Y	Osteogenic sarcoma,	10	2.5
3	M	2.5	ALL	NA	NA	NA	Astrocytoma, brain	10.1	2.7
4	F	7.2	ALL	Y (B+S)	Y	Y	Glioma, brain	7.9	2.5
5	F	8.8	NHL	Y (B+S)	Y	Y	Meningioma,	15.5	11.7
6	F	5.8	NHL	Y (F)	Y	Y	Osteogenic sarcoma, face	12.5	6.5
7	F	1.5	MB	Y (B+S)	Y	Y	Meningioma	9.0	4.5
8	F	7.9	MB	Y (B+S)	Y	Y	Mucoepidermoid carcinoma, parotid	11.6	4.7
9	M	1.0	MB	Y (B+S)	Y	Y	Meningioma	8.1	3.8
10	M	2.0	MB	Y (B+S)	Y	Y	Meningioma	5.6	2.1
11	M	10.8	PNET	Y (B+S)	Y	Y	Meningioma	12.7	9.4
12	M	4.8	Glioma	Y (B)	N	N	Adenocarcinoma, colon	8.5	5.8
13	M	7.4	GCT	Y (B+S)	Y	Y	Meningioma	10.1	6.5
14	F	6.6	RMS, nspx	Y (F+N)	Y	Y	Spindle cell sarcoma, neck	17	2.8
15	M	4.6	RMS, nspx	Y (F+N)	Y	Y	Sarcoma, tongue	16.1	6.9

ALL, Acute lymphoblastic leukemia; NHL, non-Hodgkin's lymphoma; MB, medulloblastoma; PNET, primitive neuroectodermal tumor; GCT, germ cell tumor; RMS, rhabdomyosarcoma; nspx, nasopharynx; RT, radiation therapy; Chemo, chemotherapy; AA, alkylating agent; Y, yes; N, no; NA, data not available; B, brain; TBI, total body irradiation; S, spine; F, face; N, neck; LE, lower extremity.

TABLE 5. Risk factors for occurrence of second neoplasms

Covariate	RR (95% CI)	*P*
Univariate model		
Sex		<0.0001
Female	1.00	
Male	0.56 (0.45–0.69)	
Age at diagnosis (risk/yr)	1.06 (1.05–1.08)	<0.0001
Alkylating agent		<0.0001
No	1.00	
Yes	1.58 (1.27–1.97)	
Radiation		<0.0001
No	1.00	
Yes	2.94 (2.10–4.11)	
GH		0.0003
No	1.00	
Yes	2.63 (1.56–4.41)	
Chemotherapy		0.3261
No	1.00	
Yes	1.14 (0.87–1.49)	
Multivariate model		
GH		<0.0001
No	1.00	
Yes	3.21 (1.88–5.46)	
Sex		<0.0001
Female	1.00	
Male	0.55 (0.44–0.69)	
Age at diagnosis (risk/yr)	1.06 (1.02–1.08)	<0.0001
Radiation		<0.0001
No	1.00	
Yes	2.71 (1.94–3.79)	
Alkylating agent		0.0013
No	1.00	
Yes	1.44 (1.15–1.79)	

TABLE 6. Multivariate analysis of risk of second neoplasm in patients treated with GH by initial diagnosis

Diagnosis	RR (95% CI)	*P*
Acute leukemia	4.98 (1.95–12.74)	<0.001
CNS tumors	2.34 (0.96–5.70)	0.06
CNS tumors (meningiomas excluded)	1.46 (0.31–6.79)	0.69
Rhabdomyosarcoma	1.82 (0.41–8.01)	0.43

number of SN observed in the GH-treated survivors of acute leukemia (Table 6). There was marginal evidence for an increased RR of SN in survivors of CNS tumors treated with GH. When the analysis was restricted to malignant SN (*i.e.* meningiomas excluded), however, there was no longer an effect of GH on the risk of developing SN in this group. The number of SN estimated in GH-treated survivors compared with the number of SN in survivors who were not treated with GH is illustrated in Fig. 2.

Risk of death

Among the 361 GH-treated patients, 23 were deceased; 1102 patients had died among those never treated with GH. After adjusting for the covariate effects of age at diagnosis, sex, radiation, and chemotherapy in the multivariate model, the RR of death for GH-treated patients compared with those not treated with GH was 1.21 (95% CI, 0.75–1.94; $P = 0.43$).

Discussion

The data from this study do not suggest that administering GH therapy to survivors of childhood cancer is associated with an increased risk of recurrence of the primary malignancy. The results are particularly reassuring for survivors of acute leukemia, several CNS tumors (*e.g.* medulloblastoma and astroglial tumors), and those treated for soft tissue sarcoma, as these groups included relatively large numbers of cases, which provided considerable statistical power.

For survivors of most pediatric CNS tumors, the existing data are now quite extensive and consistent, effectively excluding the likelihood that GH increases the risk of tumor recurrence. Of note, recently two large series reporting on survivors of pediatric brain tumors both found a reduced risk of disease recurrence among the cases treated with GH (13, 14). Our findings in survivors of CNS tumors are similar. Most likely these reduced RRs reflect an inherent selection

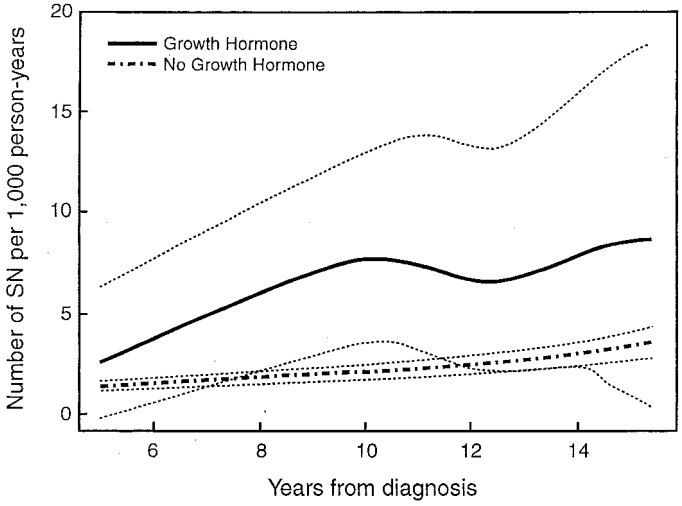

FIG. 2. Comparison of the number of second neoplasms estimated per 1000 person yr for survivors who did and did not receive treatment with GH plotted against time from diagnosis. The plot includes 95% CIs.

bias that favors GH treatment in survivors with a better prognosis.

Survivors of childhood cancer are known to be at increased risk of developing SN later in life (17). This heightened risk of developing subsequent cancers appears to be the consequence primarily of exposure to specific therapies (*e.g.* radiation, alkylating agents, and topoisomerase II inhibitors) during the treatment of the initial cancer (19–22). Genetic factors may also be important for the small subset with an underlying genetic predisposition to cancer. Earlier studies suggested the possibility that the incidence of leukemia might be increased in individuals treated with GH (6, 7). The latter studies are difficult to interpret, however, as many of the patients had other exposures (*e.g.* radiation) that predisposed them to the development of cancer and leukemia. Although more recent studies have cast doubt on the association between GH therapy and the development of *de novo* leukemias in subjects without additional risk factors (*i.e.* subjects with idiopathic GH deficiency) (23, 24), little has been published on the risks of secondary cancers/leukemias in cancer survivors treated with GH.

Our data indicate that treatment with GH may increase the risk of a childhood cancer survivor developing a secondary solid tumor. The data, however, do not support the idea that these individuals are at an increased risk of developing secondary leukemias. The RR of developing an SN was elevated for our entire cohort of GH-treated survivors (RR, 3.21), although the overall increased risk was driven in large part by a small excess number of SN observed in the subgroup of acute leukemia survivors (RR, 4.98). Most striking was the occurrence of osteogenic sarcoma in 3 of the leukemia/lymphoma survivors treated with GH; only 2 cases of osteogenic sarcoma were recorded in the more than 4500 leukemia/lymphoma survivors in CCSS who did not receive GH replacement therapy. Of note, a possible association between GH therapy and the development of osteogenic sarcoma has been reported in patients with Diamond-Blackfan anemia (25). There was also marginal evidence for GH-treated survivors of CNS tumors developing an increased number of tumors, mostly meningiomas. Both osteogenic sarcomas and meningiomas have been shown to express receptors for GH and IGF-I (9). Furthermore, the growth of these two neoplasms can be altered by manipulating GH and IGF-I (9, 26).

It is extremely important that our data on SN be placed in proper perspective. Despite an element of biological plausibility, our findings need to be interpreted with caution. First, the number of events is small, and the CIs are wide, raising concerns about the stability of the data. Nevertheless, when we performed a sensitivity analysis of our findings by removing GH-treated subjects with the shortest time to SN, the risk of developing an SN in GH-treated survivors ceased to be significant only when the total number of SN dropped from 15 to 10 cases. Second, this is a retrospective observational study, and thus there may have been inherent, but unrecognized, biases in the selection of patients who received therapy with GH. Although we have attempted to control for a variety of known risk factors for the development of SN, we cannot exclude the possibility that there might be important covariates that were not included as potential confounders. Finally, if our results prove to be correct, the absolute number of excess solid tumors that would occur as a result of GH therapy is small (3–4/1000 person yr at 15 yr from diagnosis). That small risk needs to be weighed against the potential benefits of GH therapy, which may be quite substantial in certain clinical settings.

Our particular study design required that patients had to have been alive 5 yr after diagnosis to be eligible for entry into the cohort. Our findings, therefore, may not be applicable to individuals who are currently less than 5 yr from diagnosis.

In conclusion, in this study, the largest to date, we did not find evidence that treating childhood cancer survivors with GH increased the risk of either disease recurrence or death. Although we did not observe an increased risk of secondary leukemias after GH replacement therapy, the number of secondary solid tumors was increased in the patients treated with GH compared with those who were not. The overall risk was small and appeared to be confined primarily to survivors of acute leukemia/lymphoma. The clinical importance of the latter findings remains uncertain, and the data will require corroboration in future studies.

Acknowledgments

Following is the list of CCSS institutions and investigators: Arthur Ablin, M.D.* (University of California, San Francisco, CA); Roger Berkow, M.D.* (University of Alabama, Birmingham, AL); John Boice, Sc.D.† (International Epidemiology Institute, Rockville, MD); Norman Breslow, Ph.D.† (University of Washington, Seattle, WA); George R. Buchanan, M.D.* (The University of Texas–Southwestern Medical Center, Dallas, TX); Lisa Diller, M.D.*, Holcombe Grier, M.D.‡, Frederick Li, M.D.† (Dana-Farber Cancer Institute, Boston, MA); Zoann Dreyer, M.D.* (Texas Children's Center, Houston, TX); Debra Friedman, M.D., M.P.H.*, Thomas Pendergrass, M.D.‡ (Children's Hospital and Medical Center, Seattle, WA); Daniel M. Green, M.D.* † (Roswell Park Cancer Institute, Buffalo, NY); Mark Greenberg, M.B., Ch.B.* (Hospital for Sick Children, Toronto, Canada); Robert Hayashi, M.D.*, Teresa Vietti, M.D.‡ (St. Louis Children's Hospital, St. Louis, MO); Melissa Hudson, M.D.* † (St. Jude Children's Research Hospital, Memphis, TN); Raymond Hutchinson, M.D.* (University of Michigan, Ann Arbor, MI); Michael P. Link, M.D.*, Sarah S. Donaldson, M.D.† (Stanford University School of

Medicine, Stanford, CA); Anna Meadows, M.D.* †, Bobbie Bayton† (Children's Hospital of Philadelphia, Philadelphia, PA); John Mulvihill, M.D.† (Children's Hospital, Oklahoma City, OK); Lorrie Odom, M.D.* (Children's Hospital, Denver, CO); Maura O'Leary, M.D.* (Children's Hospital, Minneapolis, MN); Amanda Rauck, M.D.*, Frederick Ruymann, M.D.‡, Stephen Qualman, M.D.† (Columbus Children's Hospital, Columbus, OH); Gregory Reaman, M.D.*, Roger Packer, M.D.† (Children's National Medical Center, Washington D.C.); A. Kim Ritchey, M.D.*, Julie Blatt, M.D.‡ (Children's Hospital of Pittsburgh, Pittsburgh, PA); Leslie L. Robison, Ph.D.*, Ann Mertens, Ph.D.†, Joseph P. Neglia, M.D., M.P.H.* †, Mark Nesbit, M.D.†, Stella Davies, M.D., Ph.D.† (University of Minnesota, Minneapolis, MN); Kathy Ruccione, R.N., M.P.H.* (Children's Hospital, Los Angeles, CA); Charles Sklar, M.D.* † (Memorial Sloan-Kettering Cancer Center, New York, NY); Malcolm Smith, M.D.†, Martha Linet, M.D.† (National Cancer Institute, Bethesda, MD); W. Anthony Smithson, M.D.*, Gerald Gilchrist, M.D.‡ (Mayo Clinic, Rochester, MN); Louise Strong, M.D.* †, Marilyn Stovall, Ph.D.† (The University of Texas M.D. Anderson Cancer Center, Houston, TX); Terry A. Vik, M.D.*, Robert Weetman, M.D.‡ (Riley Hospital for Children, Indianapolis, IN); Yutaka Yasui, Ph.D.*, John Potter, M.D., Ph.D.† ‡ (Fred Hutchinson Cancer Center, Seattle, WA); Lonnie Zeltzer, M.D.†, Jerry Finkelstein, M.D. (University of California, Los Angeles, CA). Key: *, Institutional Principal Investigator; †, Member of the CCSS Steering Committee; ‡, Former Institutional Principal Investigator.

Received January 8, 2002. Accepted March 12, 2002.

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

This work was supported by NIH Grant U24-CA-55727 and the Genentech Foundation for Growth and Development.

References

1. **Ries LAG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL, Bunin GR, eds** 1999 Cancer Incidence and survival among children and adolescents: United States SEER program 1975–1995. National Cancer Institute, SEER Program. NIH Publication 99-4649, Bethesda: NIH
2. **Sklar CA** 1999 Overview of the effects of cancer therapies: the nature, scale, and breadth of the problem. Acta. Paediatr Scand 433(Suppl):1–4
3. **Sklar CA, Grumbach MM, Kaplan SL, Conte FA** 1981 Hormonal and metabolic abnormalities associated with central nervous system germinoma in children and adolescents and the effect of therapy: report of 10 patients. J Clin Endocrinol Metab 52:9–16
4. **Sklar CA, Constine LS** 1995 Chronic neuroendocrinological sequelae of radiation therapy. Int J Radiat Oncol Biol Phys 31:1113–1121
5. **Orme SM, Mcnally RJQ, Cartwright RA, Belchetz PE** 1998 Mortality and cancer incidence in acromegaly: a retrospective cohort study. J Clin Endocrinol Metab 83:2730–2734
6. **Watanabe S, Tsuenematsu Y, Fujimoto J, Komiyama A** 1988 Leukemia in patients treated with growth hormone. Lancet 1:1159
7. **Fradkin JE, Mills JL, Schonberger LB, Wysowski DK, Thomson R, Durako SJ, Robison LL** 1993 Risk of leukemia after treatment with pituitary growth hormone. JAMA 270:2829–2832
8. **Pollak M** 2000 Insulin-like growth factor physiology and cancer risk. Eur J Cancer 36:1224–1228
9. **Khandwala HN, McCutcheon IE, Flyvbjerg A, Friend KE** 2000 The effects of insulin-like growth factors on tumorigenesis and neoplastic growth. Endocr Rev 21:215–244
10. **Arslanian SA, Becker DJ, Lee PA, Drash AL, Foley Jr TP** 1985 Growth hormone therapy and tumor recurrence. Findings in children with brain neoplasms and hypopituitarism. Am J Dis Child 139:347–350
11. **Ogilvy-Stuart AL, Ryder WD, Gattamaneni HR, Clayton PE, Shalet SM** 1992 Growth hormone and tumour recurrence. Br Med J 304:1601–1605
12. **Moshang Jr T** 1995 Is brain tumor recurrence increased following growth hormone treatment? Trends Endocrinol Metab 6:205–209
13. **Swerdlow AJ, Reddingius REHHA, Spoudeas HA, Phipps K, Qiao Z, Ryder WDJ, Brada M, Hayward RD, Brook CGD, 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
14. **Packer RJ, Boyett JM, Janss AJ, Stavrou T, Kun LE, Wisoff J, Russo C, Geyer R, Phillips P, Kieran M, Greenberg M, Goldman S, Hyder D, Heideman R, Jones-Wallace D, August GP, Smith SH, Moshang T** 2001 Growth hormone replacement therapy in children with medulloblastoma: use and effect on tumor control. J Clin Oncol 19:480–487
15. **Tuffli GA, Johanson A, Rundle AC, Allen DB** 1995 Lack of increased risk for extracranial, nonleukemic neoplasms in recipients of recombinant deoxyribonucleic acid growth hormone. J Clin Endocrinol Metab 80:1416–1422
16. **Sklar C, Whitton J, Mertens A, Stovall M, Green D, Marina N, Greffe B, Wolden S, Robison L** 2000 Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the Childhood Cancer Survivor Study. J Clin Endocrinol Metab 85:3227–3232
17. **Neglia JP, Friedman DL, Yasui Y, Mertens AC, Hammond S, Stovall M, Donaldson SS, Meadows AT, Robison LL** 2001 Second malignant neoplasms in five-year survivors of childhood cancer: Childhood Cancer Survivor Study. J Natl Cancer Inst 93:618–629
18. **Andersen PK, Borgan O, Gill RD, Keiding N** 1991 Statistical models based on counting processes. New York: Springer-Verlag
19. **Tucker MA, D'Angio GJ, Boice Jr JD, Strong LC, Li FP, Stovall M, Stone BJ, Green DM, Lombardi F, Newton W, Hoover RN, Fraumeni Jr JF** 1987 Bone sarcomas linked to radiotherapy and chemotherapy in children. N Eng J Med 317:588–593
20. **Meadows AT, Baum E, Fossati-Ballani F, Green D, Jenkin RDT, Marsden B, Nesbit M, Newton W, Oberlin O, Sallan SG, Siegel S, Strong LC, Voute PA** 1985 Second malignant neoplasms in children: an update from the Late Effects Study Group. J Clin Oncol 3:532–538
21. **Bhatia S, Robison LL, Oberlin O, Greenberg M, Bunin G, Fossati-Bellani F, Meadows A** 1996 Breast cancer and other second neoplasms after childhood Hodgkin's disease. N Engl J Med 334:745–751
22. **Socié G, Curtis RE, Deeg HJ, Sobocinski KA, Filipovich AH, Travis LB, Sullivan KM, Rowlings PA, Kingma DW, Banks PM, Travis WD, Witherspoon RP, Sanders J, Jaffe ES, Horowitz MM** 2000 New malignant diseases after allogeneic marrow transplantation for childhood acute leukemia. J Clin Oncol 18:348–357
23. **Allen DB, Rundle AC, Graves DA, Blethen SL** 1997 Risk of leukemia in children treated with human growth hormone: review and reanalysis. J Pediatr 131:S32–S36
24. **Nishi Y, Tanaka T, Takano K, Fujieda K, Igarashi Y, Hanew K, Hirano T, Yokoya S, Tachibana K, Saito T, Watanabe S** 1999 Recent status of the occurrence of leukemia in growth hormone-treated patients in Japan. J Clin Endocrinol Metab 84:1961–1965
25. **Lipton JM, Federman N, Khabbaze Y, Schwartz CL, Hilliard LM, Clark JI, Vlachos A** 2001 Osteogenic sarcoma associated with Diamond-Blackfan anemia: a report from the Diamond-Blackfan anemia registry. J Pediatr Hematol Oncol 23:39–44
26. **Chavez Kappel C, Velez-Yanguas C, Hirschfeld S, Helman LJ** 1994 Human osteosarcoma cell lines are dependent on insulin-like growth factor for in vitro growth. Cancer Res 54:2803–2807