0021-972X/98/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 83, No. 8
Printed in U.S.A.

Mortality and Cancer Incidence in Acromegaly: A Retrospective Cohort Study*

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ABSTRACT

Patients with acromegaly have a reduced life expectancy, with the accepted causes for premature death being vascular and respiratory disease. Increased mortality from malignant disease has also been reported. We, therefore, performed a multicenter retrospective cohort study of 1362 patients with acromegaly and investigated the relationships of mortality and cancer incidence with GH levels, duration of disease, and age at diagnosis.

The overall cancer incidence rate [standardized incidence ratio, 0.76; 95% confidence interval (CI), 0.60–0.95] was lower than that in the general population of the United Kingdom, and there was no significant increase in site-specific cancer incidence rates. The overall cancer mortality rate was not increased, but the colon cancer mortality rate (standardized mortality ratio, 2.47; 95% CI, 1.31–4.22) was higher than expected. Mortality rates due to colon cancer, all malignant disease, cardiovascular disease and overall mortality were increased with higher posttreatment GH levels (P for trends, <0.02, <0.05, <0.02, and <0.0001). The overall mortality rate in patients with acromegaly with posttreatment GH levels less than 2.5 ng/mL (5 mU/L) was comparable to that in the general population of the United Kingdom (standardized mortality ratio, 1.10; 95% CI, 0.89–1.35).

We conclude that high posttreatment GH levels are associated with an increased overall mortality rate and increased mortality rates due to colon cancer, cardiovascular disease, and all malignant disease. Posttreatment GH levels less than 2.5 ng/mL (5 mU/L) result in an overall mortality rate similar to that in the general population. (*J Clin Endocrinol Metab* **83:** 2730–2734, 1998)

ACROMEGALY is a chronic condition resulting from the excessive secretion of GH, generally from a pituitary adenoma (1). An increased incidence of neoplasms has been reported in females due to an excess incidence of breast cancers (1). Studies have shown an excess occurrence of gastrointestinal malignancy, particularly colonic neoplasm (2–4), which has been linked to an increased incidence of colonic adenomatous polyps (5–10).

A number of series have demonstrated an increased mortality rate in patients with acromegaly; the main cause of these excess deaths is vascular and respiratory disease (11–13). An increased mortality from malignant disease in acromegaly has been reported in elderly females (11), all females (13), and males (12). A recent small study has reported an excess overall mortality occurring only in patients whose GH level persists above 2.5 ng/mL (5 mU/L) after treatment (14). Other studies have reported a lower mortality in treated compared with untreated subjects (11, 12).

Previous studies have lacked the statistical power, due to small sample size, to determine reliably whether there is an excess cancer incidence or mortality in acromegaly. They have used different methods of ascertainment for morbidity and mortality data in cases and comparison groups (11–13) (hospital records and postmortem *vs.* general population data). Except for two small studies (14, 15), they have not had access to GH levels for the patients studied. To establish whether there is an excess cancer incidence and higher mortality in patients with acromegaly (and, if so, to determine if these are related to duration of disease, age at diagnosis, or degree of GH hypersecretion), we performed a large retrospective multicenter epidemiological cohort study that was larger in terms of cases and years of exposure than previous studies.

Subjects and Methods

Subjects

After ethical committee approval, we approached 15 tertiary referral centers, and a single observer (S.M.O.) was given access to the case notes of patients with acromegaly. Demographic and clinical data were collected on all available subjects, current and deceased, from each center with acromegaly diagnosed by standard biochemical criteria (16). Before the advent of the GH assay, radiological, clinical, and pathological

Received January 5, 1998. Revision received April 7, 1998. Accepted April 24, 1998.

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* This work was supported by Grant ST 31 from the Special Trustees of The General Infirmary at Leeds.

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evidence consistent with a diagnosis of acromegaly was accepted. Subjects with multiple endocrine neoplasia type 1, McCune-Albright syndrome, and ectopic GHRH syndrome were excluded.

Demographic information was used to trace subjects through the National Health Service Central Register at the Office for National Statistics (ONS) for England and Wales, the Scottish Central Register, and the Northern Ireland Central Services Agency and Registrar of Births and Deaths. The ONS supplied copies of death certificates, cancer registrations, or evidence of exit from the Register (*i.e.* emigration or entry into the armed services).

The ONS was able to identify 1362 subjects who represented 95% of the original number and thus formed the cohort that was analyzed for causes of death. Serial pretreatment GH levels were available in 78% of subjects, and posttreatment GH levels were available in 90% of subjects (fasting, mean of a day curve, or random level). For the purposes of analysis, we used pretreatment (at diagnosis) and last known (posttreatment) GH level. Depending on the assays used, the conversion factor between GH measured in milliunits per L and nanograms per mL ranges from about 2–2.5 (17) (Ellis, A., EQAS scheme, Edinburgh, U.K., personal communication), and we have chosen to adopt the commonly used convention of 1 ng/mL = 2 mU/L.

Methods

Causes of death and cancer registrations were coded using the International Classification of Diseases ICD-9, ninth edition, 1978 (18), and the ICD-0, second edition, 1990 (19), respectively. For each cohort member, person-years at risk were calculated by age, sex, and calendar year, commencing on the date of diagnosis of acromegaly and finishing on the date of cancer registration or death (for cancer incidence and mortality analysis, respectively), exit from the ONS Registry, 85th birthday, or end of December 1995 when the dataset was frozen. As there was no reliable cancer registry for Northern Ireland, all subjects from there were excluded from the cancer incidence analysis. Person-years of exposure to acromegaly before 1958 in England and Wales and before 1962 in Scotland were not used to calculate expected cancer incidence because cancer registries did not exist before these dates. Population disease and death rates for England and Wales were applied to the whole United Kingdom.

Statistical analysis

Cause-specific death rates (20) (Office of Population, Censuses, and Surveys Mortality Statistics Series DH2) and cancer incidence rates (21) (Cancer Statistics Series MB1) for England and Wales were obtained by age, sex, and time period from 0–85 yr for the duration of the study. Expected deaths or cancer incidences by cause in the cohort were calculated by multiplying age-, sex-, and period-specific person-years at risk within the cohort by corresponding national cause-specific mortality rates or site-specific cancer rates using the computer program PYRS (22). Standardized mortality ratios (SMRs) and standardized incidence ratios (SIRs) were calculated, and significantly excess mortality or cancer incidence was determined by calculating a one-sided Poisson probability. Ninety-five percent confidence intervals (CIs) for the SIRs and SMRs were calculated using Byar's approximation (23). We investigated linear trends in risk (pre- and posttreatment GH level, age at diagnosis, and duration of disease) using a χ^2 test for linear trends (23). Significance was assumed when $P < 0.05$. A one-sided Poisson probability was calculated as we were testing a number of prior hypotheses relating to increased cancer incidence and mortality in acromegaly (see Introduction). Mortality or cancer incidence rates significantly lower than the general population of the United Kingdom have a $P > 0.95$; this can also be noted from the two-sided confidence intervals.

Results

Cancer incidence

We observed 79 cancer incidence registrations in our analysis cohort of 1,239 subjects with acromegaly (16,778 person-years). Sixteen subject registrations occurred before the date of diagnosis of acromegaly and were therefore excluded from analysis. There was a nonsignificant increase in colon cancer incidence (SIR, 1.68; $P = 0.06$), whereas the rectal cancer incidence (SIR, 0.86; 95% CI, 0.23–2.20) and female breast cancer incidence (SIR, 0.93; 95% CI, 0.51–1.56) were similar to those in the general population of the United Kingdom. Cancer incidence rates due to all malignancies (SIR, 0.76; 95% CI, 0.60–0.95) and bronchial cancer incidence (SIR, 0.33; 95% CI, 0.12–0.72) were reduced (Table 1). There were no relationships among cancer incidence and pre- or posttreatment GH levels, age at diagnosis, or duration of disease (not shown).

Cancer mortality

The colon cancer mortality rate was higher than expected (SMR, 2.47; 95% CI, 1.31–4.22), and there was a nonsignificant increase in female breast cancer mortality (SMR, 1.60; $P = 0.07$; Table 2). Mortality rates due to all malignant disease (SMR, 1.16; 95% CI, 0.92–1.44), carcinoma of the bronchus (SMR, 0.69; 95% CI, 0.37–1.18), and carcinoma of the rectum (SMR, 1.09; 95% CI, 0.22–3.19) were similar to those in the general population of the United Kingdom (Table 2). Mortality rates due to all malignant disease and colon cancer were increased with higher posttreatment GH levels (P for trends, <0.05 and <0.02; Tables 4 and 5).

There was no relationship between pretreatment GH levels and any measure of mortality (not shown). Mortality due to malignant disease was not related to duration of disease (Table 6) or age at diagnosis (Table 7).

Mortality

Three hundred and sixty-six deaths occurred in the 1,362 subjects of our analysis cohort, representing 19,323 person-years of exposure to acromegaly. We found an increase in all cause mortality rate (SMR, 1.6; 95% CI, 1.44–1.77) and in cardiovascular (SMR, 1.76; 95% CI, 1.47–2.07), cerebrovascular (SMR, 2.06; 95% CI, 1.50–2.76), and respiratory (SMR, 1.85; 95% CI, 1.34–2.49) mortality rates (Table 3). All cause mortality rate and cardiovascular mortality rate were in-

TABLE 1. Summary of cancer incidence data

Cancer site	Observed	Expected	SIR	95% confidence interval	1-Sided Poisson Probability (P)
Female breast	14	15.09	0.93	0.51–1.56	0.65
Bronchus	6	18.33	0.33	0.12–0.72	1.00
Colon	12	7.14	1.68	0.87–2.93	0.06
Rectum	4	4.68	0.86	0.23–2.20	0.69
Thyroid	1	0.39	2.54	0.07–14.15	0.33
All malignant disease	79	104.12	0.76	0.60–0.95	1.00

Male and female data were pooled unless specified.

TABLE 2. Summary of cancer mortality data

Cancer site	Observed	Expected	SMR	95% confidence interval	1-Sided Poisson probability (*P*)
Female breast	13	8.14	1.60	0.85–2.74	0.07
Bonchus	13	18.91	0.69	0.37–1.18	0.94
Colon	13	5.26	2.47	1.31–4.22	0.003
Rectum	3	2.75	1.09	0.22–3.19	0.52
All malignant disease	83	71.72	1.16	0.92–1.44	0.10

Male and female data were pooled unless specified.

TABLE 3. Summary of mortality data

Cause of death	Observed	Expected	SMR	95% Confidence interval	1-Sided Poisson probability (*P*)
Cardiovascular disease	134	76.24	1.76	1.47–2.07	<0.001
Cerebrovascular disease	44	21.31	2.06	1.50–2.76	<0.001
Respiratory disease	43	23.25	1.85	1.34–2.49	<0.001
Malignant disease	83	71.72	1.16	0.92–1.44	0.1
Overall (all causes of mortality)	366	228.81	1.60	1.44–1.77	<0.001

Male and female data were pooled.

TABLE 4. Relationship between posttreatment GH level and mortality from specific cancers

Cancer site	SMR (95% CI), Posttreatment GH level:			χ^2 test for linear trend (*P*)
	<2.5 ng/mL (5.0 mU/L)	2.5–9.9 ng/mL (5.0–19.9 mU/L)	≥10.0 ng/mL (20 mU/L)	
Female breast cancer mortality	1.95 (0.72–4.25)	0.57 (0.07–2.06)	2.93 (0.60–8.56)	0.99
Bronchial cancer mortality	0.28 (0.03–1.01)	0.63 (0.17–1.61)	1.12 (0.31–2.87)	0.09
Colon cancer mortality	0.51 (0.01–2.84)	3.08 (1.13–6.71)	4.59 (1.25–11.75)	0.02

Male and female data were pooled unless specified.

TABLE 5. Relationship between posttreatment GH level and mortality in acromegaly

Cause of death	SMR (95% CI), Posttreatment GH level:			χ^2 test for linear trend (*P*)
	<2.5 ng/mL (5 mU/L)	2.5–9.9 ng/mL (5.0–19.9 mU/L)	≥10.0 ng/mL (20 mU/L)	
Cardiovascular disease	1.20 (0.83–1.68)	1.59 (1.15–2.15)	2.11 (1.42–3.01)	0.02
Cerebrovascular disease	1.81 (0.96–3.10)	1.66 (0.88–2.84)	2.82 (1.41–5.04)	0.33
Respiratory disease	1.15 (0.53–2.18)	2.32 (1.40–3.62)	1.54 (0.62–3.17)	0.42
Malignant disease	0.96 (0.63–1.41)	0.81 (0.50–1.24)	1.81 (1.13–2.74)	0.05
Overall (all causes of mortality)	1.10 (0.89–1.35)	1.41 (1.16–1.68)	2.12 (1.70–2.62)	<0.0001

Male and female data were pooled.

TABLE 6. Relationship between duration of acromegaly and mortality

Cause of death	(95% CI), duration of acromegaly:			χ^2 test for linear trend (*P*)
	<5 yr	5–10 yr	10+ yr	
Cardiovascular disease	1.76 (1.20–2.50)	1.54 (1.03–2.21)	1.86 (1.46–2.33)	0.67
Cerebrovascular disease	1.30 (0.48–2.83)	1.19 (0.44–2.59)	2.74 (1.87–3.87)	0.03
Respiratory disease	1.03 (0.33–2.40)	2.21 (1.14–3.86)	2.00 (1.31–2.93)	0.26
Malignant disease	1.04 (0.62–1.64)	1.10 (0.67–1.70)	1.24 (0.90–1.66)	0.49
Overall (all causes of mortality)	1.41 (1.11–1.77)	1.43 (1.14–1.78)	1.76 (1.53–2.01)	0.058

Male and female data were pooled.

creased with higher posttreatment GH levels (*P* for trends, <0.0001 and <0.02; Table 4).

There was a nonsignificant increase in all cause mortality rates with longer duration of disease (*P* for trend, <0.058), with a rise in cerebrovascular disease (*P* for trend, <0.003) being the main cause of this increase (Table 6).

The overall mortality rate was higher in subjects in whom acromegaly was diagnosed at a younger age (*P* for trend, 0.004), with deaths from cerebrovascular disease being the main cause of this increase (*P* for trend, <0.001; Table 7).

Discussion

This is the largest retrospective cohort study of mortality and cancer incidence in acromegaly, with 1,362 subjects and 19,323 years of patient follow-up. Despite the inevitable deficiencies of this type of study, which relies on historical data obtained from case records with GH levels measured at different time intervals by different assays, certain valid observations can be made. As the mortality and cancer incidence data from the population of interest and the general

TABLE 7. Relationship between age at diagnosis and mortality in acromegalics studied

Cause of death	SMR (95% CI), age at diagnosis:			χ^2 test for linear trend (P)
	0–34 yr	35–59 yr	60–84 yr	
Cardiovascular disease	3.81 (2.22–6.10)	1.50 (1.18–1.89)	1.91 (1.39–2.56)	0.38
Cerebrovascular disease	7.36 (3.18–14.51)	2.15 (1.42–3.13)	1.18 (0.54–2.24)	<0.001
Respiratory disease	3.47 (0.95–8.89)	1.97 (1.30–2.87)	1.43 (0.74–2.50)	0.14
Malignant disease	0.92 (0.30–2.15)	1.23 (0.94–1.59)	1.05 (0.63–1.64)	0.88
Overall (all causes of mortality)	2.78 (2.03–3.72)	1.55 (1.35–1.76)	1.43 (1.16–1.75)	0.004

Male and female data were pooled.

population were obtained from the same source, this negates the bias that was present in earlier studies (1, 11–13).

Rajasoorya *et al.* (15) has shown that the predominant determinant of outcome (morbidity and mortality) in acromegaly is the final serum GH level after treatment. A multivariate analysis of that cohort showed that survival was significantly influenced by the last known GH level ($P = 0.0001$), but not by the GH level at diagnosis ($P = 0.1$). These findings are confirmed by the present study. We stratified posttreatment GH levels into three broad categories using evidence from previous published work. Bates *et al.* (14) reported that mortality in patients with acromegaly whose mean posttreatment GH level was below 2.5 ng/mL (5 mU/L) was the same as that in the general population (SMR, 1.42; 95% CI, 0.46–3.31). This notional safe level for posttreatment GH is supported by an earlier study that showed normalization of total body water and total exchangeable sodium in acromegalic patients with posttreatment GH levels below 2.5 ng/mL (5 mU/L) (24). The higher cut-off level of 10 ng/mL (20 mU/L) was derived from early surgical series that considered this level to represent the normalization of GH secretion (25, 26). We felt that using a fasting GH, random GH, or mean of a day curve was appropriate, as these are highly predictive of biochemically active acromegaly, as shown by elevated insulin-like growth factor I levels (27). The vast majority of GH levels used were fasting 0900 h GH levels, which closely correlate to mean 24-h GH levels and insulin-like growth factor I levels in acromegaly (15, 28).

This study gives some support to previous series (2–4) that have shown an increased incidence of colonic carcinomas. We found no excess incidence of rectal carcinoma, which is in line with the largest previously reported study (8619 person-years of follow-up) (3). The neoplasms arose uniformly throughout the large bowel, with five cancer registrations in the right or proximal colon, five in the left or distal colon, and two from unspecified sites. We did not confirm the overall increase in incidence of neoplasms or female carcinomas of the breast reported by Nabarro (1). In fact, we found a lower than expected overall cancer incidence and a particularly low incidence of carcinoma of the bronchus. Environmental factors such as smoking habits and exposure to pollution and ionizing radiation, which are major etiological factors in the development of lung cancer (29, 30), may have been different in the acromegalic cohort and the general population. The majority of nonmalignant respiratory deaths were due to bronchopneumonia or pneumonia (thirty-one), which may have been smoking related. Deaths directly attributable to smoking, *i.e.* chronic bronchitis, emphysema, and chronic airways obstruction (eleven), represented a minority. These data do not give further insight into smoking rates or the etiology of the reduced incidence of carcinoma of the bronchus observed in this cohort.

There was no increase in mortality rate from malignant disease in general, but there was a significant increase in the colon cancer mortality rate and a nonsignificant increase in mortality due to breast cancer. Nabarro (1) reported no excess cancer mortality or breast cancer mortality, but found a marked excess breast cancer incidence (SIR, 4.23; $P < 0.0001$). We found the opposite pattern of malignancies in our cohort, with a low or normal cancer incidence rate and a normal or raised cancer mortality rate. Mortality due to all malignant disease and colon cancer were increased with higher posttreatment GH levels, but not duration of disease. These data suggest that GH hypersecretion modifies the progression of existing malignancies, particularly colonic carcinoma. This may explain the discrepancy between the cancer incidence and cancer mortality rates observed, which could be of importance outside the management of acromegaly.

Mortality rates due to cardiovascular, cerebrovascular, and respiratory disease were increased, which is broadly in line with previous series (11–13). Overall and cardiovascular mortality rates were increased with high posttreatment GH levels. Mortality due to cerebrovascular and respiratory disease was not related to posttreatment GH levels. We confirmed the work of Bates *et al.* (14) and showed that the overall mortality rate in those acromegalic patients with posttreatment GH levels below 2.5 ng/mL (5 mU/L) is comparable to that in the general population of the United Kingdom (SMR, 1.10; 95% CI, 0.89–1.35). The present study lends substantial support to efforts to reduce GH secretion to below 2.5 ng/mL (5 mU/L). The achievement of this postoperatively is less with large tumors and high GH levels (31). Radiotherapy requires up to 10 yr to achieve maximum reduction in GH secretion (32). Of the medical modalities available, somatostatin analogs (33) more frequently achieve this target than dopamine agonists (34).

Mortality in acromegaly and particularly mortality due to cerebrovascular disease rise with decreasing age at diagnosis. This supports the long held clinical impression that acromegaly occurring in the elderly has a more indolent course, whereas an early presentation is associated with more aggressive disease. The high cerebrovascular mortality occurring in acromegalic patients diagnosed under 35 yr of age (SMR, 7.36; 95% CI, 3.18–14.51) may be due to structural changes in the vascular system, such as hypertension (35), that are not ameliorated by lowering GH levels. This is supported by the positive relationship between cerebrovascular mortality and duration of acromegaly.

In summary, we have performed a large retrospective epidemiological cohort study that has shown increased mortality rates from colon cancer, cardiovascular disease, cerebrovascular disease, and respiratory disease in patients with acromegaly. Mortality rates due to colon cancer, all malignant disease, and cardiovascular disease were increased with higher posttreatment GH levels. Posttreatment GH levels below 2.5 ng/mL (5 mU/L) were associated with an overall mortality rate similar to that of the general population of the United Kingdom.

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