Cancer Risks in Patients Treated With Growth Hormone in Childhood: The SAGhE European Cohort Study

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Context: Growth hormone (GH) is prescribed for an increasing range of indications, but there has been concern that it might raise cancer risk. Published data are limited.

Objective: To examine cancer risks in relation to GH treatment.

Design: Cohort study.

Setting: Population-based.

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Abbreviations: CI, confidence interval; CNS, central nervous system; GH, growth hormone; HL, Hodgkin lymphoma; IGF, insulin-like growth factor; r-hGH, recombinant human growth hormone; SAGhE, Safety and Appropriateness of Growth Hormone Treatments in Europe; SIR, standardized incidence ratio.

Patients: Cohort of 23,984 patients treated with recombinant human GH (r-hGH) in eight European countries since this treatment was first used in 1984. Cancer expectations from country-specific national population statistics.

Main Outcome Measures: Cancer incidence and cancer mortality.

Results: Incidence and mortality risks in the cohort were raised for several cancer sites, largely consequent on second primary malignancies in patients given r-hGH after cancer treatment. There was no clear raised risk in patients with growth failure without other major disease. Only for bone and bladder cancers was incidence significantly raised in GH-treated patients without previous cancer. Cancer risk was unrelated to duration or cumulative dose of r-hGH treatment, but for patients treated after previous cancer, cancer mortality risk increased significantly with increasing daily r-hGH dose (P trend < 0.001). Hodgkin lymphoma (HL) incidence increased significantly with longer follow-up (P trend = 0.001 for patients overall and 0.002 for patients without previous cancer).

Conclusions: Our results do not generally support a carcinogenic effect of r-hGH, but the unexplained trend in cancer mortality risk in relation to GH dose in patients with previous cancer, and the indication of possible effects on bone cancer, bladder cancer, and HL risks, need further investigation. (***J Clin Endocrinol Metab*** **102: 1661–1672, 2017)**

Growth hormone (GH) has been prescribed since 1957 to treat GH deficiency and short stature due to other causes. The hormone used was initially extracted from human pituitaries (p-hGH), but after an outbreak of Creutzfeldt–Jakob disease consequent on prion infection from these pituitaries, this was discontinued in 1985 and all subsequent treatment has been with recombinant human growth hormone (r-hGH).

GH raises serum concentrations of insulin-like growth factor (IGF)-1, which is mitogenic and antiapoptotic *in vitro*, and adult levels of which have been associated in most studies with risks of subsequent breast, colorectal, and prostate cancers and in some studies with other cancers (1, 2). Furthermore, cohort studies of patients with endogenously raised GH concentrations, acromegaly, have found raised risks of several cancers, most consistently colorectal (3, 4). Potential effects on leukemia (5, 6) and other malignancy (1) risks have been suggested, and second primary malignancy risk has been shown raised in patients receiving GH after childhood cancer (7, 8). Although these data give suspicion that there might be carcinogenic effects, no risks have been shown consistently or established. Cohort studies of r-hGH treatment have either comprised at most a few hundred patients (7, 9) or been conducted by pharmaceutical companies (10–14) with too short follow-up to cover the likely lag period of carcinogenesis, and there has been an absence of dose- and duration-response data. We therefore assembled a large cross-European cohort, the Safety and Appropriateness of Growth Hormone Treatments in Europe (SAGhE) study, with follow-up and analysis independent of pharmaceutical companies, to examine whether treatment with r-hGH affects cancer incidence and mortality risks in patients who have taken this treatment.

Materials and Methods

In each of eight European countries (Table 1), we assembled cohorts of patients treated with r-hGH at pediatric ages since such treatment was first used in that country (1984 to 1986, depending on the country) and never treated with p-hGH. Data on demographic and GH-related variables were extracted from existing databases and case notes. Subjects were followed for mortality and cancer incidence via national population-based registries in Belgium, the Netherlands, Sweden, and the United Kingdom and by a range of methods in the other four countries. Details are given in (15).

In each country, appropriate ethics committee agreement was obtained. For all patients, either we obtained written informed consent or an ethics committee decided that consent was not required.

In Belgium, France, the Netherlands, Sweden, and the United Kingdom, the cohorts were national and population-based, or virtually so, whereas in Switzerland, Germany, and Italy, they were mainly clinic-based and subnational. Vital status follow-up was highly complete except for uncertainty on this in France and Italy (15). Cancer incidence follow-up based on cancer registration was highly complete in Belgium, the Netherlands, Sweden, Switzerland, and the United Kingdom, but less complete in France, Germany, and Italy, where there was no national cancer registration. We therefore restricted cancer incidence risk calculations to the former five countries (15) and present numbers of cancers from the latter three in the Supplemental Data.

Because certain rare conditions (*e.g.*, neurofibromatosis) that lead to GH therapy are themselves strong predisposing factors for cancer, we followed previous practice (11, 12, 16) in excluding individuals with such conditions (listed in Supplemental Data) from analysis.

Statistical analysis

We calculated person-years at risk for cancer incidence and mortality and used these with national population rates to calculate standardized mortality ratios, standardized incidence ratios (SIRs), absolute excess rates, and trends in risk (17) by standard methods, as detailed in the Supplemental Data. The analyses investigated risks of all primary

Table 1. The SAGhE Cohort: Descriptive Variables

Characteristic	Mortality Cohort[a]		Cancer Incidence Cohort[a]	
	n	%	n	%
Sex				
Male	13,268	55.3	11,002	54.2
Female	10,716	44.7	9312	45.8
Country				
Belgium	1363	5.7	1327	6.5
France	10,202	42.5	8614	42.4
Germany	1779	7.4	558	2.7
Italy	1361	5.7	736	3.6
The Netherlands	1746	7.3	1685	8.3
Sweden	2955	12.3	2822	13.9
Switzerland	743	3.1	737	3.6
United Kingdom	3835	16.0	3835	18.9
Age started GH treatment (y)				
0–4	2008	8.4	1801	8.9
5–9	7665	32.0	6535	32.2
10–14	12,136	50.6	10,181	50.1
15–19	2175	9.1	1797	8.8
Year started GH treatment				
<1990	5239	21.8	4685	23.1
1990–1994	10,394	43.3	9264	45.6
1995–1999	5796	24.2	4598	22.6
≥2000	2555	10.7	1766	8.7
Diagnosis leading to GH treatment				
CNS tumor	2221	9.3	1357	6.7
Non-CNS solid tumor	151	0.6	100	0.5
Hematological malignancy	730	3.0	428	2.1
Chronic renal failure and renal diseases	288	1.2	155	0.8
Turner syndrome	3503	14.6	3189	15.7
Other syndromes and chronic diseases	1446	6.0	1264	6.2
Multiple pituitary hormone deficiency	2497	10.4	2261	11.1
Skeletal dysplasias	358	1.5	337	1.7
Isolated growth failure[b]	12,468	52.0	11,062	54.5
Nonclassifiable	322	1.3	161	0.8
Total	23,984	100.0	20,314[c]	100.0

Abbreviation: CNS, central nervous system.

[a] Subjects included in follow-up for mortality, and for cancer incidence, excluding "high risk" initial diagnoses (see Methods).

[b] Including isolated GH deficiency, idiopathic short stature, and prenatal growth failure (small for gestational age).

[c] A total of 10,406 of these subjects were from Belgium, the Netherlands, Sweden, Switzerland, and the United Kingdom and are included in the person to years–based analyses of cancer incidence risk presented in Tables 2 through 5 and Supplemental Tables 1 and 2; 9908 are from France, Germany, and Italy and are presented in the Supplemental data for the reasons specified in the Methods.

malignancies except nonmelanoma skin cancer, for which cancer registration tends to be highly incomplete. All *P* values are two sided.

Results

After exclusions for high-risk diagnoses, data unavailability and lack of permission (see Supplemental Data and Fig. 1), the cohort for mortality risk analyses comprised 23,984 patients and for cancer incidence 10,406 patients. (For a further 9908 from France, Germany, and Italy, incident cancers are reported in the Supplemental Data, but risks are not analyzed; see Methods). Half the cohort was first treated at ages 10 to 14, and about half received GH for isolated growth failure (Table 1).

Follow-up for mortality totaled 396,344 person-years, an average of 16.5 years per patient, and for cancer incidence, 154,371 person-years, averaging 14.8 years per patient. The mean age at the end of follow-up was 27.1 years for the cancer mortality analyses and 25.8 years for the incidence analyses. There were 251 cancer deaths in the cohort and 137 incident cancers in the countries for which incidence risk was analyzed.

Cancer risks in the cohort overall

Cancer mortality in the cohort overall was over 13-fold raised, and cancer incidence risk doubled (Table 2). Absolute excess rates were 5.9 [95% confidence interval (CI), 5.1 to 6.7] for cancer mortality and 4.8 (95% CI, 3.4 to 6.4) for cancer incidence. There was significantly

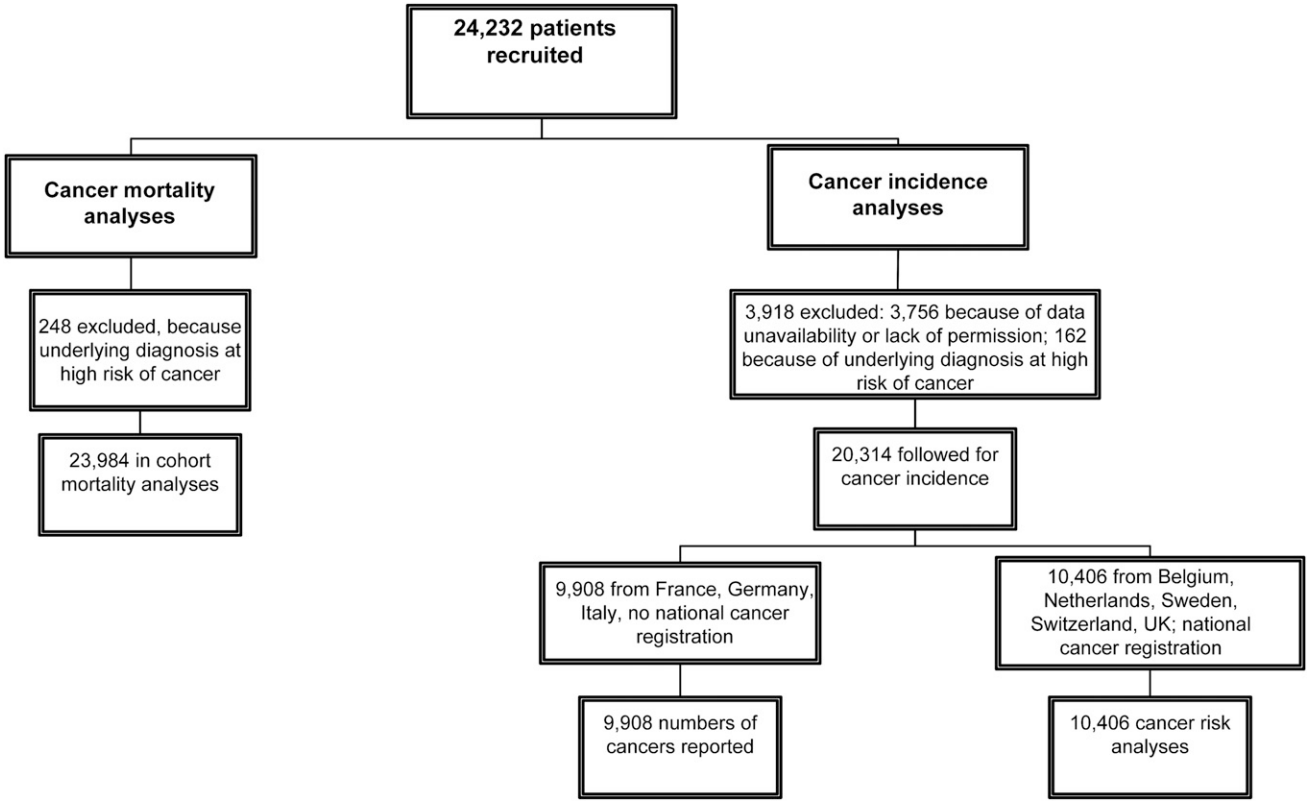

Figure 1. Numbers of patients recruited, excluded, and analyzed, SAGhE cohort.

raised risk of both cancer mortality and incidence for cancers of the bone, kidney, central nervous system (CNS), and thyroid and significantly raised risks based on >1 case for mortality from tongue, mouth, and pharynx cancer; soft tissue cancer; non-Hodgkin lymphoma (non-HL) and leukemia; and incidence of melanoma and ovarian and bladder cancers. With the exception of bone and bladder cancers, these raised risks were essentially a consequence of risks in patients whose original diagnosis leading to GH treatment was cancer. In patients treated after cancer, there was additionally a significantly raised risk based on >1 case for colorectal cancer incidence. Risk estimates for the major adult cancers (*e.g.*, breast, lung, and prostate) had wide CIs, based on few person-years of follow-up.

Risks by underlying diagnosis

In patients whose initial diagnosis was "isolated growth failure" (*i.e.*, growth failure without other major disease: isolated GH deficiency, idiopathic short stature, and prenatal growth failure), overall cancer risk was not raised and there were no significantly raised site-specific risks, based on small numbers of cases (Table 3). For patients whose initial diagnosis was not isolated growth failure or cancer, there were significantly raised risks of cancer incidence (SIR = 1.4; 95% CI, 1.1 to 1.9) and mortality (standardized mortality ratio = 2.2; 95% CI, 1.3 to 3.7) overall, and of bone (SIR = 4.1; 95% CI, 1.3 to 12.6) and bladder (SIR = 27.8; 95% CI, 7.0 to 111.3) cancer incidence, reflecting cases after several different initial diagnoses, with no obvious common factor, although based on small numbers for each cancer site.

Risks by demographic characteristics and GH treatment variables

Cancer risks in the cohort were similar in males and females (Table 4). Risks varied over twofold between countries, paralleling approximately the proportions of subjects in these countries who had cancer as their initial diagnosis (15). Cancer risk did not relate to age at starting r-hGH treatment. For cancer mortality but not incidence, risk decreased with longer duration since starting treatment, and for cancer mortality especially, risk decreased with longer duration of treatment. The effect of duration of treatment disappeared for cancer incidence ($P = 0.72$) and greatly diminished for cancer mortality ($P = 0.04$) when we censored from analysis the person-time during treatment plus the first 2 years after ending treatment (not in Tables 1 through 5), suggesting that it had been an artifact of cessations of treatment because of cancer occurrence. Risk of cancer incidence but not mortality decreased with increasing mean GH dose, and both incidence and mortality risks tended to diminish with cumulative dose.

Table 2. Cancer Mortality and Incidence Risks, SAGhE Cohort, by Site and Initial Diagnosis Leading to GH Treatment

Outcome		All Initial Diagnoses				Initial Diagnosis Cancer				Initial Diagnosis Noncancer			
		Cancer Mortality		Cancer Incidence[c]		Cancer Mortality		Cancer Incidence[c]		Cancer Mortality		Cancer Incidence[c]	
ICD 10, C code	Cancer site[a]	n	SMR[b] (95% CI)	n	SIR (95% CI)	n	SMR[b] (95% CI)	n	SIR (95% CI)	n	SMR[b] (95% CI)	n	SIR (95% CI)
01–14	Tongue, mouth, pharynx	3	6.8 (2.2–21.2)*	1	1.4 (0.0–7.5)	2	24.2 (6.1–96.8)**	1	7.9 (0.2–43.8)	1	2.8 (0.1–15.7)	0	0.0 (0.0–6.0)
18–21	Colon and rectum	2	3.6 (0.9–14.6)	4	2.3 (0.9–6.2)	1	14.7 (0.4–81.7)	2	7.4 (1.9–29.7)*	1	2.1 (0.1–11.6)	2	1.4 (0.3–5.6)
25	Pancreas	1	7.7 (0.2–42.6)	0	0.0 (0.0–28.0)	1	61.6 (1.6–343.4)*	0	0.0 (0.0–182.7)	0	0.0 (0.0–32.2)	0	0.0 (0.0–33.1)
33–34	Lung	1	1.9 (0.1–10.9)	1	2.6 (0.1–14.5)	0	0.0 (0.0–62.2)	0	0.0 (0.0–57.0)	1	2.2 (0.1–12.3)	1	3.1 (0.4–22.2)
40–41	Bone	12	6.9 (3.9–12.1)***	9	5.2 (2.7–10.1)***	8	35.5 (17.7–70.9)***	5	17.2 (7.2–41.4)***	4	2.6 (1.0–7.0)	4	2.8 (1.1–7.5)*
43	Melanoma	1	1.4 (0.0–8.0)	12	2.1 (1.2–3.8)*	0	0.0 (0.0–41.4)	5	5.8 (2.4–13.9)**	1	1.7 (0.0–9.2)	7	1.5 (0.7–3.1)
47–49	Soft tissue	5	5.9 (2.5–14.2)**	4	2.7 (1.0–7.2)	5	47.2 (19.7–113.4)***	2	8.5 (2.1–33.9)*	0	0.0 (0.0–5.0)	2	1.6 (0.4–6.4)
50	Breast	1	1.9 (0.1–10.4)	2	0.9 (0.2–3.4)	1	16.9 (0.4–94.1)	1	3.0 (0.1–16.6)	0	0.0 (0.0–7.7)	1	0.5 (0.0–2.8)
51	Vulva	0	0.0 (0.0–1749.0)	1	5.0 (0.1–27.8)	0	0.0 (0.0–9281.9)	0	0.0 (0.0–141.6)	0	0.0 (0.0–2155.1)	1	5.7 (0.2–31.9)
53	Cervix	0	0.0 (0.0–18.8)	17	0.9 (0.6–1.5)	0	0.0 (0.0–128.6)	2	0.8 (0.2–3.2)	0	0.0 (0.0–22.0)	15	0.9 (0.6–1.5)
54–55	Corpus uteri	1	24.3 (0.6–135.4)	0	0.0 (0.0–35.4)	1	259.7 (6.6–1446.7)**	0	0.0 (0.0–240.9)	0	0.0 (0.0–98.9)	0	0.0 (0.0–41.4)
56	Ovary	1	4.2 (0.1–23.4)	4	3.0 (1.1–7.9)*	1	39.7 (1.0–221.2)*	3	14.8 (4.8–45.9)**	0	0.0 (0.0–17.4)	1	0.9 (0.0–4.9)
61	Prostate	1	50.7 (1.3–282.3)*	0	0.0 (0.0–174.7)	0	0.0 (0.0–1622.2)	0	0.0 (0.0–850.4)	1	57.3 (1.5–319.1)*	0	0.0 (0.0–219.8)
62	Testis	0	0.0 (0.0–13.0)	7	1.2 (0.6–2.4)	0	0.0 (0.0–99.8)	3	2.7 (0.9–8.5)	0	0.0 (0.0–15.0)	4	0.8 (0.3–2.2)
64–66	Kidney	2	13.8 (3.5–437.5)*	3	6.8 (2.2–21.2)*	2	138.1 (34.5–552.0)***	3	44.1 (14.2–136.8)***	0	0.0 (0.0–28.4)	0	0.0 (0.0–10.0)
67–68	Bladder	1	11.7 (0.3–65.0)	3	14.0 (4.5–43.4)**	0	0.0 (0.0–397.0)	0	0.0 (0.0–123.2)	1	13.1 (0.3–72.9)	3	16.3 (5.2–50.4)**
70–72	CNS	156	45.8 (39.2–53.6)***	29	6.5 (4.5–9.4)***	153	373.4 (318.6–437.5)***	23	34.7 (23.1–52.2)***	3	1.0 (0.3–3.1)	6	1.6 (0.7–3.5)
73	Thyroid	1	54.6 (1.4–304.2)*	12	6.0 (3.4–10.5)***	1	496.6 (12.6–2767.0)**	10	32.2 (17.3–59.8)***	0	0.0 (0.0–226.3)	2	1.2 (0.3–4.7)
81	HL	0	0.0 (0.0–6.4)	8	1.8 (0.9–3.6)	0	0.0 (0.0–50.7)	1	1.3 (0.0–7.2)	0	0.0 (0.0–7.4)	7	1.9 (0.9–4.0)
82–85, 96	Non-HL	4	3.4 (1.3–9.0)*	3	1.3 (0.4–4.2)	4	26.8 (10.1–71.4)***	1	2.6 (0.1–14.4)	0	0.0 (0.0–3.6)	2	1.1 (0.3–4.3)
91–95	Leukemia	27	6.4 (4.4–9.4)***	7	2.2 (1.0–4.6)	23	45.5 (30.2–68.5)***	4	7.7 (2.9–20.4)**	4	1.1 (0.4–2.9)	3	1.1 (0.4–3.5)
00–43, 45, 47–85, 89–97	All sites except nonmelanoma skin cancer	251	13.7 (12.1–15.5)***	138	2.2 (1.9–2.6)***	230	101.9 (89.6–116.0)***	72	7.6 (6.1–9.6)***	21	1.3 (0.9–2.0)	66	1.2 (1.0–1.6)

Abbreviations: ICD = International Classification of Diseases; SMR, standardized mortality ratio.

[a]The sites selected are those for which any cancer deaths or incident cases occurred.

[b]Using Swiss rates as expecteds for Germany and Belgian rates as expecteds for both France and the Netherlands for cancer sites for which sufficient detail was not available from home-country national rates.

[c]Excluding France, Germany, and Italy.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Examining these risks within the patients whose initial diagnosis was cancer (Table 4), the only indications of different patterns from those listed previously were that incidence as well as mortality decreased with duration since starting treatment and duration of treatment, cumulative GH dose did not significantly affect mortality or incidence, and mortality but not incidence increased highly significantly ($P < 0.001$) with increasing mean GH dose. For patients whose initial diagnosis was not cancer, neither cancer mortality nor incidence was significantly related to any of the treatment variables. The diminutions in risk seen with mean GH dose and cumulative dose for cohort members overall were at least in part due to confounding by initial diagnosis: Patients with initial noncancer diagnoses tended to have received greater mean and cumulative GH doses than did cancer patients (*e.g.*, 33% of noncancer patients but only 17% of cancer patients received doses of ≥30 μg/kg/d). Analyses separately for patients with isolated growth failure, and for those with Turner syndrome (Supplemental Table 1), showed significant rising incidence risks with time since first treatment and with duration of treatment (both $P = 0.02$) for isolated growth failure patients, but otherwise no significant risks for incidence or mortality.

Table 3. Cancer Mortality and Incidence Risks, SAGhE Cohort, for Patients in Whom a Noncancer Diagnosis Led to GH Treatment

Outcome (Cancer Site)	Initial Diagnosis IGF				Initial Diagnosis Noncancer, Non-IGF			
	Cancer Mortality		Cancer Incidence		Cancer Mortality		Cancer Incidence	
	n	SMR (95% CI)	n	SIR (95% CI)	n	SMR (95% CI)	n	SIR (95% CI)
Colon and rectum	0	0.0 (0.0–12.1)	0	0.0 (0.0–5.2)	1	5.7 (0.1–31.8)	2	2.7 (0.7–10.9)
Bone	3	3.1 (1.0–9.6)	1	1.4 (0.0–8.0)	1	1.8 (0.1–10.1)	3	4.1 (1.3–12.6)*
Melanoma	1	2.6 (0.1–14.5)	3	1.5 (0.5–4.5)	0	0.0 (0.0–16.7)	4	1.5 (0.6–4.0)
Soft tissue	0	0.0 (0.0–8.2)	0	0.0 (0.0–6.0)	0	0.0 (0.0–12.7)	2	3.1 (0.8–12.6)
Cervix	0	0.0 (0.0–64.4)	7	1.1 (0.5–2.4)	0	0.0 (0.0–33.4)	8	0.8 (0.4–1.6)
Testis	0	0.0 (0.0–19.7)	3	1.0 (0.3–3.0)	0	0.0 (0.0–62.3)	1	0.5 (0.0–3.0)
Bladder	0	0.0 (0.0–83.4)	1	8.9 (0.2–49.4)	1	31.0 (0.8–172.9)	2	27.8 (7.0–111.3)**
CNS	0	0.0 (0.0–2.0)	3	1.6 (0.5–4.8)	3	2.6 (0.8–8.0)	3	1.6 (0.5–5.1)
Thyroid	0	0.0 (0.0–371.7)	0	0.0 (0.0–5.5)	0	0.0 (0.0–578.6)	2	2.0 (0.5–7.8)
HL	0	0.0 (0.0–11.5)	3	1.7 (0.6–5.4)	0	0.0 (0.0–20.3)	4	2.0 (0.8–5.4)
Non-HL	0	0.0 (0.0–5.5)	0	0.0 (0.0–3.9)	0	0.0 (0.0–10.5)	2	2.2 (0.6–8.8)
Leukemia	2	0.8 (0.2–3.4)	1	0.8 (0.0–4.2)	2	1.5 (0.4–6.1)	2	1.5 (0.4–5.9)
All sites except nonmelanoma skin cancer	8	0.8 (0.4–1.6)	23	1.0 (0.6–1.4)	13	2.2 (1.3–3.7)*	42	1.4 (1.1–1.9)*

Abbreviation: SMR, standardized mortality ratio.

*$P < 0.05$; **$P < 0.01$.

Mean daily doses of GH were 26.0 μg/kg/d for the patients with isolated GH deficiency, 33.8 μg/kg/d for those with idiopathic short stature, and 49.5 μg/kg/d for those born small for gestational age.

The rising risk of cancer mortality in cancer patients in relation to daily GH dose was similar for each of the three cancer sites with sufficient deaths for such subanalysis (Supplemental Table 2), and also separately in patients who were and were not known to have been treated with any radiotherapy, with craniospinal radiotherapy, and with chemotherapy (each based on limited data on these treatments), and in subgroups by time since starting GH treatment. Strong significant dose-response trends were seen in every subgroup, except where there were small numbers (not in Tables 1 through 5).

Examining site-specific cancer risks by duration since first GH treatment (Table 5), CNS tumor mortality decreased significantly ($P < 0.001$) and HL incidence increased significantly ($P = 0.001$), with longer follow-up. The decreasing CNS tumor trend derived from patients whose underlying diagnosis was cancer (P trend < 0.001) and the HL trend from patients whose initial diagnosis was not cancer (a wide range of noncancer diagnoses; P trend = 0.002).

There was no indication that risk related to cumulative GH dose (Supplemental Table 3), except that CNS tumor mortality diminished with increasing dose in the cohort overall and bone cancer mortality diminished with increasing dose in patients with an initial diagnosis of cancer.

Discussion

GH therapy is widely used, and a range of biological data suggest that hormone levels in the GH–IGF-1 axis may affect cancer risks (1, 2). It is therefore important clinically to determine whether cancer risks are raised by GH treatment. Information on this has been very limited, however. Generally, the larger studies have had short follow-up (10–13, 16) and the studies with long follow-up have been small. With the exception of two cohorts of patients treated with p-hGH (6, 18, 19), the only studies with mean follow-up of >6 years have been a cohort examining solely leukemia as an outcome (5) and cohorts of a few hundred GH-treated cancer patients (7, 20).

This paucity of large-scale, long-term follow-up is important because with few exceptions [*e.g.*, certain cancers after immunosuppression, several causes of leukemia (21)], most known causes of cancer act after a lag period of many years, and hence, short-term follow-up would give little information regarding risks after likely lag periods. Furthermore, most cancer types occur almost entirely in adulthood, so information on short-term cancer risks after childhood treatment (*i.e.*, when the patient is still young) would be virtually uninformative about risks of these malignancies. There have been almost no published data by duration of follow-up (12), however, and none beyond 10 years. In our cohort, for patients with an initial diagnosis of cancer, there was no indication of rising risk of cancer incidence or mortality with longer follow-up. For patients with initial noncancer diagnoses, however, cancer incidence was significantly raised beyond

Table 4. Cancer[a] Mortality and Incidence Risks, SAGhE Cohort, by Demographic and GH Treatment Variables, and Initial Diagnosis Leading to GH Treatment

Demographic or Treatment Variable	All Initial Diagnoses, Total				Initial Diagnosis Cancer				Initial Diagnosis Noncancer			
	Cancer Mortality		Cancer Incidence[c]		Cancer Mortality		Cancer Incidence[c]		Cancer Mortality		Cancer Incidence[c]	
	n	SMR[b] (95% CI)	n	SMR (95% CI)	n	SMR[b] (95% CI)	n	SMR (95% CI)	n	SMR[b] (95% CI)	n	SMR (95% CI)
Sex												
Male	138	12.4 (10.5–14.6)***	52	2.2 (1.7–2.9)***	131	90.2 (76.0–107.0)***	30	7.2 (5.0–10.3)***	7	0.7 (0.3–1.5)	22	1.1 (0.7–1.7)
Female	113	15.8 (13.1–19.0)***	86	2.2 (1.8–2.7)***	99	123.1 (101.1–149.9)***	42	8.0 (5.9–10.8)***	14	2.2 (1.3–3.7)*	44	1.3 (1.0–1.7)
Country												
Belgium	23	22.1 (14.7–33.3)***)	7	1.9 (0.9–4.0)	20	113.9 (73.5–176.6)***	3	5.0 (1.6–15.4)*	3	3.5 (1.1–10.8)*	4	1.3 (0.5–3.5)
France	88	9.9 (8.1–12.2)***	—		79	96.6 (77.5–120.5)***	—		9	1.1 (0.6–2.2)	—	
Germany	10	11.5 (6.2–21.4)***	—		9	114.9 (59.8–220.9)***	—		1	1.3 (0.0–7.0)	—	
Italy	1	1.7 (0.0–9.4)	—		0	0.0 (0.0–252.6)	—		1	1.7 (0.0–9.6)	—	
The Netherlands	27	23.6 (16.2–34.5)***	22	2.5 (1.6–3.8)***	26	138.2 (94.1–203.0)***	14	9.9 (5.8–16.7)***	1	1.0 (0.0–5.8)	8	1.1 (0.5–2.2)
Sweden	30	12.9 (9.0–18.5)***	50	1.5 (1.2–2.0)**	27	120.6 (82.7–175.9)***	21	5.6 (3.6–8.6)***	3	1.4 (0.5–4.4)	29	1.0 (0.7–1.4)
Switzerland	6	19.7 (8.8–43.7)***	2	2.5 (0.6–10.1)	5	168.4 (70.1–404.5)***	2	31.0 (7.7–123.9)**	1	3.6 (0.1–20.2)	0	0.0 (0.0–5.1)
United Kingdom	66	20.7 (16.3–26.4)***	57	3.4 (2.6–4.4)***	64	87.8 (68.7–112.1)***	32	8.9 (6.3–12.6)***	2	0.8 (0.2–3.3)	25	1.9 (1.3–2.8)**
Age started treatment (y)												
0–4	9	7.1 (3.7–13.6)***	7	1.7 (0.8–3.5)	8	127.4 (63.7–254.7)***	4	16.1 (6.1–43.0)***	1	0.8 (0.0–4.6)	3	0.8 (0.2–2.4)
5–9	70	13.9 (11.0–17.6)***	46	2.5 (1.8–3.3)***	65	100.1 (78.5–127.7)***	18	7.1 (4.5–11.3)***	5	1.1 (0.5–2.7)	28	1.7 (1.2–2.5)**
10–14	149	15.4 (13.1–18.0)***	71	2.1 (1.7–2.6)***	137	108.7 (91.9–128.5)***	42	7.3 (5.4–9.9)***	12	1.4 (0.8–2.5)	29	1.0 (0.7–1.5)
15–19	23	10.0 (6.6–15.0)***	14	2.3 (1.4–3.9)**	20	70.3 (45.4–109.0)***	8	8.6 (4.3–17.2)***	3	1.5 (0.5–4.6)	6	1.2 (0.5–2.6)
P trend		0.55		1.00		0.30		0.71		0.53		0.44
Time since started treatment (y)												
0–4	103	24.4 (20.1–29.6)***	25	3.5 (2.4–5.2)***	100	184.8 (151.9–224.8)***	20	16.0 (10.3–24.9)***	3	0.8 (0.3–2.5)	5	0.9 (0.4–2.1)
5–9	78	17.2 (13.8–21.5)***	21	1.8 (1.2–2.8)*	71	124.4 (98.6–157.0)***	12	5.9 (3.4–10.5)***	7	1.8 (0.8–3.7)	9	0.9 (0.5–1.8)
10–14	37	8.2 (6.0–11.4)***	47	2.3 (1.8–3.1)***	33	60.7 (43.2–85.4)***	24	8.2 (5.5–12.2)***	4	1.0 (0.4–2.7)	23	1.3 (0.9–2.0)
15–19	25	6.7 (4.5–9.8)***	30	1.6 (1.1–2.3)*	19	45.9 (29.3–71.9)***	11	4.5 (2.5–8.2)***	6	1.8 (0.8–4.0)	19	1.2 (0.7–1.8)
≥20	8	6.1 (3.1–12.3)***	15	2.7 (1.7–4.6)**	7	37.4 (17.8–78.4)***	5	6.1 (2.5–14.7)**	1	0.9 (0.0–5.0)	10	2.2 (1.2–4.0)*
P trend		<0.001		0.13		<0.001		0.005		0.65		0.11
Duration of treatment (y)[d]												
<3	118	21.1 (17.6–25.3)***	40	2.8 (2.1–3.9)***	110	174.9 (145.1–210.8)***	25	10.4 (7.1–15.5)***	8	1.6 (0.8–3.2)	15	1.3 (0.8–2.1)
3–6	80	12.4 (10.0–15.5)***	52	2.7 (2.1–3.5)***	74	87.0 (69.3–109.3)***	29	8.6 (6.0–12.4)***	6	1.1 (0.5–2.4)	23	1.4 (1.0–2.2)*
≥7	35	7.5 (5.4–10.4)***	33	1.9 (1.3–2.6)**	31	50.2 (35.3–71.4)***	12	4.0 (2.2–7.0)***	4	1.0 (0.4–2.6)	21	1.4 (0.9–2.2)
P trend		<0.001		0.07		<0.001		0.006		0.76		0.77
Mean GH dose (μg/kg/d)[d]												
<20	37	9.6 (7.0–13.3)***	18	4.0 (2.6–6.4)***	35	64.1 (46.0–89.3)***	12	6.5 (3.7–11.4)***	2	0.6 (0.2–2.4)	6	2.3 (1.0–5.2)
20–29	94	19.5 (15.9–23.8)***	40	3.3 (2.4–4.4)***	89	102.1 (82.9–125.6)***	26	7.6 (5.2–11.2)***	5	1.3 (0.5–3.0)	14	1.6 (0.9–2.7)
30–39	52	16.8 (12.8–22.0)***	41	2.1 (1.6–2.9)***	50	178.9 (135.6–236.1)***	19	10.2 (6.5–16.0)***	2	0.7 (0.2–2.8)	22	1.3 (0.8–1.9)
≥40	7	3.8 (1.8–8.0)**	11	1.1 (0.6–2.0)	5	101.5 (42.3–243.9)***	3	5.0 (1.6–15.5)*	2	1.1 (0.3–4.5)	8	0.9 (0.4–1.7)
P trend		0.39		<0.001		<0.001		0.59		0.74		0.05
Cumulative GH dose (mg/kg)[d]												
<25	91	14.9 (12.1–18.3)***	38	3.4 (2.5–4.7)***	87	108.8 (88.2–134.2)***	25	9.9 (6.7–14.6)***	4	0.8 (0.3–2.0)	13	1.5 (0.9–2.6)
25–49	73	16.9 (13.4–21.2)***	30	2.1 (1.5–3.0)***	70	108.1 (85.5–136.7)***	18	6.6 (4.1–10.4)***	3	0.8 (0.3–2.5)	12	1.0 (0.6–1.8)
50–99	36	11.1 (8.0–15.3)***	40	2.3 (1.7–3.2)***	30	79.5 (55.6–113.6)***	18	6.8 (4.3–10.9)***	6	2.1 (0.9–4.6)	22	1.5 (1.0–2.3)

(*Continued*)

Table 4. Continued

Demographic or Treatment Variable	All Initial Diagnoses, Total				Initial Diagnosis Cancer				Initial Diagnosis Noncancer			
	Cancer Mortality		Cancer Incidence[c]		Cancer Mortality		Cancer Incidence[c]		Cancer Mortality		Cancer Incidence[c]	
	n	SMR[b] (95% CI)	n	SMR (95% CI)	n	SMR[b] (95% CI)	n	SMR (95% CI)	n	SMR[b] (95% CI)	n	SMR (95% CI)
≥100	3	2.7 (0.9–8.3)	11	1.6 (0.9–2.9)	2	34.2 (8.6–136.9)**	5	9.6 (4.0–23.1)***	1	0.9 (0.0–5.3)	6	1.0 (0.4–2.1)
P trend		0.003		0.02		0.05		0.43		0.24		0.63
Total	251	13.7 (12.1–15.5)***	138	2.2 (1.9–2.6)***	230	101.9 (89.6–116.0)***	72	7.6 (6.1–9.6)***	21	1.3 (0.9–2.0)	66	1.2 (1.0–1.6)

Abbreviation: SMR, standardized mortality ratio.

[a] All malignancies except nonmelanoma skin cancer.

[b] Using Swiss rates as expecteds for Germany and Belgian rates as expecteds for both France and the Netherlands for cancer sites for which sufficient detail was not available from home-country national rates.

[c] Excluding France, Germany, and Italy.

[d] Unknown, all initial diagnoses: duration of treatment mortality = 18, incidence = 13; mean GH dose mortality = 61, incidence = 28; cumulative GH dose mortality = 48, incidence = 19.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

20 years of follow-up and there was a highly significant increase in incidence with longer follow-up for HL incidence. For patients with isolated growth failure, separately, there were inconsistent findings based on modest numbers: significant trends of incidence with duration of treatment and time since first treatment, but not for mean dose ($P = 0.52$), not clearly for cumulative dose ($P = 0.08$), and not for cancer mortality. For Turner syndrome separately, there were no consistent or significant relations.

Potentially, the cancer risks in GH-treated patients could reflect the underlying condition leading to GH treatment, and the non-GH treatments (*e.g.*, radiotherapy) given for this condition, as well as the effect of GH itself. This is clearest for patients receiving GH because of malignancy or chromosomal instability syndromes, but applies to some extent to virtually every underlying diagnosis, for example, hypopituitarism (9, 22) or Turner syndrome (23). The underlying diagnoses are numerous and heterogeneous, and we do not hold systematic information on the non-GH treatments, so we cannot give explanation of the results in relation to specific confounders. In principle, this might be overcome by comparing GH-treated patients with others with the same condition who had not received GH. This has been done in some studies for patients with underlying cancer (7, 24, 25). We did not have comparison data for untreated patients, however. Furthermore, this would not entirely solve the problem because selective factors leading to GH treatment may themselves cause differences in cancer risk between treated and untreated groups. Our analyses using general population rates to generate expectations need to be interpreted cautiously in this light.

High completeness of follow-up to a fixed end-date is critical if cohort study results are to be valid, especially for safety assessment, because deficient follow-up can artifactually produce an apparent lack of raised risk. Previous large r-hGH cohorts, with one exception (16), have censored follow-up at last clinic visit, not at a fixed end-date (10, 12, 13, 26). Because frequency of medical contact depends on health status, this could be seriously biased. The large postmarketing surveillance studies (10–12, 14, 16) have also depended on active reporting of cancers to the pharmaceutical company by physicians, the completeness of which is unknown, especially after patients leave pediatric endocrine care. Our follow-up for mortality and cancer incidence, like that in the p-hGH cohorts (18, 19), was to a fixed end-date, and had high completeness through routine national data systems (15).

If GH affects cancer risk, one might expect dose- and duration-response relationships for risk. No data have been published on this, however: only statements of no relation for leukemia in one cohort (5) and for overall cancer risk in another (19). Our results did not suggest an increase in cancer mortality or incidence risks with increasing cumulative GH dose: Apparent decreases in risk with higher doses appeared to be largely or entirely an artifact of confounding by initial diagnosis, and apparent increases with shorter duration an artifact of stopping GH treatment because of cancer occurrence (see Results).

However, there was a significant increase in cancer mortality with increasing mean daily r-hGH dose for patients with previous cancer. Interpretation is uncertain. Favoring a causal explanation, the association was highly significant, so very unlikely to be due to chance; the results did not appear to be due to potentially confounding treatments such as craniospinal radiotherapy, as far as data were available to assess this, and the lack of similar associations for cancer incidence or for patients with initial noncancer diagnoses could be plausible if GH affects cancer

Table 5. Cancer Mortality and Incidence Risks, Selected Cancer Sites, SAGhE Cohort, by Duration Since First Treatment and Initial Diagnosis Leading to GH Treatment

Cancer Site (Outcome), Duration Since First Treatment (y)	All Initial Diagnoses, Total				Initial Diagnosis Cancer				Initial Diagnosis Noncancer			
	Cancer Mortality		Cancer Incidence[b]		Cancer Mortality		Cancer Incidence[b]		Cancer Mortality		Cancer Incidence[b]	
	n	SMR[a] (95% CI)	n	SIR (95% CI)	n	SMR[a] (95% CI)	n	SIR (95% CI)	n	SMR[a] (95% CI)	n	SIR (95% CI)
Colorectal cancer												
0–9	1	10.2 (0.3–56.7)	2	4.2 (1.1–16.9)*	1	74.4 (1.9–414.4)*	2	24.4 (6.1–97.6)**	0	0.0 (0.0–43.5)	0	0.0 (0.0–9.4)
10–19	1	2.7 (0.1–15.1)	2	2.0 (0.5–7.9)	0	0.0 (0.0–85.4)	0	0.0 (0.0–24.7)	1	3.1 (0.1–17.1)	2	2.3 (0.6–9.3)
20–29	0	0.0 (0.0–45.2)	0	0.0 (0.0–16.4)	0	0.0 (0.0–319.9)	0	0.0 (0.0–96.7)	0	0.0 (0.0–52.6)	0	0.0 (0.0–19.7)
P trend		0.25		0.25		0.11		0.06		0.97		0.75
Bone cancer												
0–9	9	8.5 (4.4–16.3)***	5	4.6 (1.9–11.0)*	7	47.8 (22.8–100.3)***	3	14.8 (4.8–45.9)**	2	2.2 (0.5–8.7)	2	2.3 (0.6–9.0)
10–19	3	4.6 (1.5–14.2)*	4	6.8 (2.6–18.1)**	1	13.3 (0.3–74.2)	2	24.7 (6.2–98.8)**	2	3.5 (0.9–13.8)	2	3.9 (1.0–15.8)
20–29	0	0.0 (0.0–114.7)	0	0.0 (0.0–86.2)	0	0.0 (0.0–915.9)	0	0.0 (0.0–561.5)	0	0.0 (0.0–131.2)	0	0.0 (0.0–101.8)
P trend		0.30		0.76		0.19		0.82		0.76		0.74
Melanoma												
0–9	0	0.0 (0.0–25.2)	2	1.6 (0.4, 6.2)	0	0.0 (0.0–178.8)	1	4.3 (0.1–23.9)	0	0.0 (0.0–29.4)	1	0.9 (0.0–5.3)
10–19	1	2.1 (0.1–11.9)	7	1.9 (0.9, 4.0)	0	0.0 (0.0–65.6)	2	3.8 (0.9–15.1)	1	2.4 (0.1–13.6)	5	1.6 (0.7–3.9)
20–29	0	0.0 (0.0–45.4)	3	4.5 (1.4, 13.8)*	0	0.0 (0.0–299.2)	2	18.9 (4.7–75.6)*	0	0.0 (0.0–53.5)	1	1.8 (0.0–9.8)
P trend		0.86		0.25		—		0.22		0.86		0.64
CNS												
0–9	120	62.9 (52.6–75.2)***	15	6.2 (3.8–10.3)***	118	503.2 (420.1–602.7)***	11	29.3 (16.2–52.9)***	2	1.2 (0.3–4.8)	4	2.0 (0.7–5.2)
10–19	32	24.2 (17.1–34.3)***	13	7.2 (4.2–12.4)***	31	207.3 (145.8–294.8)***	11	43.4 (24.0–78.3)***	1	0.9 (0.0–4.8)	2	1.3 (0.3–5.1)
20–29	4	22.9 (8.6–61.0)***	1	4.7 (0.1–26.2)	4	155.1 (58.2–413.3)***	1	29.8 (0.8–165.9)	0	0.0 (0.0–24.8)	0	0.0 (0.0–20.6)
P trend		<0.001		0.90		<0.001		0.43		0.64		0.47
Thyroid												
0–9	0	0.0 (0.0–1284.3)	6	10.9 (4.9–24.2)***	0	0.0 (0.0–10035.5)	5	51.3 (21.4–123.3)***	0	0.0 (0.0–1472.7)	1	2.2 (0.1–12.3)
10–19	1	78.1 (2.0–435.4)*	5	4.1 (1.7–9.8)*	1	772.6 (19.6–4304.7)**	4	22.5 (8.4–59.9)***	0	0.0 (0.0–320.7)	1	1.0 (0.0–5.3)
20–29	0	0.0 (0.0–1393.9)	1	4.4 (0.1–24.6)	0	0.0 (0.0–10488.7)	1	28.4 (0.7–158.1)	0	0.0 (0.0–1607.5)	0	0.0 (0.0–19.3)
P trend		0.98		0.14		0.99		0.29		—		0.41
HL												
0–9	0	0.0 (0.0–17.0)	0	0.0 (0.0–1.8)	0	0.0 (0.0–123.2)	0	0.0 (0.0–9.3)	0	0.0 (0.0–19.8)	0	0.0 (0.0–2.3)
10–19	0	0.0 (0.0–11.3)	6	2.7 (1.2–6.0)*	0	0.0 (0.0–95.4)	1	2.9 (0.4–20.7)	0	0.0 (0.0–12.8)	5	2.6 (1.1–6.3)*
20–29	0	0.0 (0.0–119.2)	2	9.6 (2.4–38.2)*	0	0.0 (0.0–887.9)	0	0.0 (0.0–116.5)	0	0.0 (0.0–137.7)	2	11.3 (2.8–45.1)*
P trend		—		0.001		—		0.40		—		0.002
Leukemia												
0–9	20	7.7 (5.0–11.9)***	4	2.0 (0.8–5.4)	18	55.7 (35.1–88.4)***	3	8.8 (2.9–27.4)*	2	0.9 (0.2–3.5)	1	0.6 (0.0–3.4)
10–19	7	4.7 (2.3–9.9)**	3	2.7 (0.9–8.4)	5	29.9 (12.5–71.9)***	1	6.2 (0.2–34.3)	2	1.5 (0.4–6.1)	2	2.1 (0.5–8.4)
20–29	0	0.0 (0.0–32.6)	0	0.0 (0.0–30.5)	0	0.0 (0.0–239.3)	0	0.0 (0.0–186.3)	0	0.0 (0.0–37.7)	0	0.0 (0.0–36.5)
P trend		0.16		0.98		0.10		0.63		0.74		0.47

Abbreviation: SMR, standardized mortality ratio.

[a]Using Swiss rates as expecteds for Germany, and Belgian rates as expecteds for both France and the Netherlands, for cancer sites for which sufficient detail was not available from home-country national rates.

[b]Excluding France, Germany, and Italy.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

survival rather than cancer occurrence. Against a causal explanation is the lack of relation of risk to increasing cumulative GH dose or treatment duration, and the existence of potential for confounding by underlying disease or non-GH treatment factors not captured by the relatively crude measures of these we had available. Further data are needed to resolve whether high GH doses affect cancer survival.

For the three cancer sites for which there is most published support for an association with IGF-1 levels—colorectum, breast, and prostate (2)—the evidence from our cohort and previously (9, 10, 18, 19) is too sparse to reach a conclusion on relations to GH treatment, reflecting the rarity of these cancers at childhood and young adult ages. Concerns about leukemia risk after GH were raised by case reports (5) and a significantly raised risk in a cohort of p-hGH patients (6). However, others (19), and cohorts that excluded "high-risk" patients (11, 12), have found no excess, although several leukemias occurred in the high-risk group. In our cohort, there was a highly significant excess of leukemia incidence and mortality confined to patients with prior cancer. The data overall suggest that GH treatment does not substantially increase leukemia risk in patients without prior high risk, but leave it unclear whether risk is affected in high-risk individuals.

A cohort study of p-hGH patients found a significant excess of HL mortality (19). The only other cohort findings have been a nonsignificant excess (18), or deficit (12), based on small numbers. In our cohort, eight HL cases occurred, a nonsignificant excess, but there was a

highly significant trend with longer follow-up (although no trend with GH dose). The previous studies finding raised HL risk have been those with longest follow-up, so it remains possible that GH treatment at young ages may affect long-term HL risk.

Our cohort showed a significant raised bone cancer incidence in GH-treated patients, both those with and without an initial cancer diagnosis. Bone cancer has been one of the most common second primaries in previous childhood GH-treated cohorts (18, 24). The few risk analyses have been nonsignificant, based on very small numbers (12, 19). The three bone cancer deaths after isolated growth failure in our data were included in a French SAGhE publication (27), but the other bone cancer deaths, and all of the incident cases of bone cancer, were not. There was no evidence in our data that bone cancer risk was related to GH dose, but the significant bone cancer excess in both cancer and noncancer patients, and the anatomical and age distributions of bone cancer and association with height in the general population (28), argue that the relation needs reexamination in future data.

Bladder cancer risk was greatly and significantly (P = 0.002) raised in patients without previous cancer, but based on small numbers. There appear to be no previous data about this and until such data are available, little weight can be put upon it.

We found significant excesses of incidence and mortality from cancers of the soft tissue, kidney, CNS, and thyroid, and of incidence of melanoma and cancer of the ovary and mortality from non-HL, all restricted to patients with cancer as the reason for GH treatment. Mainly, these are cancer sites for which raised risk of second cancer after radiotherapy and/or chemotherapy is well known (29, 30), although this does not preclude GH raising the risks further. Melanoma, however, is not a tumor usually raised after radiotherapy and chemotherapy, although it has been in at least one instance (31). Only for CNS tumors are there previous data on risks as a second malignancy after GH, with no raised risk relating to GH (25). An excess of CNS tumors has been found in patients treated with GH who did not have previous malignancy (12).

Our study had weaknesses, detailed further in ref. 15. We did not have information on GH treatment beyond pediatric ages, so we may have underestimated treatment duration for some patients with consequent dilution of any true effect of duration on cancer risk. Aggregation of data from eight countries adds the complexity of heterogeneity in patient mix and treatments, but without such a pooling the large numbers and hence statistical power of this study could not have been achieved. We did not have information on IGF-1 levels. In addition, although our follow-up was much longer than in previous large cohort studies of childhood-treated patients (10–14), it still included few person-years beyond age 35, and hence had limited power for cancers prevalent at middle ages and older (and indeed for cancers prevalent at younger ages: even though the cohort is large, numbers of cases are often not large and therefore CIs tended to be wide). Interpretation of our data must therefore be cautious, and future longer follow-up of the cohort will be important. In Germany and Italy, ascertainment of GH-treated patients may have been substantially incomplete; in Italy, there was incompleteness in mortality follow-up; and in France and Italy, regulations and reimbursement rules gave incentives to prescribers to overstate isolated growth failure as an underlying diagnosis. These weaknesses seem unlikely to have biased the cancer analyses presented, however, as removal of France, Germany, and Italy from the analyses did not alter the conclusions.

Overall, our study, with much larger numbers of GH-treated patients followed long-term than previously, does not suggest that GH treatment affects the risk of cancer incidence or mortality for the outcomes and durations of follow-up for which our analyses have substantial data. The lack of increased risk with greater cumulative dose or duration of treatment, key variables for which data have not been published previously, makes a causal relation less likely. There was also no clear raised risk in patients with isolated growth failure. These factors argue against a major risk of cancer overall within the length of follow-up currently available. Nevertheless, continued vigilance during follow-up is desirable, both because of the lack of data for longer follow-up than in our study and because of the presence of some significant raised risks in the results. The rising cancer mortality with greater daily dose in cancer patients, however, leaves open the possibility of an effect on cancer survival. Also, the raised risks of bone and bladder cancers in patients with initial noncancer diagnoses and the rising risk of HL with longer follow-up in such patients leave possibilities of effects on site-specific cancer causation for which further data are needed.

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