Cancer Incidence in Patients With Acromegaly: A Cohort Study and Meta-Analysis of the Literature

Jakob Dal,[1]* Michelle Z. Leisner,[2]* Kasper Hermansen,[3]* Dóra Körmendiné Farkas,[2] Mads Bengtsen,[1] Caroline Kistorp,[4] Eigil H. Nielsen,[5] Marianne Andersen,[6] Ulla Feldt-Rasmussen,[7] Olaf M. Dekkers,[2,8] Henrik Toft Sørensen,[2] and Jens Otto Lunde Jørgensen[1]

[1]Department of Endocrinology and Internal Medicine, Aarhus University Hospital, 8000 Aarhus, Denmark; [2]Department of Clinical Epidemiology, Aarhus University Hospital, 8200 Aarhus, Denmark; [3]Department of Medicine, Sydvestjysk Sygehus, 6700 Esbjerg, Denmark; [4]Department of Internal Medicine, Copenhagen University Hospital, 2730 Herlev, Denmark; [5]Department of Endocrinology, Aalborg University Hospital, 9000 Aalborg, Denmark; [6]Department of Endocrinology, Odense University Hospital, 5000 Odense, Denmark; [7]Department of Endocrinology, National University Hospital Rigshospitalet, 2100 Copenhagen, Denmark; and [8]Department of Clinical Epidemiolgy and Metabolism, Leiden University Medical Centre, 2333 ZA Leiden, The Netherlands

Context: Acromegaly has been associated with increased risk of cancer morbidity and mortality, but research findings remain conflicting and population-based data are scarce. We therefore examined whether patients with acromegaly are at higher risk of cancer.

Design: A nationwide cohort study (1978 to 2010) including 529 acromegaly cases was performed. Incident cancer diagnoses and mortality were compared with national rates estimating standardized incidence ratios (SIRs). A meta-analysis of cancer SIRs from 23 studies (including the present one) was performed.

Results: The cohort study identified 81 cases of cancer after exclusion of cases diagnosed within the first year [SIR 1.1; 95% confidence interval (CI), 0.9 to 1.4]. SIRs were 1.4 (95% CI, 0.7 to 2.6) for colorectal cancer, 1.1 (95% CI, 0.5 to 2.1) for breast cancer, and 1.4 (95% CI, 0.6 to 2.6) for prostate cancer. Whereas overall mortality was elevated in acromegaly (SIR 1.3; 95% CI, 1.1 to 1.6), cancer-specific mortality was not.

The meta-analysis yielded an SIR of overall cancer of 1.5 (95% CI, 1.2 to 1.8). SIRs were elevated for colorectal cancer, 2.6 (95% CI, 1.7 to 4.0); thyroid cancer, 9.2 (95% CI, 4.2 to 19.9); breast cancer, 1.6 (1.1 to 2.3); gastric cancer, 2.0 (95% CI, 1.4 to 2.9); and urinary tract cancer, 1.5 (95% CI, 1.0 to 2.3). In general, cancer SIR was higher in single-center studies and in studies with <10 cancer cases.

Conclusions: Cancer incidence rates were slightly elevated in patients with acromegaly in our study, and this finding was supported by the meta-analysis of 23 studies, although it also suggested the presence of selection bias in some earlier studies. (***J Clin Endocrinol Metab*** **103: 2182–2188, 2018)**

Acromegaly is a rare disease caused by hypersecretion of growth hormone (GH), usually from a pituitary adenoma, with an annual incidence of 4 cases per million individuals and a prevalence of 85 per million individuals (1). Continuous hypersecretion of GH induces the hepatic and peripheral production of insulinlike growth factor 1 (IGF-1). Both GH and IGF-1 are implicated in cancer promotion, based on experimental and epidemiological data (2), and acromegaly has been linked with elevated risk of cancer, both in general and with thyroid and

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Abbreviations: CI, confidence interval; DCR, Danish Cancer Registry; GH, growth hormone; ICD, International Classification of Diseases; IGF-1, insulinlike growth factor 1; SA, somatostatin analog; SD, standard deviation; SIR, standardized incidence ratio.

colorectal cancer in particular (3). However, not all studies have found this association (4, 5). Although acromegaly has been associated consistently with increased mortality (6, 7), it remains uncertain whether death from cancer is also increased.

A major reason for the inconsistent epidemiological data on cancer risk is differences in study design, and the need for population-based studies persists (8). Danish databases provide an opportunity to conduct a study with virtually complete follow-up, using valid population-based data, rather than at a single-center or multicenter level.

We therefore conducted a nationwide population-based cohort study to examine the long-term risk of cancer incidence and mortality in patients with acromegaly. We also conducted a meta-analysis of the literature on cancer standardized incidence ratios (SIRs) in acromegaly.

Materials and Methods

Population-based Danish cohort study

The source population comprised the cumulative population of Denmark, with ~8.1 million inhabitants during the period 1991 to 2010. The Danish National Health Service provides tax-supported health care, with universal free access to hospital-based and primary medical care, including care for acromegaly. To ensure unambiguous data linkage, we used the Danish Civil Registration System, which assigns a unique personal identifier, the civil personal registration number, to each Danish resident at time of birth or upon immigration. We identified members of the acromegaly cohort from the Danish National Patient Registry, which contains records on all hospitalizations since 1 January 1977, together with primary and secondary diagnoses coded according to the *International Classification of Diseases* (ICD) (9). The *Eighth Revision* (ICD-8) was used until 1993 and then replaced by the *Tenth Revision* (ICD-10). To identify cancers among patients with acromegaly, we used the Danish Cancer Registry (DCR), which has recorded all cases of incident cancer in Denmark since 1943 (10). ICD-10 codes are used in the DCR's current format. Finally, we identified causes of mortality from the Danish Registry of Causes of Death, which contains individual digitalized classification of causes of death in accordance with World Health Organization rules and, since 1994, by ICD-10 codes (11).

We validated each individual acromegaly diagnosis as previously described (1). Briefly, hospital records and charts for each possible patient with acromegaly were reviewed by an expert endocrinologist. All patients with validated acromegaly diagnoses who resided in Denmark between 1978 and 2010 were eligible for our cohort study. Those who received a cancer diagnosis before their acromegaly diagnosis were excluded from the study.

Disease-specific clinical variables were retrieved from patient records, including pituitary tumor size (maximal diameter), serum GH and IGF-1 levels (at diagnosis, 1 year after diagnosis, and 2 years after diagnosis), and acromegaly treatment modality [surgery only, somatostatin analog (SA) treatment with and without surgery, and irradiation with and without other treatment]. These biochemical and treatment-related data were available only for patients diagnosed after 1991.

All incident cancers were identified in the DCR between the index date (date of acromegaly diagnosis) and 30 November 2013. Cancer types of specific interest were colorectal cancer, breast cancer, lung cancer, thyroid cancer, gastric cancer, and prostate cancer. Cancer of any type and colorectal, breast, and lung cancers were classified further as localized or nonlocalized. Aggregated groupings were created for urinary tract cancers and hematological cancers. Causes of death were categorized as cancer, cardiovascular disease, other conditions not including cancer, and unknown. Each patient was followed from the date of the acromegaly diagnosis until first occurrence of a cancer diagnosis, death, emigration, or end of the study period (30 November 2013), whichever came first.

SIRs were used to compare the number of cancers observed in patients with acromegaly with the expected number, calculated from national cancer incidence rates obtained from the DCR (10). Patients with incident acromegaly were not excluded from the general population before calculation of SIRs. For all SIRs, 95% confidence intervals (CIs) were also calculated. All estimates were standardized to the general population by age, sex, and calendar period (5-year intervals). To reduce the risk of surveillance bias, cancer cases identified within the first year after the acromegaly diagnosis were not included in the primary analysis. However, in a sensitivity analysis, we included cancer cases diagnosed within the first year after the acromegaly diagnosis.

To explore whether variation in clinical variables (pituitary tumor size and GH and IGF-1 levels before and 1 to 2 years after diagnosis) predicted the outcomes of cancer incidence, cancer mortality, and overall mortality, we used a Cox proportional hazards model to calculate hazard ratios with 95% CIs. All analyses were performed in SAS version 9.4 (SAS Institute Inc., Cary, NC).

Meta-analysis

To identify published studies on the risk of cancer in acromegaly, we searched the PubMed and Scopus databases in January 2018 for publications in English, Danish, Dutch, Norwegian, and Swedish (languages spoken by the authors). The search string focused on acromegaly AND overall cancer or specific cancers. Studies were chosen that provided data permitting calculation of SIRs for cancer in patients with acromegaly compared with a control population. Initial selection of studies by title and abstract was performed by one reviewer (M.B.). Selected studies were retrieved for closer scrutiny by three reviewers (M.B., J.O.L.J., and O.M.D.), and disagreements were resolved by consensus.

SIRs were computed by dividing the number of observed events by the number of expected events in the selected studies. The meta-analysis of SIRs used a random-effects model (12), and heterogeneity was assessed via χ^2 tests and I^2 statistics (13). Funnel plots were used when $\geq$10 studies were available for analysis. All statistical analyses were performed in Comprehensive Meta-Analysis version 3.3 (Biostat, Englewood, NJ).

Results

Cohort study

Five hundred twenty-nine patients with acromegaly (51% male) were included in the cohort study. The mean age [standard deviation (SD)] at acromegaly diagnosis

was 47.4 (14.2) years, and of these, 25% (n = 132) received a diagnosis of acromegaly between 35 and 44 years of age and 13% (n = 67) after the age of 65 (Table 1). Regarding prevalence of comorbid conditions at the time of diagnosis, 8.3% presented with diabetes, 7.8% with hypertension, and 3.0% with chronic obstructive pulmonary disease. As treatments, 46% received SA treatment, 34% underwent surgery only, and 17% underwent radiation therapy (with and without additional treatment). In total, 90 patients with acromegaly (17%) were diagnosed with cancer during the follow-up period. The mean follow-up time was 13.6 (8.3) years, and the mean age at cancer diagnosis was 63.5 (12.5) years.

Within the first year after the diagnosis of acromegaly, nine patients were diagnosed with cancer and excluded from subsequent SIR analysis to reduce surveillance bias. The SIR of all cancers was 1.1 (95% CI, 0.9 to 1.4) (Table 2). Inclusion of the nine cases diagnosed within the first year after an acromegaly diagnosis increased the overall cancer risk marginally [SIR 1.2 (95% CI, 1.0 to 1.5)] (Supplemental Table 1). The SIR for colorectal cancer was 1.4 (95% CI, 0.7 to 2.6), slightly elevated. The estimates as regards associations between pituitary tumor size and biochemical biomarkers (GH and IGF-1 levels) and cancer risk were imprecise, with wide CIs, and therefore are not reported.

Table 1. Descriptive Characteristics of the Danish Acromegaly Cohort

	Patients, N (%)	Median (Interquartile Range)
No. of patients	529 (100)	
Sex, male	268 (51)	
Age at acromegaly diagnosis		
Mean age, y (SD)	47.4 (14.2)	
<35 y	112 (21)	
35–44 y	132 (25)	
45–54 y	125 (24)	
55–64 y	93 (18)	
65+ y	67 (13)	
Year of acromegaly diagnosis		
1978–1993	201 (38)	
1994–2010	328 (62)	
Clinical variables (n = 408)		
At diagnosis		
Tumor diameter, mm		16 (10–25)
GH nadir, μg/L		12 (6–29)
IGF-1, μg/L		679 (440–930)
1 y after diagnosis		
GH nadir, μg/L		1.5 (0.3–4.9)
IGF-1, μg/L		267 (158–481)
2 y after diagnosis		
GH nadir, μg/L		1.6 (0.4–5.0)
IGF-1, μg/L		224 (135–375)

The clinical variables derive from patients diagnosed after 1991 (N = 408).

Table 2. Cancer Incidence Among Patients With Acromegaly in Denmark, Excluding the First Year After Acromegaly Diagnosis

	Observed	Expected	SIR (95% CI)
Overall, cancer	81	72.7	1.1 (0.9–1.4)
Localized cancer	43	36.6	1.2 (0.9–1.6)
Nonlocalized cancer	25	22.0	1.1 (0.7–1.7)
Colorectal cancer	10	7.1	1.4 (0.7–2.6)
Localized	5	2.7	1.9 (0.6–4.3)
Nonlocalized	5	3.6	1.4 (0.5–3.3)
Breast cancer	9	8.1	1.1 (0.5–2.1)
Localized	4	4.0	N/A
Nonlocalized	5	3.6	1.4 (0.5–3.2)
Lung cancer	4	7.9	NA
Localized	0	1.5	NA
Nonlocalized	4	5.8	NA
Thyroid cancer	1	0.3	NA
Gastric cancer	4	1.1	NA
Prostate cancer	9	6.6	1.4 (0.6–2.6)
Urinary tract cancers	5	4.9	1.0 (0.3–2.4)
Hematological cancers	5	3.9	1.3 (0.4–3.0)

Abbreviation: NA, <5 cancers observed, so SIRs are not reported.

During the follow-up period, 141 patients died, of whom 46 were <55 years old. Cancer was the cause of death for 16% (n = 22) and cardiovascular disease for 30% (n = 42). Mortality risk in acromegaly was 1.4 times higher than in the general population (95% CI, 1.1 to 1.6); mortality risk after exclusion of the first year was 1.3 (95% CI, 1.1 to 1.6) (l). Mortality was elevated in the small group of patients who were not treated for acromegaly (n = 16) (data not shown). No difference in mortality was detected when different treatment groups were compared (data not shown).

Meta-analysis and literature review

Our initial search yielded 5365 publications, of which 5333 were excluded based on title or abstract. Thirty-two publications were retrieved for more detailed evaluation, of which 21 publications were eligible, and scrutiny of these identified 1 additional publication (4, 5, 14–33). Only 1 of these studies (23) excluded cancer cases diagnosed within the first year. Data from the current study including cancer cases detected within the first year after acromegaly diagnosis were included in the meta-analysis. Thus, 23 studies with a total of 9677 patients were included in the meta-analysis (Table 3). The mean weighted age at time of acromegaly diagnosis was 47.9 years, and the mean weighted follow-up time was 10.1 years (range: 4.5 to 15.0 years). The mean weighted age at time of cancer diagnosis was 62.0 years. The sex distribution was approximately equal (male/female ratio 53:47).

In general, SIRs for overall cancer were similar across studies, with 12 of 14 (14–16, 18, 23, 24, 26, 27, 29, 30, 33) reporting a SIR >1.0. The pooled SIR

Table 3. Characteristics of Studies Included in the Meta-Analysis

Study (Year)	Country	Patients (N)	Men (%)	Mean Age at Acromegaly Diagnosis, y (SD)	Mean Age at Cancer Diagnosis, y (SD)	Mean Follow-Up, y (SD)	Design
Dal *et al.* (2018)	Denmark	529	51	47.4 (14.2)	63.5 (12.5)	13.6 (8.3)	Population-based
Terzolo *et al.* (14) (2017)	Italy	1512	41	45.0 (13.0)		8.3	Multicenter
Maione *et al.* (15) (2017)	France, Switzerland, and Belgium	999	46	46.0		6.7	Multicenter
Wolinski *et al.* (16) (2017)	Poland	200	36	47.6 (13.0)		5.6 (7.1)	Single-center
Petroff *et al.* (5) (2015)	Germany	445	45	45.7 (14.2)		15.0	Multicenter
Dos Santos *et al.* (17) (2013)	Brazil	124	39	45.1 (13.4)			Multicenter
Kauppinen *et al.* (18) (2010)	Finland	331				14.6	Population-based
Kurimoto *et al.* (19) (2008)	Japan	140	39				Single-center
Matano *et al.* (20) (2005)	Japan	19	58	46.7 (16.3)	65.3 (10.8)		Single-center
Tita *et al.* (21) (2005)	Italy	125	44	49.9 (14.1)	52.0 (9.0)	8.2[a]	Multicenter
Terzolo *et al.* (22) (2005)	Italy	235	49	49.1 (12.6)	50.3 (12.8)		Multicenter
Baris *et al.* (23) (2002)	Denmark and Sweden	1634	46	50.7	64.8	10.0	Population-based
Higuchi *et al.* (24) (2000)	Japan	44	57	45.7 (13.8)		15.2	Single-center
Renehan *et al.* (25) (2000)	United Kingdom	122	57	41.9[a]	69.7 (17.9)		Multicenter
Orme *et al.* (4) (1998)	United Kingdom	1239				13.5	Multicenter
Popovic *et al.* (26) (1998)	Serbia	220	38	49.5 (13.3)		4.5 (5.9)	Single-center
Cheung *et al.* (27) (1997)	Australia	50	58	48.0[a]	58.8 (12.9)	8.7	Single-center
Colao *et al.* (28) (1997)	Italy	50	50	25–70[b]			Single-center
Ron *et al.* (29) (1991)	United States	1041	100	52.7		8.3	Multicenter
Barzilay *et al.* (30) (1991)	United States	87	51	37.0[a]		13[a]	Single-center
Brunner *et al.* (31) (1990)	United States	52	54	45.2 (14.2)		12.5 (9.0)	Multicenter
Nabarro (32) (1987)	United Kingdom	256	52	43.0		6.8	Single-center
Mustacchi *et al.* (33) (1957)	United States	223	57			13.3 (7.8)	Multicenter

[a]Reported as median.

[b]Reported as age ranges.

for overall cancer in the meta-analysis was 1.5 (95% CI, 1.2 to 1.8) (Fig. 1), with considerable heterogeneity (I^2 = 84%). The funnel plot was not clearly asymmetric, and the Egger test was nonsignificant (P = 0.36) (Supplemental Fig. 1), providing no clear evidence of publication bias. Stratification based on study design revealed a higher SIR for cancer in single-center studies (pooled SIR = 3.2; 95% CI, 2.4 to 4.1) (16, 24, 26, 27,

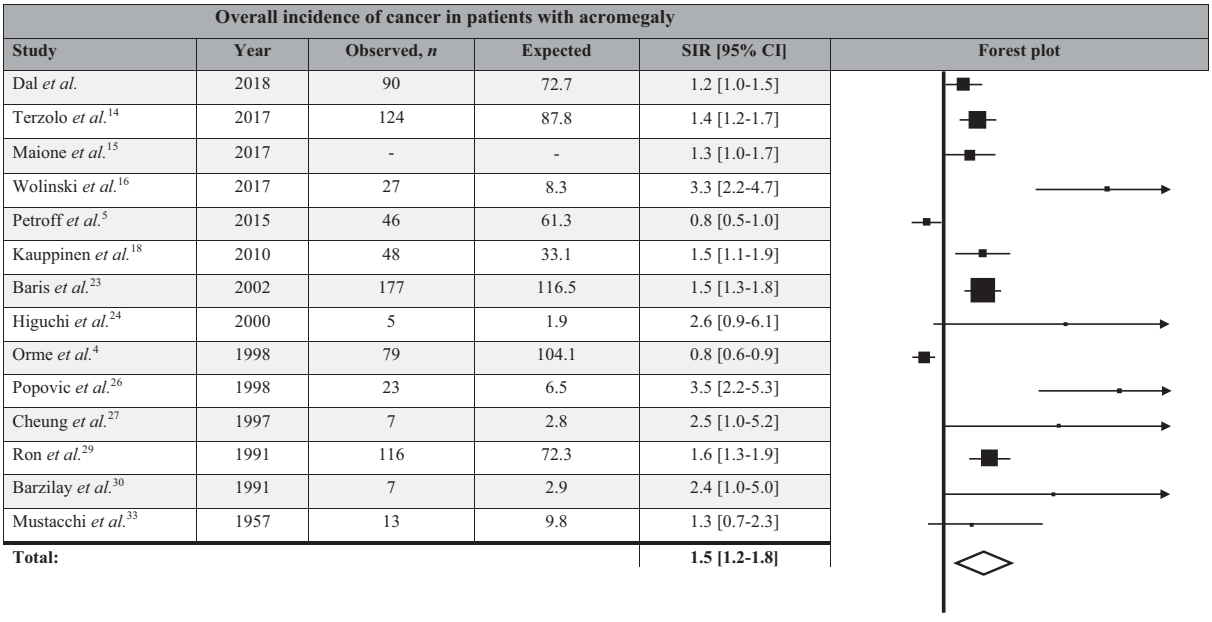

Figure 1. Overall incidence of cancer in patients with acromegaly. Reference 15 provided only SIR, as presented here.

30) compared with both multicenter studies (pooled SIR = 1.2; 95% CI, 0.9 to 1.5) (4, 5, 14, 15, 29, 33) and population-based studies (pooled SIR = 1.4; 95% CI, 1.2 to 1.6) (18, 23) (Table 4). When a partial overlap of patients between the current study and Baris *et al.* (23) became evident, we calculated the pooled SIR excluding the Baris article, which did not influence the pooled SIR (1.5; 95% CI, 1.2 to 1.9); similarly, excluding the current study did not change the estimate (SIR 1.5; 95% CI, 1.2 to 1.9). Exclusion of studies reporting <10 expected cases (16, 24, 26, 27, 30, 33) changed the pooled SIR to 1.2 (95% CI, 1.0 to 1.5).

Stratification based on sex in 9 studies (14, 15, 23, 24, 26, 27, 29, 30, 33) yielded similar SIRs for men and women: 1.5 (95% CI, 1.3 to 1.7) and 1.9 (95% CI, 1.4 to 2.5). Stratification based on study period (calendar year) did not clearly affect the outcome (Table 4). Stratified by cancer type, elevated risks were shown for colorectal cancer (pooled SIR = 2.6; 95% CI, 1.7 to 4.0), thyroid cancer (pooled SIR = 9.2; 95% CI, 4.2 to 19.9), gastric cancer (pooled SIR = 2.0; 95% CI, 1.4 to 2.9), breast cancer (pooled SIR = 1.6; 95% CI, 1.1 to 2.3), and urinary tract cancer (pooled SIR = 1.5; 95% CI, 1.0 to 2.3). SIRs for other cancers were as follows: lung cancer (0.8; 95% CI, 0.5 to 1.2), prostate cancer (1.2; 95% CI, 0.8 to 1.9), and hematological cancers (1.3; 95% CI, 0.8 to 2.3).

The increase in colorectal cancer incidence was reported in 13 out of 14 studies (4, 14, 16, 18–20, 22, 23, 25, 28, 29, 31) (Fig. 2), without evidence of funnel plot asymmetry (Egger test result; $P = 0.67$) (Supplemental Fig. 2). The colorectal cancer incidence rates among single-center studies (pooled SIR = 7.3; 95% CI, 2.6 to 20.6) (16, 19, 20, 28), multicenter studies (pooled SIR = 2.0; 95% CI, 1.3 to 3.1) (4, 5, 14, 22, 25, 29, 31), and population-based studies (pooled SIR = 2.2; 95% CI, 1.7 to 3.0) (18, 23) were all elevated.

No major difference was observed in thyroid cancer incidence between multicenter studies (pooled SIR = 7.6; 95% CI, 2.4 to 24.5) (4, 5, 14, 17, 21, 29) and population-based studies (pooled SIR = 8.2; 95% CI, 3.6 to 18.7) (18, 23); only two single-center studies (16, 19) evaluated thyroid cancer incidence (SIR = 20.3; 95% CI, 1.2 to 332.0).

Table 4. SIRs for Overall Cancer in Patients With Acromegaly, Subgroup Analyses Within the Meta-Analysis

Subgroup	Studies (N)	Patients (N)	SIR (95% CI)
Stratified by sex			
Men	9	3180	1.5 (1.3–1.7)
Women	8	2630	1.9 (1.4–2.5)
Stratified by study population			
Single center	5	601	3.2 (2.4–4.1)
Multicenter	6	5459	1.2 (0.9–1.5)
Population based	3	2494	1.4 (1.2–1.6)
Stratified by study period			
1950–1974	5[a]	4224	1.3 (0.9–1.9)
1975–1999	11[a]	6645	1.5 (1.2–1.8)
2000–2017	5[a]	3685	1.4 (1.0–1.8)

[a]Studies may be included in >1 subgroup.

Discussion

The findings from our population-based study and the meta-analysis suggest that overall cancer risk is slightly elevated in patients with acromegaly compared with the general population.

Data from laboratory, animal, and human studies strongly indicate that GH and IGF-1 are closely associated with cancer development and progression (2). Moreover, circulating IGF-1 levels within the upper normal range have been associated with elevated risk of breast, prostate, colorectal, and lung cancers in the general population (2).

Our study has several strengths stemming from its use of population-based nationwide data with virtually complete follow-up. This design reduces the risk of selection bias. This advantage is reinforced by free health care access in Denmark, implying that care is equally and openly accessible. Our study also excluded cancer cases detected within the first year after an acromegaly diagnosis, to minimize the risk of surveillance bias. Moreover, the diagnosis of each patient in our study was validated, as previously reported (1).

The results of the meta-analysis added support to our finding of increased cancer incidence among patients with acromegaly but also revealed potential sources of bias. The elevated overall cancer incidence risk in the meta-analysis was more pronounced in single-center studies (Table 4) and was lower when we excluded studies with <10 cases, suggesting the presence of selection or sample bias (8). It is possible that the patient population in single centers represents difficult cases with previous treatment failure and increased comorbidity. It is also possible that the comparator group in single-center studies derived from screening programs, which poses the risk of healthy user bias. This possibility is of particular relevance in the context of colorectal cancer and breast cancer, for which screening programs are often available. The risks of surveillance bias or diagnostic workup bias are also present. As mentioned, we reduced this risk by excluding cancer cases detected within the first year after the acromegaly diagnosis. Indeed, 9 out of

Incidence of colorectal cancer in patients with acromegaly					
Study	**Year**	**Observed, *n***	**Expected**	**SIR [95% CI]**	**Forest plot**
Dal *et al.*	2018	11	7.5	1.5 [0.7-2.6]	
Terzolo *et al.*[14]	2017	20	12.0	1.7 [1.0-2.6]	
Wolinski *et al.*[16]	2017	4	1.4	N/A	
Petroff *et al.*[5]	2015	4	6.6	N/A	
Kauppinen *et al.*[18]	2010	6	3.2	1.9 [0.7-4.1]	
Kurimoto *et al.*[19]	2008	10	0.6	18.2 [8.7-33.4]	
Matano *et al.*[20]	2005	3	0.5	N/A	
Terzolo *et al.*[22]	2004	10	2.0	5.0 [2.4-9.2]	
Baris *et al.*[23]	2002	36	14.3	2.5 [1.8-3.5]	
Renehan *et al.*[25]	2000	3	1.0	N/A	
Orme *et al.*[4]	1998	16	11.8	1.4 [0.8-2.2]	
Colao *et al.*[28]	1997	1	0.6	N/A	
Ron *et al.*[29]	1991	14	6.5	2.2 [1.2-3.6]	
Brunner *et al.*[31]	1990	2	0.4	N/A	
Total:				**2.6 [1.7-4.0]**	

Figure 2. Incidence of colorectal cancer in patients with acromegaly. N/A, <5 cancers observed, so SIRs are not reported.

90 cancer cases were diagnosed within the first year in our study. When we included these 9 cancer cases in a sensitivity analysis, risk estimates increased for overall cancer, colorectal cancer, and lung cancer (Supplemental Table 1). This approach was used only in one additional study (23), which may have introduced bias and overestimation of cancer risks in the remaining studies. Surveillance bias is of particular concern for thyroid cancer, because thyroid volume is enlarged in acromegaly, which may lead to more frequent use of ultrasonography and subsequent overdiagnosis of occult thyroid cancer (34), and endocrinologists are generally more likely to focus on endocrine diseases. In our own study, only a single case of thyroid cancer was diagnosed (Table 2), even when the first year of follow-up after acromegaly diagnosis was included (Supplemental Fig. 1).

A possible association between colorectal cancer risk and acromegaly has attracted particular interest and controversy, as has been extensively reviewed (3). A number of biological mechanisms have been proposed in addition to the fact that the bowel in patients with acromegaly is ~15% to 20% longer, which by itself has been estimated to increase bowel cancer risk by 15% to 20% (3). The meta-analysis confirmed an elevated risk of colorectal cancer, which was more pronounced in single-center studies.

Taken together, our cohort study and the meta-analysis suggest only a slightly elevated overall risk of cancer in patients with acromegaly. This finding does not call into question nonhuman data on the carcinogenic effects of GH and IGF-1, nor should it deter patients or health care professionals from adhering to current cancer surveillance guidelines. However, our findings agree with the previously drawn conclusion that excessive GH in humans is not a serious cancer risk (8).

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Correspondence and Reprint Requests: Jens Otto Lunde Jørgensen, MD, DMSc, Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Norrebrogade 44, 8000 Aarhus C, Denmark. E-mail: joj@clin.au.dk.

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