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Cancer risks in patients treated with growth hormone in childhood: the SAGhE European cohort study

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Abstract

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.

Patients—The cohort comprised 23,984 patients treated with recombinant GH (r-hGH) in 8 European countries since this treatment was first used in 1984. Cancer expectations were 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 (standardised incidence ratio 2.8 (95% confidence interval 1.1-7.5) and bladder (16.3 (5.2-50.4)) 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, risk of cancer mortality increased significantly with increasing daily r-hGH dose (p trend<0.001). Hodgkin lymphoma 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 Hodgkin lymphoma risks, need further investigation.

Key terms

Cancer; incidence; mortality; risk; growth hormone

Introduction

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 hormone (r-hGH).

GH raises serum concentrations of IGF-1 (insulin-like growth factor-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 leukaemia(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). While these data give suspicion that there might be carcinogenic effects, however, no risks have been consistently shown 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 SAGhE (Safety and Appropriateness of Growth Hormone Treatments in Europe) study, with follow-up and analysis independent of pharmaceutical companies, to examine whether or not 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 paediatric ages since such treatment was first used in that country (1984-6, 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 UK 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 UK the cohorts were national and population-based, or virtually so, while in Switzerland, Germany and Italy they were mainly clinic-based and sub-national. 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 UK, 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.

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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 of cancer incidence and mortality, and used these with national population rates to calculate standardised mortality ratios (SMRs), standardised incidence ratios (SIRs), absolute excess rates (AERs) and trends in risk(17) by standard methods, as detailed in the Supplemental data. The analyses investigated risks of all primary malignancies except non-melanoma skin cancer, for which cancer registration tends to be highly incomplete. All p values are 2-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 9,908 from France, Germany and Italy, incident cancers are reported in the Supplemental data but risks not analysed (see Methods)). Half the cohort were first treated at ages 10-14, and about half received GH for isolated growth failure (Table 1).

Follow-up for mortality totalled 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 analysed.

Cancer risks in the cohort overall

Cancer mortality in the cohort overall was over 13-fold raised and cancer incidence risk doubled (Table 2). AERs were 5.9 (95% confidence interval (CI) 5.1-6.7) for cancer mortality and 4.8 (3.4-6.4) for cancer incidence. There was significantly raised risk of both cancer mortality and incidence for cancers of the bone, kidney, 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 and leukaemia, 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 confidence intervals, 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 growth hormone 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 1.1-1.9) and mortality (SMR 2.2; 95% CI 1.3-3.7) overall, and of bone (SIR 4.1; 95% CI 1.3-12.6) and bladder SIR 27.8 (7.0-111.3) 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 risks did not relate to age at starting r-hGH treatment, but for cancer mortality not incidence risks decreased with duration since starting treatment, and for cancer mortality especially risks 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 Table), suggesting that it had been an artefact 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.

Examining these risks within the patients whose initial diagnosis was cancer (Table 4), the only indications of different patterns from above 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 non-cancer diagnoses tended to have received greater mean and cumulative GH doses than did cancer patients (e.g. 33% of non-cancer patients but only 17% of cancer patients received doses of ≥30μg/Kg/day). 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. Mean daily doses of GH were 26.0μg/Kg/day for the patients with isolated growth hormone deficiency, 33.8 for those with idiopathic short stature, and 49.5 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.

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Strong significant dose-response trends were seen in every sub-group, except where there were small numbers (not in Table).

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

There was no indication that risk related to cumulative GH dose (Supplemental Table 3), except that CNS tumour 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-IGF1 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 leukaemia 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 leukaemia(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 non-cancer diagnoses, however, cancer incidence was significantly raised beyond 20 years of follow-up and there was a highly significant increase in incidence with longer follow-up for Hodgkin lymphoma 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, e.g. hypopituitarism(9, 22) or Turner syndrome(23). The underlying diagnoses are numerous and heterogeneous, and we do not hold 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 since 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 artefactually 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). Since frequency of medical contact depends on health status, this could be seriously biased. The large post-marketing 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 paediatric 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 leukaemia 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 artefact of confounding by initial diagnosis, and apparent increases with shorter duration an artefact 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. Favouring 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 non-cancer diagnoses could be plausible if GH affects cancer 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 IGF1 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 leukaemia 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 leukaemias occurred in the high-risk group. In our cohort there was a highly significant excess of leukaemia incidence and mortality confined to patients with prior cancer. The data overall suggest that GH treatment does not substantially increase leukaemia 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 Hodgkin lymphoma (HL) mortality(19). The only other cohort findings have been a non-significant excess(18), or deficit(12), based on small numbers. In our cohort, 8 HL cases occurred, a non-significant 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 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 non-significant, 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 non-cancer patients, and the anatomical and age distributions of bone cancer and association with height in the general population(28), argue that the relation needs re-examination 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 NHL, 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 tumour usually raised after radiotherapy and chemotherapy, although it has been in at least one instance(31). Only for CNS tumours are there previous data on risks as a second malignancy after GH, with no raised risk relating to GH(25). An excess of CNS tumours has been found in patients treated with GH who did not have previous malignancy(12).

Our study had weaknesses, detailed further in(15). We did not have information on GH treatment beyond paediatric 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-I 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 confidence intervals 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, since 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 non-cancer diagnoses, and the rising risk of Hodgkin lymphoma with longer follow-up in such patients, leave possibilities of effects on site-specific cancer causation for which further data are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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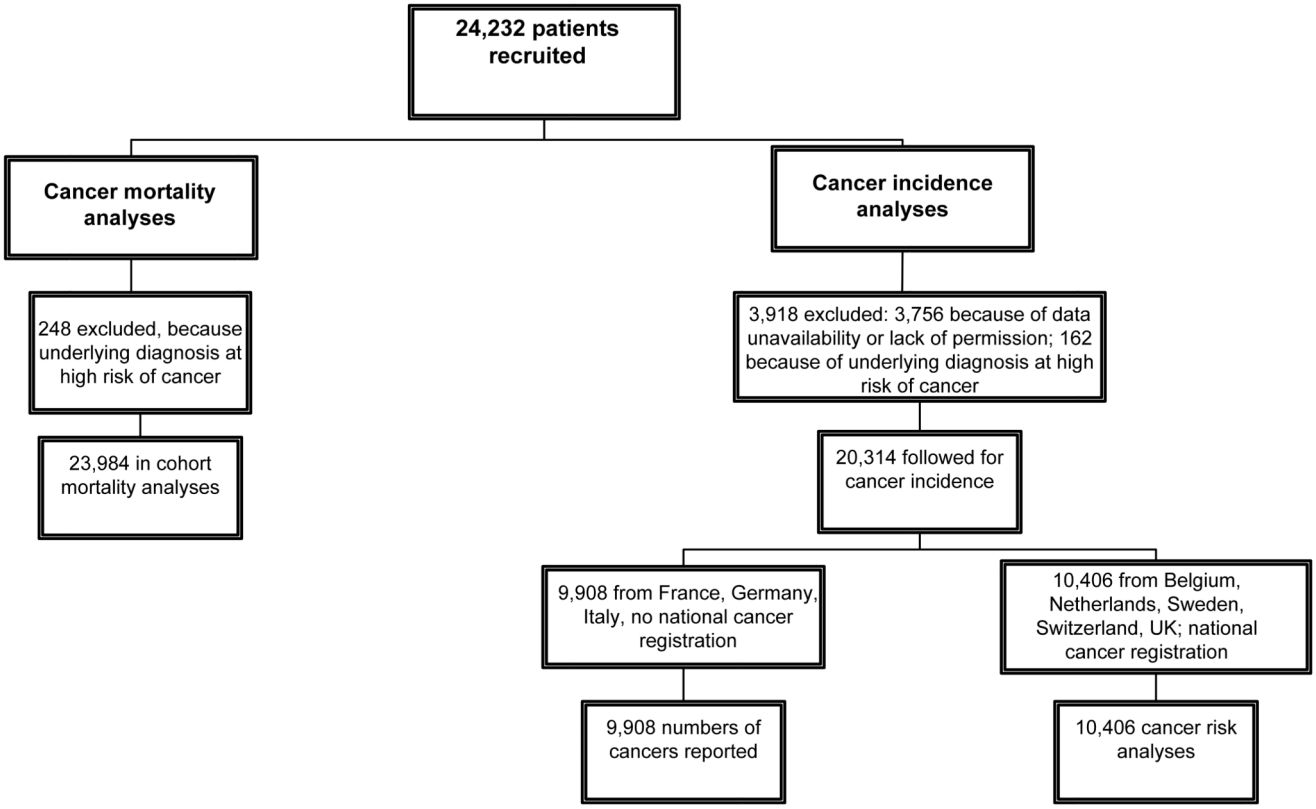

Figure 1.
Numbers of patients recruited, excluded, and analysed, SAGhE cohort

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Table 1

The SAGhE cohort: descriptive variables

Characteristic		Mortality cohort[a]		Cancer incidence cohort[a]	
		No.	%	No.	%
Sex	Male	13268	55.3	11002	54.2
	Female	10716	44.7	9312	45.8
Country	Belgium	1363	5.7	1327	6.5
	France	10202	42.5	8614	42.4
	Germany	1779	7.4	558	2.7
	Italy	1361	5.7	736	3.6
	Netherlands	1746	7.3	1685	8.3
	Sweden	2955	12.3	2822	13.9
	Switzerland	743	3.1	737	3.6
	UK	3835	16.0	3835	18.9
Age started GH treatment (years)	0-4	2008	8.4	1801	8.9
	5-9	7665	32.0	6535	32.2
	10-14	12136	50.6	10181	50.1
	15-19	2175	9.1	1797	8.8
Year started GH treatment	<1990	5239	21.8	4685	23.1
	1990-94	10394	43.3	9264	45.6
	1995-99	5796	24.2	4598	22.6
	≥2000	2555	10.7	1766	8.7
Diagnosis leading to GH treatment	CNS tumour	2221	9.3	1357	6.7
	Non CNS solid tumour	151	0.6	100	0.5
	Hematological malignancy	730	3.0	428	2.1
	Chronic renal failure and renal diseases 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 organic GHD	2497	10.4	2261	11.1
	Skeletal dysplasias	358	1.5	337	1.7
	Isolated growth failure[b]	12468	52.0	11062	54.5
	Non-classifiable	322	1.3	161	0.8
Total		23984	100.0	20314[c]	100.0

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

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

[c] 10,406 of these subjects were from Belgium, the Netherlands, Sweden, Switzerland and the UK, and are included in the person-years based analyses of cancer incidence risk presented in Tables 2-5, and Supplemental Tables 1 and 2; 9,908 are from France, Germany and Italy and are presented in the Supplement for the reasons specified in the Methods.

Table 2

Cancer mortality and incidence risks, SAGhE cohort, by site and initial diagnosis leading to GH treatment

Outcome		All initial diagnoses			
		Cancer mortality		Cancer incidence[c]	
ICD 10, C code	Cancer site[a]	No. of cases	SMR[b] (95% CI)	No. of cases	SIR (95% CI)
01-14	Tongue, mouth, pharynx	3	6.8 (2.2- 21.2)[d]	1	1.4 (0.0-7.5)
18-21	Colon and rectum	2	3.6 (0.9-14.6)	4	2.3 (0.9-6.2)
25	Pancreas	1	7.7 (0.2-42.6)	0	0.0 (0.0-28.0)
33-34	Lung	1	1.9 (0.1-10.9)	1	2.6 (0.1-14.5)
40-41	Bone	12	6.9 (3.9-12.1)[f]	9	5.2 (2.7-10.1)[f]
43	Melanoma	1	1.4 (0.0-8.0)	12	2.1 (1.2-3.8)[d]
47-49	Soft tissue	5	5.9 (2.5-14.2)[e]	4	2.7 (1.0-7.2)
50	Breast	1	1.9 (0.1-10.4)	2	0.9 (0.2-3.4)
51	Vulva	0	0.0 (0.0-1749.0)	1	5.0 (0.1-27.8)
53	Cervix	0	0.0 (0.0-18.8)	17	0.9 (0.6-1.5)
54-55	Corpus uteri	1	24.3 (0.6-135.4)	0	0.0 (0.0-35.4)
56	Ovary	1	4.2 (0.1-23.4)	4	3.0 (1.1-7.9)[d]
61	Prostate	1	50.7 (1.3-282.3)[d]	0	0.0 (0.0-174.7)
62	Testis	0	0.0 (0.0-13.0)	7	1.2 (0.6-2.4)
64-66	Kidney	2	13.8 (3.5-437.5)[d]	3	6.8 (2.2-21.2)[d]
67-68	Bladder	1	11.7 (0.3-65.0)	3	14.0 (4.5-43.4)[e]
70-72	CNS	156	45.8 (39.2-53.6)[f]	29	6.5 (4.5-9.4)[f]
73	Thyroid	1	54.6 (1.4-304.2)[d]	12	6.0 (3.4-10.5)[f]
81	Hodgkin lymphoma	0	0.0 (0.0-6.4)	8	1.8 (0.9-3.6)
82-85,96	Non-Hodgkin lymphoma	4	3.4 (1.3-9.0)[d]	3	1.3 (0.4-4.2)
91-95	Leukaemia	27	6.4 (4.4-9.4)[f]	7	2.2 (1.0-4.6)
00-43, 45, 47-85, 89-97	All sites except non-melanoma skin cancer	251	13.7 (12.1-15.5)[f]	138	2.2 (1.9-2.6)[f]

ICD 10, C code	Cancer site	Initial diagnosis cancer				Initial diagnosis non- cancer			
		Cancer mortality		Cancer incidence		Cancer mortality		Cancer incidence	
		n.	SMR (95% CI)	n.	SIR (95% CI)	n.	SMR (95% CI)	n.	SIR (95% CI)
01-14	Tongue, mouth, pharynx	2	24.2 (6.1-96.8)[e]	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	1	14.7 (0.4-81.7)	2	7.4 (1.9-29.7)[d]	1	2.1 (0.1-11.6)	2	1.4 (0.3-5.6)
25	Pancreas	1	61.6 (1.6-343.4)[d]	0	0.0 (0.0-182.7)	0	0.0 (0.0-32.2)	0	0.0 (0.0-33.1)
33-34	Lung	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	8	35.5 (17.7-70.9)[f]	5	17.2 (7.2-41.4)[f]	4	2.6 (1.0-7.0)	4	2.8 (1.1-7.5)[d]
43	Melanoma	0	0.0 (0.0-41.4)	5	5.8 (2.4-13.9)[e]	1	1.7 (0.0-9.2)	7	1.5 (0.7-3.1)
47-49	Soft tissue	5	47.2 (19.7-113.4)[f]	2	8.5 (2.1-33.9)[d]	0	0.0 (0.0-5.0)	2	1.6 (0.4-6.4)
50	Breast	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)

ICD 10, C code	Cancer site	Initial diagnosis cancer				Initial diagnosis non- cancer			
		Cancer mortality		Cancer incidence		Cancer mortality		Cancer incidence	
		n.	SMR (95% CI)	n.	SIR (95% CI)	n.	SMR (95% CI)	n.	SIR (95% CI)
51	Vulva	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 (0.0-128.6)	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	259.7 (6.6-1446.7)[e]	0	0.0 (0.0-240.9)	0	0.0 (0.0-98.9)	0	0.0 (0.0-41.4)
56	Ovary	1	39.7 (1.0-221.2)[d]	3	14.8 (4.8-45.9)[e]	0	0.0 (0.0-17.4)	1	0.9 (0.0-4.9)
61	Prostate	0	0.0 (0.0-1622.2)	0	0.0 (0.0-850.4)	1	57.3 (1.5-319.1)[d]	0	0.0 (0.0-219.8)
62	Testis	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	138.1 (34.5-552.0)[f]	3	44.1 (14.2-136.8)[f]	0	0.0 (0.0-28.4)	0	0.0 (0.0-10.0)
67-68	Bladder	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)[e]
70-72	CNS	153	373.4 (318.6-437.5)[f]	23	34.7 (23.1-52.2)[f]	3	1.0 (0.3-3.1)	6	1.6 (0.7-3.5)
73	Thyroid	1	496.6 (12.6-2767.0)[e]	10	32.2 (17.3-59.8)[f]	0	0.0 (0.0-226.3)	2	1.2 (0.3-4.7)
81	Hodgkin lymphoma	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-Hodgkin lymphoma	4	26.8 (10.1-71.4)[f]	1	2.6 (0.1-14.4)	0	0.0 (0.0-3.6)	2	1.1 (0.3-4.3)
91-95	Leukaemia	23	45.5 (30.2-68.5)[f]	4	7.7 (2.9-20.4)[e]	4	1.1 (0.4-2.9)	3	1.1 (0.4-3.5)
00-43, 45, 47-85, 89-97	All sites except non-melanoma skin cancer	230	101.9 (89.6-116.0)[f]	72	7.6 (6.1-9.6)[f]	21	1.3 (0.9-2.0)	66	1.2 (1.0-1.6)

ICD = International Classification of Diseases; SMR = Standardised mortality ratio; SIR = Standardised incidence ratio; CI = Confidence interval

[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.

[d]p<0.05

[e]p<0.01

[f]p<0.001

ICD = International Classification of Diseases; SMR = Standardised mortality ratio; SIR = Standardised incidence ratio; CI = Confidence interval

[d]p<0.05

[e]p<0.01

[f]p<0.001

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Table 3

Cancer mortality and incidence risks, SAGhE cohort, for patients in whom a non-cancer diagnosis led to GH treatment

Outcome (cancer site)	Initial diagnosis isolated growth failure				Initial diagnosis non-cancer, non-isolated growth failure			
	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)[a]
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)[b]
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)
Hodgkin lymphoma	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)
NHL	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)
Leukaemia	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 non-melanoma skin cancer	8	0.8 (0.4-1.6)	23	1.0 (0.6-1.4)	13	2.2 (1.3-3.7)[a]	42	1.4 (1.1-1.9)[a]

SMR = Standardised mortality ratio; SIR = Standardised incidence ratio; CI = Confidence interval

[a] $p<0.05$

[b] $p<0.01$

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			
		Cancer mortality		Cancer incidence[c]	
		n	SMR[b] (95% CI)	n	SMR (95% CI)
Sex	Male	138	12.4 (10.5-14.6)[g]	52	2.2 (1.7-2.9)[g]
	Female	113	15.8 (13.1-19.0)[g]	86	2.2 (1.8-2.7)[g]
Country	Belgium	23	22.1 (14.7-33.3)[g]	7	1.9 (0.9-4.0)
	France	88	9.9 (8.1-12.2)[g]	-	
	Germany	10	11.5 (6.2-21.4)[g]	-	
	Italy	1	1.7 (0.0-9.4)	-	
	Netherlands	27	23.6 (16.2-34.5)[g]	22	2.5 (1.6-3.8)[g]
	Sweden	30	12.9 (9.0-18.5)[g]	50	1.5 (1.2-2.0)[f]
	Switzerland	6	19.7 (8.8-43.7)[g]	2	2.5 (0.6-10.1)
	UK	66	20.7 (16.3-26.4)[g]	57	3.4 (2.6-4.4)[g]
Age started treatment (years)	0-4	9	7.1 (3.7-13.6)[g]	7	1.7 (0.8-3.5)
	5-9	70	13.9 (11.0-17.6)[g]	46	2.5 (1.8-3.3)[g]
	10-14	149	15.4 (13.1-18.0)[g]	71	2.1 (1.7-2.6)[g]
	15-19	23	10.0 (6.6-15.0)[g]	14	2.3 (1.4-3.9)[f]
	p trend		0.55		1.00
Time since started treatment (years)	0-4	103	24.4 (20.1-29.6)[g]	25	3.5 (2.4-5.2)[g]
	5-9	78	17.2 (13.8-21.5)[g]	21	1.8 (1.2-2.8)[e]
	10-14	37	8.2 (6.0-11.4)[g]	47	2.3 (1.8-3.1)[g]
	15-19	25	6.7 (4.5-9.8)[g]	30	1.6 (1.1-2.3)[e]
	≥20	8	6.1 (3.1-12.3)[g]	15	2.7 (1.7-4.6)[f]
	p trend		<0.001		0.13
Duration of treatment (years)[d]	<3	118	21.1 (17.6-25.3)[g]	40	2.8 (2.1-3.9)[g]
	3-6	80	12.4 (10.0-15.5)[g]	52	2.7 (2.1-3.5)[g]
	≥7	35	7.5 (5.4-10.4)[g]	33	1.9 (1.3-2.6)[f]
	p trend		<0.001		0.07
Mean GH dose (μg/kg/day)[d]	<20	37	9.6 (7.0-13.3)[g]	18	4.0 (2.6-6.4)[g]
	20-9	94	19.5 (15.9-23.8)[g]	40	3.3 (2.4-4.4)[g]
	30-9	52	16.8 (12.8-22.0)[g]	41	2.1 (1.6-2.9)[g]
	≥40	7	3.8 (1.8-8.0)[f]	11	1.1 (0.6-2.0)
	p trend		0.39		<0.001

Demographic or treatment variable		All initial diagnoses, total			
		Cancer mortality		Cancer incidence[c]	
		n	SMR[b] (95% CI)	n	SMR (95% CI)
Cumulative GH dose (mg/kg)[d]	<25	91	14.9 (12.1-18.3)[g]	38	3.4 (2.5-4.7)[g]
	25-49	73	16.9 (13.4-21.2)[g]	30	2.1 (1.5-3.0)[g]
	50-99	36	11.1 (8.0-15.3)[g]	40	2.3 (1.7-3.2)[g]
	≥100	3	2.7 (0.9-8.3)	11	1.6 (0.9-2.9)
	p trend		0.003		0.02
Total		251	13.7 (12.1-15.5)[g]	138	2.2 (1.9-2.6)[g]

			Initial diagnosis cancer				Initial diagnosis non-cancer		
			Cancer mortality		Cancer incidence[c]		Cancer mortality		Cancer incidence[c]
		n	SMR[b] (95% CI)	n	SIR (95% CI)	n	SMR[b] (95% CI)	n	SIR (95%CI)
Sex	Male	131	90.2 (76.0-107.0)[g]	30	7.2 (5.0-10.3)[g]	7	0.7 (0.3-1.5)	22	1.1 (0.7-1.7)
	Female	99	123.1 (101.1-149.9)[g]	42	8.0 (5.9-10.8)[g]	14	2.2 (1.3-3.7)[e]	44	1.3 (1.0-1.7)
Country	Belgium	20	113.9 (73.5-176.6)[g]	3	5.0 (1.6-15.4)[e]	3	3.5 (1.1-10.8)[e]	4	1.3 (0.5-3.5)
	France	79	96.6 (77.5-120.5)[g]	-		9	1.1 (0.6-2.2)	-	
	Germany	9	114.9 (59.8-220.9)[g]	-		1	1.3 (0.0-7.0)	-	
	Italy	0	0.0 (0.0-252.6)	-		1	1.7 (0.0-9.6)		-
	Netherlands	26	138.2 (94.1-203.0)[g]	14	9.9 (5.8-16.7)[g]	1	1.0 (0.0-5.8)	8	1.1 (0.5-2.2)
	Sweden	27	120.6 (82.7-175.9)[g]	21	5.6 (3.6-8.6)[g]	3	1.4 (0.5-4.4)	29	1.0 (0.7-1.4)
	Switzerland	5	168.4 (70.1-404.5)[g]	2	31.0 (7.7-123.9)[f]	1	3.6 (0.1-20.2)	0	0.0 (0.0-5.1)
	UK	64	87.8 (68.7-112.1)[g]	32	8.9 (6.3-12.6)[g]	2	0.8 (0.2-3.3)	25	1.9 (1.3-2.8)[f]
Age started treatment (years)	0-4	8	127.4 (63.7-254.7)[g]	4	16.1 (6.1-43.0)[g]	1	0.8 (0.0-4.6)	3	0.8 (0.2-2.4)
	5-9	65	100.1 (78.5-127.7)[g]	18	7.1 (4.5-11.3)[g]	5	1.1 (0.5-2.7)	28	1.7 (1.2-2.5)[f]
	10-14	137	108.7 (91.9-128.5)[g]	42	7.3 (5.4-9.9)[g]	12	1.4 (0.8-2.5)	29	1.0 (0.7-1.5)
	15-19	20	70.3 (45.4-109.0)[g]	8	8.6 (4.3-17.2)[g]	3	1.5 (0.5-4.6)	6	1.2 (0.5-2.6)
	p trend		0.30		0.71		0.53		0.44
Time since started treatment (years)	0-4	100	184.8 (151.9-224.8)[g]	20	16.0 (10.3-24.9)[g]	3	0.8 (0.3-2.5)	5	0.9 (0.4-2.1)
	5-9	71	124.4 (98.6-157.0)[g]	12	5.9 (3.4-10.5)[g]	7	1.8 (0.8-3.7)	9	0.9 (0.5-1.8)
	10-14	33	60.7 (43.2-85.4)[g]	24	8.2 (5.5-12.2)[g]	4	1.0 (0.4-2.7)	23	1.3 (0.9-2.0)
	15-19	19	45.9 (29.3-71.9)[g]	11	4.5 (2.5-8.2)[g]	6	1.8 (0.8-4.0)	19	1.2 (0.7-1.8)
	≥20	7	37.4 (17.8-78.4)[g]	5	6.1 (2.5-14.7)[f]	1	0.9 (0.0-5.0)	10	2.2 (1.2-4.0)[e]
	p trend		<0.001		0.005		0.65		0.11
Duration of treatment (years)	<3	110	174.9 (145.1-210.8)[g]	25	10.4 (7.1-15.5)[g]	8	1.6 (0.8-3.2)	15	1.3 (0.8-2.1)
	3-5	74	87.0 (69.3-109.3)[g]	29	8.6 (6.0-12.4)[g]	6	1.1 (0.5-2.4)	23	1.4 (1.0-2.2)[e]

			Initial diagnosis cancer				Initial diagnosis non-cancer		
			Cancer mortality		Cancer incidence *c*		Cancer mortality		Cancer incidence *c*
		n	SMR[b] (95% CI)	n	SIR (95% CI)	n	SMR[b] (95% CI)	n	SIR (95%CI)
	≥6	31	50.2 (35.3-71.4)[g]	12	4.0 (2.2-7.0)[g]	4	1.0 (0.4-2.6)	21	1.4 (0.9-2.2)
	p trend		<0.001		0.006		0.76		0.77
Mean GH dose (μg/kg/day)	<20	35	64.1 (46.0-89.3)[g]	12	6.5 (3.7-11.4)[g]	2	0.6 (0.2-2.4)	6	2.3 (1.0-5.2)
	20-9	89	102.1 (82.9-125.6)[g]	26	7.6 (5.2-11.2)[g]	5	1.3 (0.5-3.0)	14	1.6 (0.9-2.7)
	30-9	50	178.9 (135.6-236.1)[g]	19	10.2 (6.5-16.0)[g]	2	0.7 (0.2-2.8)	22	1.3 (0.8-1.9)
	≥40	5	101.5 (42.3-243.9)[g]	3	5.0 (1.6-15.5)[e]	2	1.1 (0.3-4.5)	8	0.9 (0.4-1.7)
	p trend		<0.001		0.59		0.74		0.05
Cumulative GH dose (mg/kg)	<25	87	108.8 (88.2-134.2)[g]	25	9.9 (6.7-14.6)[g]	4	0.8 (0.3-2.0)	13	1.5 (0.9-2.6)
	25-49	70	108.1 (85.5-136.7)[g]	18	6.6 (4.1-10.4)[g]	3	0.8 (0.3-2.5)	12	1.0 (0.6-1.8)
	50-99	30	79.5 (55.6-113.6)[g]	18	6.8 (4.3-10.9)[g]	6	2.1 (0.9-4.6)	22	1.5 (1.0-2.3)
	≥100	2	34.2 (8.6-136.9)[f]	5	9.6 (4.0-23.1)[g]	1	0.9 (0.0-5.3)	6	1.0 (0.4-2.1)
	p trend		0.05		0.43		0.24		0.63
Total		230	101.9 (89.6-116.0)[g]	72	7.6 (6.1-9.6)[g]	21	1.3 (0.9-2.0)	66	1.2 (1.0-1.6)

SMR = Standardised mortality ratio; SIR = Standardised incidence ratio; CI = Confidence interval

[a] All malignancies except non-melanoma 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.

[e] p<0.05

[f] p<0.01

[g] p<0.001

SMR = Standardised mortality ratio; SIR = Standardised incidence ratio; CI = Confidence interval

[a] All malignancies except non-melanoma 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.

[d] Excluding France, Germany and Italy.

[e] p<0.05

[f] p<0.01

[g] p<0.001

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Table 5

Cancer mortality and incidence risks at selected cancer sites, SAGhE cohort, by duration since first treatment and initial diagnosis leading to GH treatment

		All initial diagnoses, total			
		Cancer mortality		Cancer incidence[b]	
Cancer site (outcome)	Duration since first treatment (years)	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)[c]
	10-19	1	2.7 (0.1-15.1)	2	2.0 (0.5-7.9)
	20-29	0	0.0 (0.0-45.2)	0	0.0 (0.0-16.4)
	p trend		0.25		0.25
Bone cancer	0-9	9	8.5 (4.4-16.3)[e]	5	4.6 (1.9-11.0)[c]
	10-19	3	4.6 (1.5-14.2)[c]	4	6.8 (2.6-18.1)[d]
	20-29	0	0.0 (0.0-114.7)	0	0.0 (0.0-86.2)
	p trend		0.30		0.76
Melanoma	0-9	0	0.0 (0.0-25.2)	2	1.6 (0.4, 6.2)
	10-19	1	2.1 (0.1-11.9)	7	1.9 (0.9, 4.0)
	20-29	0	0.0 (0.0-45.4)	3	4.5 (1.4, 13.8)[c]
	p trend		0.86		0.25
CNS	0-9	120	62.9 (52.6-75.2)[e]	15	6.2 (3.8-10.3)[e]
	10-19	32	24.2 (17.1-34.3)[e]	13	7.2 (4.2-12.4)[e]
	20-29	4	22.9 (8.6-61.0)[e]	1	4.7 (0.1-26.2)
	p trend		<0.001		0.90
Thyroid	0-9	0	0.0 (0.0-1284.3)	6	10.9 (4.9-24.2)[e]
	10-19	1	78.1 (2.0-435.4)[c]	5	4.1 (1.7-9.8)[c]
	20-29	0	0.0 (0.0-1393.9)	1	4.4 (0.1-24.6)
	p trend		0.98		0.14
Hodgkin lymphoma	0-9	0	0.0 (0.0-17.0)	0	0.0 (0.0-1.8)
	10-19	0	0.0 (0.0-11.3)	6	2.7 (1.2-6.0)[c]
	20-29	0	0.0 (0.0-119.2)	2	9.6 (2.4-38.2)[c]

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		All initial diagnoses, total			
		Cancer mortality		Cancer incidence[b]	
Cancer site (outcome)	Duration since first treatment (years)	n	SMR[a] (95% CI)	n	SIR (95% CI)
	p trend		-		0.001
Leukaemia	0-9	20	7.7 (5.0-11.9)e	4	2.0 (0.8-5.4)
	10-19	7	4.7 (2.3-9.9)[d]	3	2.7 (0.9-8.4)
	20-29	0	0.0 (0.0-32.6)	0	0.0 (0.0-30.5)
	p trend		0.16		0.98

		Initial diagnosis cancer				Initial diagnosis non-cancer			
		Cancer mortality		Cancer incidence[b]		Cancer mortality		Cancer incidence[b]	
Cancer site (outcome)	Duration since first treatment (years)	n	SMR[a] (95% CI)	n	SIR (95% CI)	n	SMR[a] (95% CI)	n	SIR (95% CI)
Colorectal cancer	0-9	1	74.4 (1.9-414.4)[c]	2	24.4 (6.1-97.6)[d]	0	0.0 (0.0-43.5)	0	0.0 (0.0-9.4)
	10-19	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 (0.0-319.9)	0	0.0 (0.0-96.7)	0	0.0 (0.0-52.6)	0	0.0 (0.0-19.7)
	p trend		0.11		0.06		0.97		0.75
Bone cancer	0-9	7	47.8 (22.8-100.3)[e]	3	14.8 (4.8-45.9)[d]	2	2.2 (0.5-8.7)	2	2.3 (0.6-9.0)
	10-19	1	13.3 (0.3-74.2)	2	24.7 (6.2-98.8)[d]	2	3.5 (0.9-13.8)	2	3.9 (1.0-15.8)
	20-29	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		0.19		0.82		0.76		0.74
Melanoma	0-9	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	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 (0.0-299.2)	2	18.9 (4.7-75.6)[c]	0	0.0 (0.0-53.5)	1	1.8 (0.0-9.8)
	p trend		-		0.22		0.86		0.64
CNS	0-9	118	503.2 (420.1-602.7)[e]	11	29.3 (16.2-52.9)[e]	2	1.2 (0.3-4.8)	4	2.0 (0.7-5.2)
	10-19	31	207.3 (145.8-294.8)[e]	11	43.4 (24.0-78.3)[e]	1	0.9 (0.0-4.8)	2	1.3 (0.3-5.1)
	20-29	4	155.1 (58.2-413.3)[e]	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		0.43		0.64		0.47
Thyroid	0-9	0	0.0 (0.0-10035.5)	5	51.3 (21.4-123.3)[e]	0	0.0 (0.0-1472.7)	1	2.2 (0.1-12.3)
	10-19	1	772.6 (19.6-4304.7)[d]	4	22.5 (8.4-59.9)[e]	0	0.0 (0.0-320.7)	1	1.0 (0.0-5.3)

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		Initial diagnosis cancer				Initial diagnosis non-cancer			
		Cancer mortality		Cancer incidence[b]		Cancer mortality		Cancer incidence[b]	
Cancer site (outcome)	**Duration since first treatment (years)**	**n**	**SMR[a] (95% CI)**	**n**	**SIR (95% CI)**	**n**	**SMR[a] (95% CI)**	**n**	**SIR (95% CI)**
	20-29	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		0.99		0.29		-		0.41
Hodgkin lymphoma	0-9	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 (0.0-95.4)	1	2.9 (0.4-20.7)	0	0.0 (0.0-12.8)	5	2.6 (1.1-6.3)[c]
	20-29	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)[c]
	p trend		-		0.40		-		0.002
Leukaemia	0-9	18	55.7 (35.1-88.4)[e]	3	8.8 (2.9-27.4)[c]	2	0.9 (0.2-3.5)	1	0.6 (0.0-3.4)
	10-19	5	29.9 (12.5-71.9)[e]	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 (0.0-239.3)	0	0.0 (0.0-186.3)	0	0.0 (0.0-37.7)	0	0.0 (0.0-36.5)
	p trend		0.10		0.63		0.74		0.47

SMR = Standardised mortality ratio; SIR = Standardised incidence ratio; CI = Confidence interval

[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.

[c]p<0.05

[d]p<0.01

[e]p<0.001

SMR = Standardised mortality ratio; SIR = Standardised incidence ratio; CI = Confidence interval

[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

[c]p<0.05

[d]p<0.01

[e]p<0.001