

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

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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% con-

fidence 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  $t$ ,  $\beta$  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<br>(n = 361) | Non-GH treated<br>(n = 12,963) |
|--|-------------------------|--------------------------------|
| Sex: M:F                                       | 237:124                 | 6,874:6,089                    |
| Age at cancer diagnosis (yr)<br>median (range) | 3.5 (0–17.2)            | 7.2 (0–21)                     |
| Diagnoses                                      |                         |                                |
| Tumors of the CNS                              | 172                     | 1,489                          |
| Medulloblastoma <sup>a</sup>                   | 73                      | 245                            |
| Astroglial                                     | 68                      | 979                            |
| Ependymoma                                     | 15                      | 104                            |
| Germ cell                                      | 14                      | 34                             |
| Miscellaneous                                  | 2                       | 127                            |
| Acute leukemia <sup>b</sup>                    | 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<br>(range)      | 10 (3.1–20.8)           |                                |
| Duration of GH therapy (yr)<br>median (range)  | 4.6 (0.1–14)            |                                |
| GH preparations                                |                         |                                |
| Human pituitary only                           | 43                      |                                |
| Recombinant only                               | 279                     |                                |
| Both   | 27                      |                                |
| Unknown  | 12                      |                                |

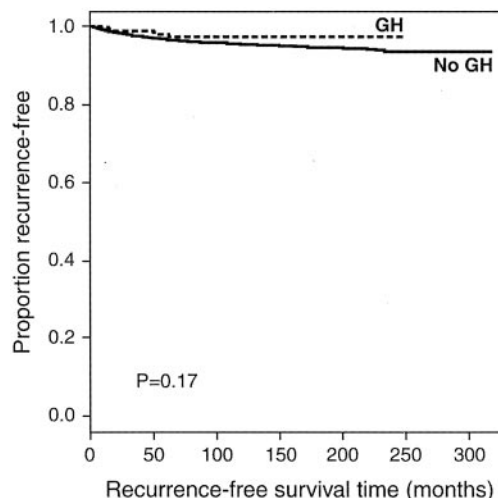
<sup>a</sup> Includes cases diagnosed with primitive neuroectodermal tumors.

<sup>b</sup> 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) <sup>a</sup> | 0.41         |
| Germ cell        |                       | <sup>b</sup> |
| Acute leukemia   | 0.85 (0.12–6.14)      | 0.87         |
| Rhabdomyosarcoma | 0 (0–4) <sup>a</sup>  | 0.31         |
| Neuroblastoma    | 0 (0–35) <sup>a</sup> | 0.73         |

<sup>a</sup> 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.

<sup>b</sup> 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 | Age at diagnosis (yr) | Primary malignancy |            |       | Second neoplasm |                                   |                             |      |
|-------------|-----|-----------------------|--------------------|------------|-------|-----------------|-----------------------------------|-----------------------------|------|
|             |     |                       | 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) |         |

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

**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   |

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

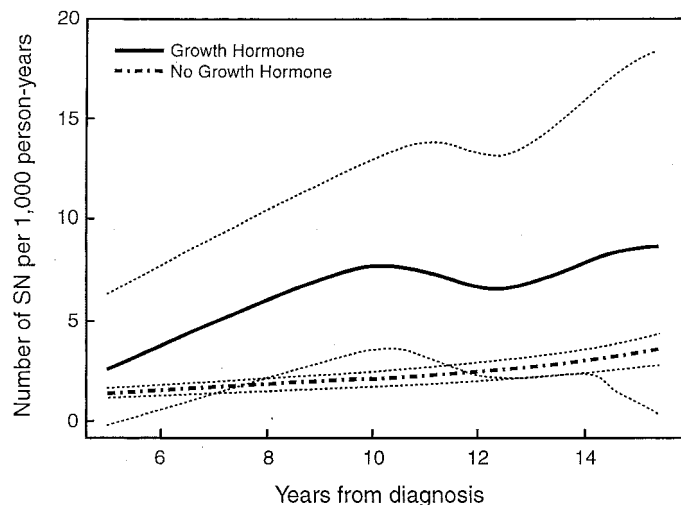


FIG. 2. Comparison of the number of second neoplasms estimated per 1000 person yr for survivors who did and did not receive treatment with GH plotted against time from diagnosis. The plot includes 95% CIs.

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 sur-

vivors 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.

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