Growth Hormone Exposure as a Risk Factor for the Development of Subsequent Neoplasms of the Central Nervous System: A Report From the Childhood Cancer Survivor Study

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Context: Cranial radiation therapy (CRT) predisposes to GH deficiency and subsequent neoplasms (SNs) of the central nervous system (CNS). Increased rates of SNs have been reported in GH-treated survivors.

Objective: The objective of the study was to evaluate the association between GH treatment and the development of CNS-SNs.

Design: The study was designed with a retrospective cohort with longitudinal follow-up.

Setting: The setting of the study was multiinstitutional.

Participants: A total of 12 098 5-year pediatric cancer survivors from the Childhood Cancer Survivor Study, diagnosed with cancer prior to age 21 years, of whom 338 self-reported GH treatment, which was verified through medical record review.

Interventions: Interventions included subject surveys, medical records abstraction, and pathological review.

Outcome Measures: Incidence of meningioma, glioma, and other CNS-SNs was measured.

Results: Among GH-treated survivors, 16 (4.7%) developed CNS-SN, including 10 with meningioma and six with glioma. Two hundred three survivors without GH treatment (1.7%) developed CNS-SN, including 138 with meningioma, 49 with glioma, and 16 with other CNS-SNs. The adjusted rate ratio in GH-treated compared with untreated survivors for development of any CNS-SN was 1.0 [95% confidence interval (CI) 0.6–1.8, $P = .94$], for meningiomas, 0.8 (95% CI 0.4–1.7, $P = .61$), and for gliomas, 1.9 (95% CI 0.7–4.8, $P = .21$). Factors associated with meningioma development included female gender ($P = .001$), younger age at primary cancer diagnosis ($P < .001$), and CRT/longer time since CRT ($P < .001$). Glioma was associated with CRT/shorter time since CRT ($P < .001$).

Conclusions: There was no statistically significant increased overall risk of the occurrence of a CNS-SN associated with GH exposure. Specifically, occurrence of meningiomas and gliomas were not associated with GH treatment. **(*J Clin Endocrinol Metab* 99: 2030–2037, 2014)**

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Abbreviations: CCSS, Childhood Cancer Survivor Study; CI, confidence interval; CNS, central nervous system; CRT, cranial radiation therapy; SN, subsequent neoplasm.

GH deficiency is common among pediatric cancer survivors who received radiation exposure to the hypothalamus and/or pituitary (1–4). Concern has been raised about GH treatment having a causal role in recurrence or second malignancies because the GH/IGF-I axis has been implicated in mitogenesis, and there have been reports of higher rates of second malignancies in cancer survivors treated with GH (4–6). GH and IGF-I receptors have been identified in many tumor types, and IGF-I and the IGF-I receptor are potential drug targets in oncology (7).

Assessing the impact of GH treatment on tumor risk in the clinical setting, prior reports have demonstrated no increase in relative risk of recurrence of primary neoplasms in those who received GH treatment compared with those not so treated (8, 9). The relative risk of subsequent neoplasm, including the central nervous system (CNS) and other sites, in the GH-treated Childhood Cancer Survivor Study (CCSS) participants was initially estimated at 3.21 [95% confidence interval (CI) 1.88–5.46] (9) but was updated to 2.15 (95% CI 1.3–3.5) with a longer follow-up period (10). Similar results have been observed in GH postmarketing studies (11). In GH postmarketing studies, overall 5-year cumulative incidence of subsequent neoplasms (SNs) in GH treated pediatric cancer survivors was estimated to be 6.2% (5). This was similar to the earlier CCSS findings. In contrast, some have reported no association between GH and subsequent malignancies (12, 13).

Although the data from Sklar et al (9) suggest an association between GH and SNs in general, the association of GH therapy and occurrence of a subsequent CNS neoplasm, such as meningioma, glioma, or other subsequent CNS neoplasm, has not been definitively established (9, 10). Likewise, whether GH therapy might augment the risk of some specific types of CNS tumors, but not other types, is not known. However, these are important questions because the population at risk for meningioma and glioma, eg, those treated with high doses of radiation to the CNS, overlap considerably with those at risk for GH deficiency (2). The purpose of this study is to assess whether GH is an independent risk factor for development of subsequent CNS neoplasms. This analysis provides a longer duration of follow-up than prior CCSS reports and focuses specifically on subsequent CNS neoplasms for which the association with GH treatment has not been previously reported within this large institution-based cohort. Additionally, the association of the two most common types of subsequent CNS neoplasms, meningioma and glioma, are specifically investigated.

Materials and Methods

The CCSS is a retrospective cohort study with prospective follow-up of 14 358 childhood cancer survivors diagnosed prior to age 21 years and surviving cancer for at least 5 years (14). Participants were diagnosed between 1970 and 1986 and treated at 26 institutions in the United States and Canada. Eligible diagnoses included leukemia, CNS tumor (all histologies), Hodgkin lymphoma, non-Hodgkin lymphoma, kidney tumor, neuroblastoma, soft tissue sarcoma, or bone tumor. Benign neoplasms, such as meningioma and craniopharyngioma, were ineligible diagnoses. The CCSS study methodology has been previously described, and it includes a baseline questionnaire and multiple follow-up questionnaires assessing a wide range of health behaviors and health outcomes (14–16). The CCSS questionnaires are available (https://ccss.stjude.org/documents/questionnaires). The present study includes data through follow-up number 4 (completed in November 2009). The protocol was approved by the Human Subjects Committee at each of participating institution, and all participants provided informed consent.

Because GH treatment is a self-reported variable in the CCSS questionnaire, an attempt was made previously to verify GH treatment through medical records abstraction in those subjects self-reporting GH treatment or self-reporting unsure about GH treatment. Due to concerns regarding false-positive self-report of GH treatment, prior analyses in CCSS have used verified GH treatment only (9, 10). We used the same approach in the present study: subjects were considered GH exposed if they had self-reported yes or unsure about GH treatment, and GH treatment was verified by medical record abstraction as described by Sklar et al (9). Subjects for whom GH treatment was not verified were excluded from the analysis. Overall, 11 660 GH unexposed subjects were available for analysis, and 338 subjects with verified GH exposure were available for analysis. Figure 1 provides details about the inclusion and exclusion of subjects.

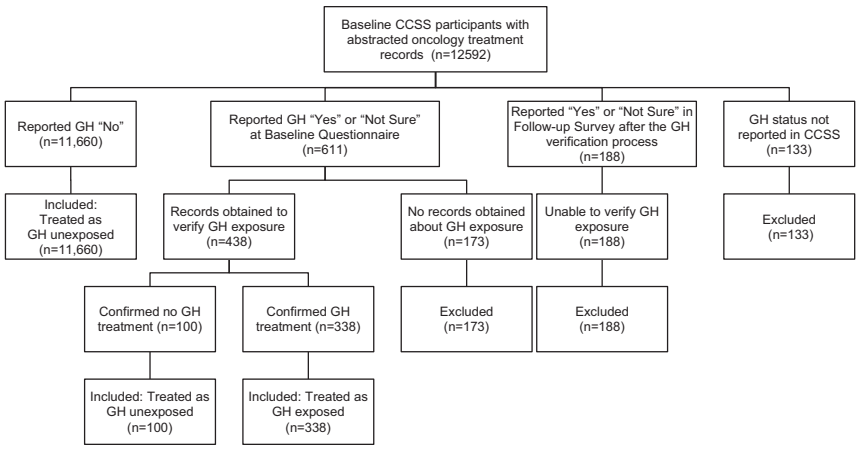

Figure 1. Inclusion and exclusion of CCSS subjects.

A subsequent CNS neoplasm was defined as a new primary tumor, occurring in the CNS. Risk of recurrence of the primary malignancy was not evaluated in this analysis. Subsequent CNS neoplasms were determined by self-report, verified through review of pathology re-

Table 1. Demographics of Study Subjects With and Without GH Treatment

	GH Treatment (n = 338)			No GH Treatment (n = 11 760)			
	GH Treatment (n = 338)	Meningioma (n = 10)	Glioma (n = 6)	No GH Treatment (n = 11 760)	Meningioma (n = 138)	Glioma (n = 49)	Other CNS SN (n = 16)
Sex[a]							
Male	220 (65.1%)	6	3	6147 (52.3%)	53	28	6
Female	118 (34.9%)	4	3	5613 (47.7%)	85	21	10
Race/ethnicity							
White, non-Hispanic	294 (87.0%)	10	6	9951 (84.6%)	118	39	15
Black, non-Hispanic	9 (2.7%)			453 (3.9%)	3	3	
Hispanic	13 (3.8%)			532 (4.5%)	5	2	
Other, not specified	22 (6.5%)			824 (7.0%)	12	5	1
Primary cancer diagnosis[a]							
Leukemia	101 (29.9%)	1	3	3980 (33.8%)	80	23	9
CNS tumor	165 (48.8%)	7	2	1353 (11.5%)	47	15	2
Hodgkin lymphoma	1 (0.3%)			1640 (13.9%)	4	4	2
Non-Hodgkin lymphoma	10 (3.0%)	1		881 (7.5%)	2	3	
Wilms' tumor	1 (0.3%)			1061 (9.0%)			1
Neuroblastoma	16 (4.7%)		1	800 (6.8%)		1	1
Soft tissue sarcomas	42 (12.4%)	1		1013 (8.6%)	3	1	1
Bone malignancies	2 (0.6%)			1032 (8.8%)	2	2	
Age at primary cancer diagnosis, y[a]							
0–4	221 (65.4%)	5	4	4579 (38.9%)	67	25	12
5–9	97 (28.7%)	4	1	2556 (21.7%)	38	7	2
10–14	19 (5.6%)	1	1	2444 (20.8%)	20	12	2
15+	1 (0.3%)			2181 (18.5%)	13	5	
Age at diagnosis of CNS SN, y							
0–9.9		2				8	1
10–19.9		3	4		12	16	6
20–29.9		5	2		69	12	5
30–39.9					45	10	3
40+					12	3	1
Treatment for original cancer[a]							
Surgery only	1 (0.3%)			900 (7.7%)	1	3	
Radiation only	2 (0.6%)			36 (0.3%)	1	1	
Chemotherapy only	6 (1.8%)		1	879 (7.5%)	2	1	
Surgery/radiation	71 (21.0%)	2	2	1358 (11.5%)	37	11	2
Surgery/chemotherapy	8 (2.4%)			2222 (18.9%)	1	1	2
Radiation/chemotherapy	43 (12.7%)		1	1563 (13.3%)	56	9	5
Surgery/radiation/chemotherapy	205 (60.7%)	8	2	4662 (39.6%)	40	23	7
Unknown	2 (0.6%)			140 (1.2%)			
Recurrence prior to first SN[a]							
Yes	8 (2.4%)	1	1	178 (1.5%)	19	7	6
Radiation dose to brain[a]							
No CRT radiation	22 (6.5%)		1	7392 (62.9%)	8	10	4
<10 Gy	13 (3.8%)			370 (3.1%)	2	1	2
10–19.9 Gy	32 (9.5%)			1168 (9.9%)	17	9	1
20–29.9 Gy	50 (14.8%)	1	1	1303 (11.1%)	55	13	5
30–45 Gy	36 (10.7%)	1		295 (2.5%)	12	1	3
>45 Gy	172 (50.9%)	7	4	838 (7.1%)	43	13	1
Unknown	13 (3.8%)	1		394 (3.4%)	1	2	

(*Continued*)

Table 1. Continued

	GH Treatment (n = 338)			No GH Treatment (n = 11 760)			
	GH Treatment (n = 338)	Meningioma (n = 10)	Glioma (n = 6)	No GH Treatment (n = 11 760)	Meningioma (n = 138)	Glioma (n = 49)	Other CNS SN (n = 16)
Estrogen/progesterone treatment							
Yes	80 (23.7%)	1	2	3393 (28.9%)	47	10	2
Intrathecal methotrexate							
Yes	128 (37.9%)	1	3	4251 (36.1%)	75	23	9
Alkylating agent[a]							
Yes	218 (64.5%)	7	3	6060 (51.5%)	44	22	10

[a] $P < .05$, comparing those with GH treatment with those without GH treatment.

ports and medical records from the treating institutions, and categorized using the *International Classification of Diseases for Oncology*, second edition, nomenclature as meningioma, glioma, or other subsequent CNS neoplasm. Therapeutic exposures to chemotherapy and radiotherapy (including quantitative doses of 26 chemotherapy agents and radiation doses) were determined through abstraction of the medical records. Estrogen and/or progesterone exposure was determined by self-report. Demographic characteristics and oncological treatment exposures of study subjects are listed in Table 1.

Cumulative incidence was calculated for meningioma and glioma as subsequent CNS neoplasm, stratified by GH treatment status and cranial radiation. The cumulative incidence start time was set at 15 years after the childhood cancer diagnosis because all GH treatment reported in the cohort had been initiated by this time. For the purpose of determining cumulative incidence, meningioma and glioma that had developed within 15 years from the childhood cancer diagnosis were included as prevalent cases.

Multivariable Poisson regression was performed to evaluate the effect of GH treatment on the rates of CNS SNs. The regression model was adjusted for the attained age at follow-up, the cranial radiation dose with possible effect modifications by time since cranial radiation, use of estrogen and/or progesterone (yes/no), sex, age at primary cancer diagnosis, intrathecal methotrexate use (potentially associated with GH deficiency, yes/no), and alkylating agent use (yes/no). Attained age at follow-up, time since cranial radiation, and estrogen and/or progesterone use were time dependent variables. The duration of follow-up was defined as starting from 5 years after the childhood cancer diagnosis and ending at the earliest of the incidence of the CNS subsequent neoplasm of interest, death, or the last questionnaire completion. The same analysis was performed after stratifying by the cranial radiation dose (≤45 Gy and >45 Gy).

To assess the association of GH treatment with mortality due to glioma and mortality due to any CNS subsequent neoplasms, multivariable Poisson regression was used, adjusting for the same covariates as the incidence analysis above.

Results

Demographic and clinical data for the participants stratified by GH treatment are shown in Table 1. Those who received GH treatment were more likely to be male, to have a CNS tumor as their primary diagnosis, to have been diagnosed with their primary cancer at a younger age, and to have received cranial radiation. GH treated subjects were exposed to higher radiation doses and were more likely to receive alkylating agents than those not treated with GH. Among GH treated survivors, 10 (3.0%) developed meningioma, six (1.8%) developed glioma, and none developed another type of subsequent CNS neoplasm. Among those not treated with GH, 138 (1.2%) developed meningioma, 49 (0.4%) developed glioma, and 16 (0.1%) developed another type of CNS subsequent neoplasm.

Figure 2 depicts the cumulative incidence of meningioma and glioma stratified by GH treatment and cranial radiation exposure. Incidence of meningioma increases with time in all those with prior cranial radiation, regardless of GH exposure. With respect to glioma, cumulative incidence was the highest in those treated with GH without prior cranial radiation; however, this incidence rate reflects the occurrence of glioma in only one subject among 22 subjects. Most gliomas occurred within the first 20

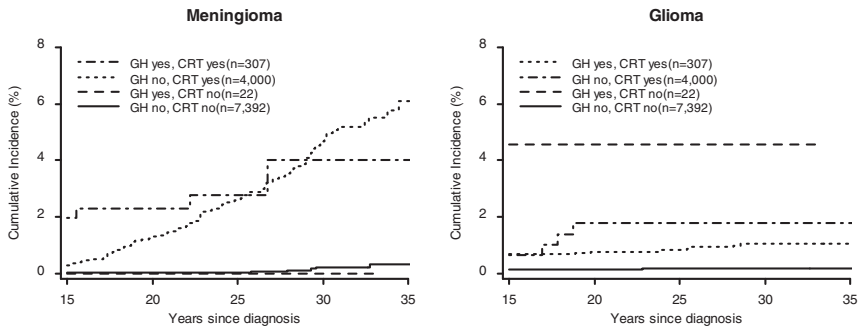

Figure 2. Cumulative incidence of meningioma and glioma stratified by GH treatment and cranial radiation exposure status.

Table 2. Adjusted Rate Ratios (RRs) for Meningioma, Glioma, and Any CNS SN[a]

	Meningioma (n = 146)			Glioma (n = 53)			Any CNS SN (n = 212)		
	RR	95% CI	*P* Value	RR	95% CI	*P* Value	RR	95% CI	*P* Value
Growth hormone treatment									
No	1		.61	1		.21	1		.94
Yes	0.8	0.4–1.7		1.9	0.7–4.8		1.0	0.6–1.8	
Sex									
Male	1		<.001	1		.79	1		.002
Female	1.8	1.3–2.6		0.9	0.5–1.7		1.6	1.2–2.2	
Age at primary cancer diagnosis, y									
≥15	1		<.001	1		.22	1		<.001
0–4	4.8	2.1–11.0		2.0	0.5–7.8		4.8	2.4–9.7	
5–9	2.6	1.2–5.5		0.9	0.2–3.5		2.5	1.3–4.7	
10–14	1.2	0.6–2.6		1.8	0.6–5.6		1.7	0.9–3.0	
CRT/time between cranial radiation and CNS SN									
No CRT	1		<.001	1		<.001	1		<.001
CRT ≤45 Gy and <10 y	0.0	0.0–6.7		7.9	2.7–23.0		9.5	4.3–20.8	
CRT ≤45 Gy and 10–19 y	23.1	9.9–53.7		4.1	1.5–11.3		11.1	6.3–19.5	
CRT ≤45 Gy and ≥20 y	22.0	9.7–50.2		1.5	0.3–6.3		9.9	5.5–17.5	
CRT >45 Gy and <10 y	55.1	15.3–198.1		13.5	4.0–46.1		23.9	10.2–55.9	
CRT >45 Gy and 10–19 y	47.3	19.4–115.2		13.4	4.8–37.6		24.9	13.6–45.8	
CRT >45 Gy and ≥20 y	58.5	25.5–134.2		10.7	3.1–36.7		25.3	14.0–46.0	
Intrathecal methotrexate									
No	1		.3	1		.39	1		.29
Yes	1.3	0.8–2.0		1.3	0.8–2.0		1.3	0.8–2.0	
Estrogen and/or progesterone									
No	1		.19	1		.71	1		.09
Yes	0.7	0.5–1.2		0.7	0.5–1.2		0.7	0.5–1.2	
Alkylating agent									
No	1		.03	1		.65	1		.08
Yes	0.7	0.5–1.0		0.7	0.5–1.0		0.7	0.5–1.0	

[a] Adjusted for age at follow-up.

years of follow-up. This is in contrast to meningiomas that are continuing to accumulate incident cases at 35 years after diagnosis.

Considering all subjects regardless of exposure to prior cranial radiation, rate ratios for the occurrence of meningioma, glioma or other CNS subsequent neoplasm are shown in Table 2. The rate ratio for the development of any CNS subsequent neoplasm for survivors treated with GH as compared with those not treated with GH was 1.0 (95% CI 0.6–1.8, $P = .94$), controlling for sex; age at primary diagnosis; attained age at follow-up; cranial radiation dose/time since cranial radiation; and treatment with intrathecal methotrexate, estrogen, and/or progesterone treatment or alkylating agents (Table 2). With respect to specific CNS SNs, the adjusted rate ratios for the development of meningioma and glioma were 0.8 (95% CI 0.4–1.7, $P = .61$) and 1.9 (95% CI 0.7–4.8, $P = .21$), respectively, for those treated with GH as compared with those not so treated. Younger age at diagnosis, female gender, higher cranial radiation dose, and a longer elapsed time since cranial radiation were associated with increased rates of meningioma. Higher cranial radiation dose and a shorter elapsed time since cranial radiation were associated with increased rates of glioma.

Regardless of the GH treatment status, a majority (94.5% of meningiomas; 79.2% of gliomas) of the subsequent CNS neoplasms occurred in patients exposed to prior cranial radiation. Table 3 shows the rate ratios for the associations between GH exposure and the occurrence of meningioma or glioma in subjects who had prior cranial irradiation, stratified by radiation dose (≤45 Gy and >45 Gy). GH treatment was not associated with higher rates of meningioma or glioma in subjects with prior cranial radiation, irrespective of the dose.

A total of 66 survivors died after the diagnosis of a CNS subsequent neoplasm; seven had been treated with GH and 59 had not. Four of the GH treated subjects died due to complications of a CNS subsequent neoplasm, and in all four of those cases, the subsequent neoplasm was a glioma. None of the GH-treated survivors died of complications of a meningioma as a subsequent neoplasm. Thirty-nine of the survivors without GH treatment died due to complication of a CNS subsequent neoplasm, of which six had meningioma, 26 had glioma, and seven had other CNS

Table 3. Among Subjects With Prior Cranial Irradiation, Growth Hormone Treatment Exposure and the Adjusted Rate Ratios for Meningioma and Glioma as Second Neoplasms, Stratified by Radiation Dose to the Brain (Multivariate)[a]

	Meningioma RR (95% CI)		Glioma RR (95% CI)	
	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
Prior cranial radiation ≤45 Gy				
No GH treatment (n = 3136)	1	.8	1	.93
GH treatment (n = 131)	0.8 (0.2–3.5)		1.1 (0.1–8.4)	
Prior cranial radiation >45 Gy				
No GH treatment (n = 838)	1	.52	1	.23
GH treatment (n = 172)	0.8 (0.3–1.7)		2.1 (0.6–7.4)	

[a] Adjusted for age at the follow-up, sex, age at primary diagnosis, CRT/time since CRT radiation (time dependent), intrathecal methotrexate, estrogen and/or progesterone treatment (time dependent), and alkylating agents (yes/no). GH treatment is the time-dependent variable.

SNs. After adjustment for attained age at follow-up, sex, age at primary diagnosis, cranial radiation dose/time since Cranial radiation therapy (CRT) radiation, intrathecal methotrexate, estrogen and/or progesterone treatment, and alkylating agent exposure, the adjusted rate ratio for death due to any CNS subsequent neoplasm associated with GH exposure was 1.6 (95% CI 0.5–4.9, $P = .39$).

Discussion

Overall, we found no increase in the risk for the occurrence of subsequent CNS neoplasms in childhood cancer survivors who have been treated with GH. This is an important observation because many pediatric cancer survivors who have been exposed to prior cranial radiation will develop GH deficiency and will be potential candidates for GH therapy (1, 2). These patients are known to be at increased risk for CNS SNs due to radiation exposure (17, 18). Thus, evaluating exposures that may modify the risk of SNs is important for counseling these survivors and their families. In this analysis, when controlling for cranial radiation, there was no increase in the risk for the development of any CNS SNs. Specifically, there was no increase in the risk of meningioma and glioma, the two most commonly occurring CNS SNs.

Prior research in this cohort has shown a small increase in the overall risk for subsequent neoplasms associated with GH treatment (9, 10). The relative risk was initially estimated to be 3.21 (95% CI 1.88–5.46) but later was revised to 2.15 (95% CI 1.3–3.5) with longer duration of follow-up. In these reports, meningiomas were the most common incident subsequent neoplasm. The current report differs in that additional follow-up has occurred since the two prior reports, and this analysis focused specifically on subsequent CNS neoplasms because of their relatively higher incidence compared with other types of SNs. Radiation dose confounds the relationship between GH and the occurrence of subsequent CNS neoplasms because higher radiation doses are associated with higher likelihood of GH deficiency (3, 4) and increased risk of subsequent CNS neoplasms (17). Results of multivariable models clearly demonstrated that the risk of subsequent CNS neoplasms was largely independently associated with CRT dose, time from CRT exposure, age at cancer diagnosis, and sex. Having adjusted for these confounding risk factors, a contribution of GH treatment to risk of subsequent CNS neoplasm was not apparent, with the possible exception of a nonstatistically significant increased risk for secondary glioma.

Other research has provided a biological basis by which GH could influence the development of CNS tumors. Meningiomas express both GH and IGF-I receptors (19, 20). In both in vitro and in vivo xenobiotic studies, meningioma cell growth activity has been shown to increase in the presence of IGF-I and to decrease in the presence of GH receptor antagonists (19, 21). Interruption of IGF-I receptor binding also decreases meningioma growth in vitro (22, 23). Gliomas have also been reported to express GH receptors and IGF-I receptors (24). In vitro, IGF-I has been shown to increase glioma tissue cell growth (24). However, in cell culture models, it has been proposed that GH may induce immunological changes that promote antiglioma activity by natural killer cells (25).

With respect to clinical research on SNs occurring in the CNS, in a CCSS report by Neglia et al (17), 116 subsequent CNS tumors were reviewed and analyzed. Of these, meningioma (n = 66) and glioma (n = 40) were most common. Occurrence of meningiomas and gliomas was associated with radiation therapy in a dose response fashion. GH was not evaluated as a risk factor. Risk for glioma was higher in subjects who were irradiated before the age of 5 years, and gliomas typically occurred earlier, often 5–15 years after the original cancer diagnosis and treatment. Risk for meningiomas was higher in children irradiated after the age of 5 years; meningiomas presented later, with the cumulative incidence increasing with time since original cancer diagnosis and treat-

ment. Thus, the diagnosis of glioma would tend to be more temporally associated with pediatric GH therapy.

Mackenzie et al (12) showed no significant association between GH treatment and the development of SNs of the CNS in a mixed-age single institutional cohort of patients who all received cranial radiation for their primary cancer. Although the conclusions of the current study and that by Mackenzie et al (12) are similar, there are important methodological differences. Using a single-institution cohort of subjects, all with prior cranial radiation exposure, they found no increase in the risk of subsequent CNS neoplasms in subjects treated with GH for at least 1 year compared with those not treated with GH. They reported a long period of follow-up (14.5 y in the GH treated group). However, this study was relatively small and included subjects with radiation therapy for their primary cancer in childhood and adulthood. In fact, the group of patients treated in adulthood was larger than those treated in childhood. Our data suggest that younger age at time of exposure to radiotherapy is an important risk factor for the development of subsequent CNS neoplasms, particularly meningiomas. Due to their small sample size, Mackenzie et al did not have the power to detect small changes in risk, nor were they able to assess risk for different subtypes of CNS neoplasms.

Other types of endocrine replacements may influence subsequent CNS neoplasm development as well. Exogenous estrogen and/or progesterone treatments, when used as postmenopausal hormone replacement therapy or in contraceptive formulations, have also been proposed as risk factors for the development of meningioma in the general population (26–28). It is not known whether this exposure is a risk factor for meningioma as a second neoplasm in pediatric cancer survivors. Estrogen and progesterone have not been reported to increase the risk for glioma. In fact, estrogen receptor-β agonists and progestins have been shown to exert suppressive effects on glioma in vitro (29, 30). This study documents no association between estrogen and/or progesterone treatment and the development of meningioma or glioma as second malignancies in pediatric cancer survivors.

Due to prior reports of increased risk for subsequent neoplasm in survivors treated with GH, subjects treated with GH within the CCSS may have experienced more rigorous clinical surveillance for SNs than those not on GH. The frequency of CNS imaging surveillance for SNs in this cohort is not known, could not be controlled for, and is unlikely to be uniform throughout the cohort as there is considerable heterogeneity within the CCSS with respect to frequency of follow-up health care (31). However, if subjects being treated with GH did undergo more frequent CNS imaging than those not on GH, this would tend to bias the results toward increased detection of CNS subsequent neoplasms (in particular, less aggressive neoplasms such as meningioma) in the GH-treated group. Another limitation is that not all subjects who reported GH treatment within the CCSS underwent the verification process to be included for analysis. Some subjects with GH treatment may have been excluded because their GH treatment status could not be verified. However, there were a large number of subjects self-reporting GH treatment who were later confirmed through medical record review to be GH unexposed (see Figure 1). Thus, only those with confirmed GH treatment were considered exposed in this analysis. This study was confined to assessing the risk of CNS neoplasms and GH exposure; future research should investigate whether there is an association between GH treatment and the development of other types of SNs, such as breast and colon cancer. Finally, it remains unclear whether the dosage of GH, the duration of the GH therapy, or the age of the patient when they receive GH modify the risk of SNs in pediatric cancer survivors. Future research should address these questions.

In conclusion, the most recent follow-up of the CCSS cohort indicates that GH exposure is not associated with an increased risk of development of subsequent CNS neoplasms in survivors of childhood cancer. When subsequent CNS neoplasms occur, meningiomas are more common than gliomas and occur later than gliomas. Although the cumulative incidence of meningioma in this cohort continues to increase with longer duration of follow-up, meningiomas do not appear to be associated with GH exposure.

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