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This is the author's manuscript

Original Citation:

Availability:

This version is available http://hdl.handle.net/2318/1661234 since 2020-06-18T11:16:48Z

Published version:

DOI:10.1530/ERC-16-0553

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20 April 2024

UNIVERSITÀ DEGLI STUDI DI TORINO

***This is an author version of the contribution published on**:*
Questa è la versione dell'autore dell'opera:

Acromegaly is associated with increased cancer risk: a survey in Italy.

Endocrine Related Cancer; 2017 Sep; 24(9):495-504; DOI: 10.1530/ERC-16-0553

The definitive version is available at:

http://erc.endocrinology-journals.org/content/24/9/495.full.pdf+html

ACROMEGALY IS ASSOCIATED WITH INCREASED CANCER RISK: A SURVEY IN ITALY.

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Short Title: Cancer risk in acromegaly

Keywords: Acromegaly, cancer, GH, IGF-I

Word count: 3053

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ABSTRACT

It is debated if acromegalic patients have an increased risk to develop malignancies.

The aim of the present study was to assess the standardized incidence ratios (SIRs) of different types of cancer in acromegaly on a large series of acromegalic patients managed in the somatostatin analogs era.

It was evaluated the incidence of cancer in an Italian nationwide multicenter cohort study of 1512 acromegalic patients, 624 men and 888 women, mean age at diagnosis 45 +/- 13 years, followed–up for a mean of 10 years (12573 person-years) in respect to the general Italian population.

Cancer was diagnosed at 124 patients, 72 women and 52 men. The SIRs for all cancers was significantly increased compared to the general Italian population (expected: 88, SIR 1.41; 95%CI, 1.18-1.68, p<0.001). In the whole series, we found a significantly increased incidence of colorectal cancer (SIR 1.67; 95% CI,1.07-2.58, p=0.022), kidney cancer (SIR 2.87; 95% CI 1.55-5.34, p<0.001) and thyroid cancer (SIR 3.99; 95% CI, 2.32-6.87, p<0.001). **The exclusion of 11 cancers occurring before diagnosis of acromegaly (all in women) did not change remarkably the study outcome.** In multivariate analysis, the factors significantly associated with an increased risk of malignancy were age and family history of cancer, with a non-significant trend for the estimated duration of acromegaly before diagnosis.

In conclusion we found evidence that acromegaly in Italy is associated with a moderate increase in cancer risk.

INTRODUCTION

Acromegaly is an uncommon disease sustained by hypersecretion of GH and IGF-I and is associated with remarkable complications that may reduce life expectancy of these patients (Melmed 2009, Katznelson *et al.* 2014). However, the effective control of GH and IGF-I excess is able to reduce considerably the burden of disease. Recent population-based studies have showed that acromegalic patients have lower standard mortality ratios than previously reported (Sherlock *et al.* 2010), reflecting improved treatment modalities that became available in recent years, such as somatostatin-receptor ligands (SRL) and pegvisomant (Bogazzi *et al.* 2013, Biermasz 2014, Mercado *et al.* 2014) The impact of acromegaly on life expectancy comes mainly through cardiovascular and cerebrovascular events, since diabetes mellitus and hypertension are frequent complications of GH and IGF-I excess (Melmed 2001) Recently, we did a large-scale epidemiological analysis on 1512 acromegalic Italian patients and found that vascular disease and cancer were the main causes of death. Mortality was higher in patients with persistently active disease, and IGF-I levels at diagnosis, GH at the last follow-up, cancer, and pituitary radiotherapy were independent predictors of mortality (Arosio *et al.* 2012).

That acromegaly may cause cancer, and that mortality due to cancer contributes to shorten survival of patients with acromegaly, remains an unsolved issue (Melmed 2001, Loeper & Ezzat 2008, Boguszewski & Ayuk 2016). A wealth of preclinical data supports the view that the GH-IGF system plays an important role in cancer development and progression (Loeper & Ezzat 2008, Pollak 2008, Weroha & Haluska 2012, Brahmkhatri *et al.* 2015). Moreover, in human studies there is convincing evidence that circulating IGF-I concentrations at the higher limit of the normal range are linked with an increased risk of several types of cancers, although the excess risk seems moderate (Renehan *et al.* 2004, Clayton *et al.* 2011). Despite a sound rationale, studies that addressed the association between acromegaly and cancer produced controversial results, partly due to the different methodological approaches used (case-control and population-based design) (Loeper & Ezzat 2008, Ayuk & Boguszewski 2016). Moreover, it is plainly evident that most studies did not have the statistical power to demonstrate a moderate excess risk of cancer, as

expected from the outcome of studies in the general population and case-control studies on acromegaly (Figure 1).

A recent meta-analysis of case-control studies employing colonoscopy showed that acromegaly is associated with an increased risk of colon neoplasms, both colon adenomas, a premalignant condition that may lead to overt cancer, and colon cancers. Results were consistent among the different studies with no significant heterogeneity and showed an overall excess risk of about two times (Rokkas *et al.* 2008). Another meta-analysis of case-control studies focusing on thyroid cancer showed an increased risk of both nodular thyroid disease and thyroid cancer in acromegaly, and again results were quite homogeneous across studies, although with less precise estimate due to the low number of events (Wolinski *et al.* 2014).

Population-based studies addressing cancer incidence in acromegaly produced controversial findings that may be likely explained by difference in methodology and variable sample size (Table 1). Also population-based studies addressing whether cancer mortality may contribute to overall mortality of acromegaly came to mixed conclusions, with some studies showing an association while others did not (Table 2). However, it has been already argued that studies focusing on mortality are less helpful in answering the question whether acromegaly is associated with cancer because the prevalent cardiovascular mortality may have obscured cancer mortality. In the reported series, the median age at death was less than 60 years, thus most patients died before they could develop clinically evident cancer (Loeper & Ezzat 2008, Boguszewski & Ayuk 2016).

The aim of the present study was to assess the standardized incidence ratios (SIRs) of different types of cancer in acromegaly in a nationwide multicenter cohort study in Italy on a large series of acromegalic patients who have been treated in the SRL era.

MATERIALS AND METHODS

Subjects

We have evaluated the prevalence of neoplasia from an Italian series of 1512 patients who were proactively followed in 24 tertiary referral centers in Italy. **Patient characteristics are given in Table 3.**

Inclusion criteria were age at diagnosis >18 years and diagnosis of acromegaly made between 1 January 1980 and 31 December 2002 according to standard biochemical criteria at the time of enrollment, with at least 1-year follow-up after diagnosis. The mean follow-up time from diagnosis to the end of the study was 120 months (median: 90 months; interquartile range [IQR]: 42–170 months). **Follow-up was closed in 2011.** Data were collected retrospectively by local investigators in a computerized dataform developed using Access 2000 software (Microsoft Corporation 1999) and approved by all participants. All patients gave their informed consent to the collection of data according to the local ethic committee indications. Briefly, we collected for each patients: demographics, estimated date of appearance of typical acromegalic signs, GH and IGF-I levels at diagnosis and last follow-up, novel diagnosis of malignancies during follow-up, data on family history of cancer, smoking, drinking, participation in oncology screening programs. For further details on data capture and assessment see Arosio et al. (Arosio *et al.* 2012).

Statistical analysis

Cancer registrations were coded using the International Classification of Diseases ICD-9, and data were compared to the general Italian population using the cancer registry AIRTUM (Associazione Italiana Registri Tumori, www.registri-tumori.it). The expected number of cancers was calculated by multiplying the number of person-years by the appropriate national, gender-, age-, calendar year-, and site-specific cancer incidence rate for each five-year age group and calendar year of observation. Risks of cancer were estimated by computing the SIRs, defined as the observed to expected number of cancers for all acromegaly patients combined, and by gender, age, and years of follow-up. The 95% confidence intervals (CI) were computed assuming that the observed number follows a Poisson distribution (Liddell 1984).

Descriptive statistics were worked out. Continuous data were presented as medians and interquartile ranges, or means and standard deviations. Discrete data are given as counts and percentages. Chi-square test was performed to compare categorical data between groups and the Mann-Whitney U test was used to compare continuous data. Levels of significance were set at $p<0.05$.

The individual effect of patient and clinical variables on the risk of cancer was evaluated by a logistic regression model and a univariate estimate of the Odds Ratios (OR) were presented along with their 95%

confidence intervals (CI). A multivariable model was then considered. Variables were entered into the model following a variable selection strategy, which was based on clinical judgement and statistical selection procedures. Model fit was considered as significantly improved on the basis of the Akaike Information Criterion (AIC) applied backwards for each model (i.e. starting from a model with all relevant variables, eliminating those that were not significant), at a significance level of 0.05. Interactions among variables were assessed by the Wald's test.

RESULTS

Cancer incidence

We found 124 patients with diagnosis of cancer in our study cohort of 1512 acromegalic followed-up for a mean period of 10 years (12573 person-years). Fourteen patients had multiple cancers. Eleven subject registrations occurred before the date of diagnosis of acromegaly **(8 breast, 2 colorectal, 1 uterus cancers)** but were included in the analysis, since diagnosis of cancer preceded that of acromegaly of less than 5 years, which is within the time lag occurring between onset and clinical diagnosis of acromegaly in our cohort (Arosio *et al.* 2012). **Raw data of observed malignancies are given in supplemental table 1. In a separate analysis, we restricted SIR calculation to the malignancies observed only after the clinical diagnosis of acromegaly.**

Overall, SIR for all cancers was increased compared to the general Italian population (SIR 1.41; 95%CI, 1.18-1.68, p<0.001). In the whole series, we found a significantly increased incidence of colorectal cancer (SIR 1.67; 95% CI, 1.07-2.58, p=0.022), kidney cancer (SIR 2.87; 95% CI 1.55-5.34, p<0.001) and thyroid cancer (SIR 3.99; 95% CI, 2.32-6.87, p<0.001). We assessed the SIRs of different cancer types in the female and male gender, respectively (Table 4). In female patients, incidence of all malignancies was increased (SIR 1.51; 95% CI, 1.20-1.91, p<0.001), as it was incidence of thyroid cancer, colorectal cancer, and breast cancer. In male patients, incidence of all malignancies was increased (SIR 1.29; 95% CI, 1.0-1.7, p=0.06), as it was incidence of thyroid cancer, kidney cancer, and colorectal cancer.

The analysis of the malignancies observed only after the clinical diagnosis of acromegaly confirmed an increased SIR for all cancer in the overall population (SIR 1.28; 95%CI, 1.07-1.55, p<0.007). All the prevalent malignancies were observed in female patients; however, the incidence of all malignancies was still increased (SIR 1.28; 95%CI, 1.00-1.65, p<0.05) while the incidence of breast cancer (SIR 0.83; 95% CI, 0.50-1.41, p=NS) and colorectal cancer (SIR 1.55; 95% CI, 0.84-2.89, p=NS) were not different from the general female population.

A comparable number of patients with or without cancer were submitted to proactive oncologic screening as part of their management (65% in patients with cancer vs. 60% in patients without cancer).

Predictive factors of cancer were analyzed in univariate analysis (age, gender, duration of acromegaly before diagnosis, presence of diabetes, active disease at last follow-up, GH/IGF-I at baseline and last follow-up, pituitary radiotherapy, family history of cancer). Factors significantly associated with an increased risk of cancer were age, family history of cancer, disease duration before diagnosis, presence of diabetes and previous pituitary radiotherapy. **Pertinently, we observed only 3 cases of brain cancer.** In multivariable analysis, factors significantly associated with an increased risk of cancer were age and family history of cancer, while there was a non-significant trend for duration of acromegaly (Table 5).

DISCUSSION

Whether acromegaly is associated with increased risk of cancer remains an endless debate. In general, case-control studies focusing on a specific tumor type produced more homogeneous figures, as demonstrated by a meta-analysis of colonoscopy-based studies (Rokkas *et al.* 2008). Since case-control studies may lead to overestimation of risk due to ascertainment bias and problems related to matching with specific patient groups, the "well-worried" bias, it has been suggested that population-based studies are more appropriate for assessing cancer risk (Renehan & Brennan 2008).

However, population-based studies produced discrepant data for a number of reasons. First, due to the rarity of acromegaly only nationwide surveys may have adequate statistical power. Second, coverage and accuracy of national cancer registries, as well as duration and completeness of follow-up, are keys for an adequate comparison with the general population. Third, the retrospective nature of these studies is an obvious limitation, particularly when considering that some studies date back to the sixties (Wright *et al.* 1970, Alexander *et al.* 1980), when treatment of acromegaly was far less effective. As a consequence, patients with uncontrolled acromegaly may have died before entering the age when cancer usually occurs; thus, competitive cardiovascular morbidity may have hindered cancer incidence and, particularly, cancer mortality (Loeper & Ezzat 2008, Boguszewski & Ayuk 2016).

The aim of the present study was to evaluate the incidence of cancer in a series of 1512 acromegalic patients followed up for 10 years at 24 tertiary referral centers in Italy. Most patients were treated after the introduction of SRL in clinical practice, thus representing a modern series. We found that the overall incidence of cancer was increased compared to the general population with a SIR of 1.41 (95%CI, 1.18-1.68). The excess risk is only moderate and this may explain why less powered studies produced controversial findings. **Since acromegaly is usually recognized many years after its biological onset, we included in the analysis the malignancies diagnosed within a period of 5 years prior to the clinical diagnosis of acromegaly, to account for the long period of exposure to excess GH and IGF-I preceding the diagnosis. Even if malignancies detected during this time span are considered formally as prevalent, they**

occur under the influence of hormone excess that is present albeit undiagnosed. Pertinently, a recent survey in Denmark identified increased morbidity over the 3 years preceding diagnosis of acromegaly (Dal et al., 2016). However, we also did a separate analysis including only the malignancies diagnosed after the clinical diagnosis of acromegaly to provide a more conservative estimate of the risk. The results of this analysis overall confirmed an excess cancer risk with the exception of breast cancer.

Only three studies in the literature have a size comparable to the present one, but only two were nationwide surveys. Ron et al. (Ron *et al.* 1991) analyzed a cohort of 1041 male inpatients with acromegaly in the US and found an increased incidence compared to non-acromegalic hospitalized patients, who served as controls (SIR, 1.6; 95% CI, 1.3-1.9). This increased risk was mainly attributable to gastrointestinal cancers, in particular colon cancer. However, the study may be criticized for the inclusion of only male patients admitted to hospital and for not having used tumor incidence rates of the general population as reference (Loeper & Ezzat 2008). Orme et al. (Orme *et al.* 1998) made a large epidemiological study in the UK, analyzing a cohort of 1239 subjects with acromegaly, and found that the risk for all malignancies was reduced compared to the general population (SIR, 0.76; 95% CI, 0.60-0.95), although there was a non-significant increase in the incidence of colon cancer (SIR, 1.68; P=0.06). However, they excluded approximately 17% of cancer registrations that occurred before the diagnosis of acromegaly. Since the diagnosis of acromegaly is usually made years after its biological onset, excluding such cases may cause an underestimation of the phenomenon (Loeper & Ezzat 2008, Boguszewski & Ayuk 2016). Baris et al. (Baris *et al.* 2002) made an epidemiological study in Sweden and Denmark, analyzing a cohort of 1634 patients, and found an increased risk for all malignancies (SIR, 1.5; 95% CI, 1.3-1.8), in particular of the digestive tract.

More recently, three smaller studies have been published that provided controversial results. Kauppinen-Makelin et al. (Kauppinen-Makelin *et al.* 2005), in a nation-wide survey in Finland, analyzed 334 patients and found an increased cancer incidence (SIR, 1.5; 95% CI, 1.1-1.9). Due to the low number of events, it was impossible to make stratification per cancer type, but colon and thyroid cancer were the most frequently observed. Petroff et al. (Petroff *et al.* 2015) analyzed 446 patients from the German Acromegaly Registry and found that cancer incidence was non-significantly lower than the general population (SIR, 0.75; 95% CI, 0.55-1.00). They found a two times higher incidence of thyroid cancer in acromegalic patients that was not

significant due to the low number of events. However, the study has limits in representing only a sample of the German Acromegaly Registry and in the methodology used to ascertain cancer registration, which was not always based on referring to medical records but included also phone interview. Moreover, 16% of patients were lost to follow-up. Cheng et al. (Cheng *et al.* 2015) reported on 408 acromegalic patients followed at 3 referral centers in Canada and found that cancer incidence was higher than in the general population (OR, 2.87; 95% CI, 1.57-5.25). In this cohort, diabetes was associated to the risk of malignancy.

The present study has strengths in the large population sample and long follow-up with all cancer registrations confirmed by the physicians who proactively managed the patients. Our study cohort was collected in many referral centers; thus it is representative of the acromegalic population in Italy. It is also representative of a cohort treated in a modern way as demonstrated by the overall mortality data (Arosio *et al.* 2012) in a range comparable to those observed in more recent studies (Katznelson *et al.* 2014, Sherlock *et al.* 2010, Mercado *et al.* 2014). Our findings on cancer incidence are in close agreement with the nationwide survey in Finland (Kauppinen-Makelin *et al.* 2005) that was done in the same time period (SIR of the present study, 1.41; SIR of the Finnish study, 1.5). The outcome of the German study (Petroff *et al.* 2015), which is also a contemporary series, is at variance but the above-mentioned differences in study methodology may explain the discrepancy.

Due to our large sample size, we were able to consider separately cancer incidence between sexes and make a meaningful stratification of different cancer types. Risk of cancer was higher in women (SIR 1.51; 95% CI, 1.20-1.91) than in men (SIR 1.29; 95% CI, 1.0-1.7), and this may be attributable to the fact that women were older in our series. **Cancers found to be more consistently increased were thyroid cancer, kidney cancer and colorectal cancer.** These findings are consistent with abundant evidence linking the IGF system with development and progression of all these cancers (Loeper & Ezzat 2008, Pollak 2008, Weroha & Haluska 2012, Brahmkhatri *et al.* 2015, Renehan *et al.* 2004, Clayton *et al.* 2011, Giovannucci *et al.* 2000, Pekic & Popovic 2013).

The increased risk of colon neoplasia in acromegaly is the most widely agreed; thus, the Endocrine Society Guidelines suggested incorporating colonoscopy at diagnosis in the management of acromegaly-related comorbidities (Katznelson *et al.* 2014). Higher risk of breast cancer has been reported in an old study

(Nabarro 1987), while recent studies found only non-significant increase in risk (Baris *et al.* 2002, Kauppinen-Makelin *et al.* 2005, Petroff *et al.* 2015). However, assessing the prevalence in acromegaly of breast cancer is particularly challenging since it may be looked at only in women, thus substantially halving the sample size. In addition, IGF-I excess could have different effects depending on the menopausal state, and on the levels of other sex and growth hormones, further increasing complexity (Renehan *et al.* 2004, Tworoger *et al.* 2011). In recent reports, there is increasing evidence that thyroid cancer is more frequent in patients with acromegaly than in control groups (Wolinski *et al.* 2014). A recent cross-sectional prospective study in Spain found that either benign nodular thyroid disease or thyroid cancer were more frequent in 123 patients with acromegaly than in 50 matched controls applying highly sensitive ultrasound methodology and standardized use of FNA cytology (Reverter *et al.* 2014). Conversely, the association between acromegaly and kidney cancer has been less frequently reported (Cheung & Boyages 1997, Baris *et al.* 2002, Kauppinen-Makelin *et al.* 2005). Interestingly, expression of the IGF-I receptor has been associated with poor survival in patients with early-stage renal cancer (Parker *et al.* 2004).

The present study is the first to provide a multivariate analysis aiming at identifying predictors of cancer in acromegaly. We found that age and family history of cancer were significant independent factors associated to cancer risk, and these findings are biologically plausible. Moreover, a non-significant trend between cancer risk and delay in acromegaly diagnosis was apparent, but it is known that the estimate of duration of acromegaly is admittedly imprecise and operator dependent. We did not find evidence of an association between values of GH and IGF-I, or both, and cancer risk. Orme et al. (Orme *et al.* 1998) found a higher cancer-related mortality in patients with elevated post-treatment GH but no clear link between GH and IGF-I levels and cancer incidence in acromegaly has been definitively proven. This does not discredit the view that GH and IGF-I are implicated in cancer development in acromegaly. It has to be pointed out that the hormonal evaluation at diagnosis or at the last follow-up may give only a poor estimate of patient's exposure to GH and IGF-I in the course of a chronic disease such as acromegaly. Moreover, other factors may play important roles in determining the risk of neoplasia in acromegaly, such as insulin, insulin resistance, IGF-BP1 and BP3, obesity, body composition and leptin levels (Melmed 2001, Boguszewski & Ayuk 2016, Giovannucci *et al.* 2000, Pekic & Popovic 2013, Tworoger *et al.* 2011). In this line, it is interesting

the finding of Cheng et al. (Cheng *et al.* 2015) that acromegalic patients with diabetes had more malignant tumors than non-diabetic patients. In our cohort, diabetes was associated with cancer risk only in univariate analysis. The alternative hypothesis that cancer risk in acromegaly is due to common underlining genetic factors should be also considered (Loeper & Ezzat 2008, Boguszewski & Ayuk 2016, Renehan & Brennan 2008).

Limitations of our study are its retrospective nature, as for previous epidemiological studies, the consequent lack of data on the cumulative GH exposure, that has been recently suggested as a very important determinant of morbidity and mortality (Varadhan *et al.* 2016), and the fact that patients have been submitted in many centers to proactive oncologic screening, since previous studies conducted in Italy have suggested an association between acromegaly and colon neoplasia (Terzolo *et al.* 2005) or thyroid cancer (Gasperi *et al.* 2002, Tita *et al.* 2005). However, the rate of patients who underwent cancer screening was alike between patients with and without cancer; thus, it is unlikely that our findings are explained by an ascertainment bias.

In conclusion, we found evidence that acromegaly is associated with a moderate increase in cancer risk in a nation-wide survey in Italy.

Declaration of Interest: PB, EF, EM, LDM, SG, DF, MM, MB, EDM, CM, EP, AV, MFF, PT, FP, GP, GB, CS, NB, AB, AB, ALS, RB, LMF, MA have nothing to declare. MT received lecture fees from Pfizer. GR received grant support from Novartis. RP received grant support from Novartis, Pfizer, Ipsen. ML received lecture fees from Pfizer, Ipsen. SC received grant support from Novartis, Ipsen, Italfarmaco, Pfizer. AP received grant support from Novartis. AC received grant support from Novartis, Pfizer, Ipsen.

Funding: This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector

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FIGURE LEGENDS

Figure 1 – Sample size of the population-based studies on acromegaly and cancer.