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

2 Massimo Terzolo[1], Giuseppe Reimondo[1], Paola Berchialla[2], Emanuele Ferrante[3], Elena Malchiodi[3], Laura

3 De Marinis[4], Rosario Pivonello[5], Silvia Grottoli[6], Marco Losa[7], Salvatore Cannavo[8], Diego Ferone[9], Marcella

4 Montini[10], Marta Bondanelli[11], Ernesto De Menis[12], Chiara Martini[13], Efisio Puxeddu[14], Antonino Velardo[15],

5 Alessandro Peri[16], Marco Faustini-Fustini[17], Patrizia Tita[18], Francesca Pigliaru[19], Giulia Peraga[1], Giorgio

6 Borretta[20], Carla Scaroni[21], Nicoletta Bazzoni[22], Antonio Bianchi[4], Alessandro Berton[6], Andreea Liliana

7 Serban[3], Roberto Baldelli[23], Letizia Maria Fatti[24], Annamaria Colao[5], and Maura Arosio[3] for the Italian

8 Study Group of Acromegaly*

9

10 [1]Internal Medicine 1, Department of Clinical and Biological Sciences, University of Turin, San Luigi

11 Gonzaga Hospital, Orbassano, Italy; [2]Statistical Unit, Department of Clinical and Biological Sciences,

12 University of Turin, San Luigi Gonzaga, Hospital, Orbassano, Italy; [3]Endocrinology and Diabetology Unit,

13 Fondazione IRCCS Ca` Granda Ospedale Maggiore Policlinico, Department of Clinical Sciences and

14 Community Health, University of Milan, Milan, Italy; [4]Pituitary Unit, Department of Endocrinology,

15 Catholic University of the Sacred Heart, Rome, Italy; [5]Division of Endocrinology, Department of Clinical

16 Medicine and Surgery, University Federico II di Napoli, Naples, Italy; [6]Division of Endocrinology, Diabetes

17 and Metabolism, Department of Medical Science, University of Turin, ASOU Città della Salute e della

18 Scienza, Turin, Italy; [7]Pituitary Unit, Department of Neurosurgery, San Raffaele Scientific Institute,

19 University 'Vita- Salute', Milan, Italy; [8]Department of Clinical and Experimental Medicine-Endocrinology

20 Unit, University of Messina, Messina, Italy; [9]Endocrinology Unit, Department of Internal Medicine &

21 Medical Specialties (DiMI), Center of Excellence for Biomedical Research (CEBR) IRCCS, AOU San

22 Martino-IST, San Martino Hospital, University of Genova, Genova, Italy; [10]Ambulatori di Endocrinologia,

23 Humanitas Gavazzeni, Bergamo, Italy; [11]Section of Endocrinology and Internal Medicine, Department of

24 Medical Sciences, University of Ferrara, Ferrara, Italy; [12]Internal Medicine, San Valentino Hospital,

25 Montebelluna, Treviso, Italy; [13]Internal Medicine, Department of Medicine, DIMED, University of Padova,

26 Padova, Italy; [14]Department of Medicine, Section of Internal Medicine and Endocrine and Metabolic

27 Sciences, University of Perugia, Perugia, Italy; [15]Department of Internal Medicine, Section of Endocrinology

28   and Metabolism, University of Modena, Modena, Italy; [16]Endocrine Unit, Department of Experimental and

29   Clinical Biomedical Sciences "Mario Serio", University of Florence, Florence, Italy; [17]IRCCS Istituto delle

30   Scienze Neurologiche di Bologna (ISNB), Bologna, Italy; [18]Endocrinology, AO Garibaldi-Nesima, Catania,

31   Italy; [19]Endocrinology and Diabetes, Department of Medical Sciences, University of Cagliari, Cagliari, Italy;

32   [20]Division of Endocrinology and Metabolism, Santa Croce and Carle Hospital, Cuneo, Italy; [21]Endocrinology

33   Unit, Department of Medicine , DIMED University of Padua, Padua, Italy; [22]Endocrinology, Sant'Antonio

34   Abate Hospital, Gallarate, Varese, Italy; [23]Endocrinology Unit, Regina Elena National Cancer Institute,

35   Rome, Italy; [24]Division of Endocrine and Metabolic Diseases, San Luca Hospital, IRCCS Istituto

36   Auxologico Italiano, Milan, Italy.

37

38   Italian Study Group of Acromegaly*

39   Participating centres:

40   1. Department of Clincal Sciences and Community Health, University of Milan, Unit of Endocrine Diseases

41   and Diabetology, 'S. Giuseppe' Hospital, Multimedica Group, Arosio M, Montefusco L.

42   2. Internal Medicine 1, Department of Clinical and Biological Sciences, University of Turin, San Luigi

43   Gonzaga Hospital, Orbassano, Italy, Angeli A, Terzolo M, Reimondo G, Zaggia B, Peraga G.

44   3. Department of Clinical Sciences and Community Health, University of Milan, Unit of Endocrinology and

45   Diabetes, Fondazione IRCCS Ca` Granda Ospedale Maggiore Policlinico, Spada A, Ferrante E, Malchiodi

46   E, Ronchi CL, Serban AL

47   4. Department of Molecular and Clinical Endocrinology and Oncology, University of Naples, Lombardi G,

48   Colao A, Pivonello R.

49   5. Department of Medicine, University of Padua, Sicolo N, Martini C, Maffei P.

50   6. Department of Internal Medicine, Section of Endocrinology and Metabolism, University of Modena,

51   Velardo A.

52   7. Department of Medicine and Pharmacology, University of Messina, Trimarchi F, Cannavo` S.

53   8. Unit of Internal Medicine, S. Valentino Hospital, Montebelluna (Treviso) De Menis E.

54   9. Pituitary Unit, Pituitary Unit, Department of Endocrinology, Catholic University of the Sacred Heart,

55   Rome, Italy, De Marinis L, Bianchi A, Cimino V.

56   10. Section of Endocrinology and Internal Medicine Department of Medical Sciences, University of Ferrara,

57   Italy Degli Uberti EC, Ambrosio MR, Bondanelli M.

58   11. Division of Endocrinology, Ospedali Riuniti di Bergamo, Pagani G, Montini M, Attanasio R.

59   12. Department of Internal Medicine, Endocrine Unit, Bellaria Hospital, Bologna, Faustini-Fustini M, Kara E

60   13. Endocrine Unit, Department of Experimental and Clinical Biomedical Sciences "Mario Serio",

61   University of Florence, Florence Mannelli M, Peri A.

62   14. Endocrinology Unit, Department of Medicine DIMED, University Hospital of Padova, Padova, Padova,

63   Italy. Mantero F, Scaroni C, Ceccato F.

64   15. Pituitary Unit, Department of Neurosurgery, San Raffaele Scientific Institute, Universita` Vita-Salute,

65   Milan, Mortini P, Losa M.

66   16. Division of Endocrinology and Metabolism, S. Croce and Carle Hospital, Cuneo, Borretta G, Razzore P.

67   17. Department of Internal Medicine and Endocrine Sciences, University of Perugia, Angeletti G, Della

68   Torre D, Puxeddu E.

69   18. Endocrinology and Diabetes, Department of Medical Sciences, University of Cagliari, Mariotti S,

70   Pigliaru F.

71   19. Division of Endocrinology, Diabetology and Metabolism, Department of Internal Medicine, University

72   of Turin, Ghigo E, Grottoli S, Berton A

73   AOU Città della Salute e della Scienza di Torino, Dipartimento di Scienze Mediche, Università di Torino

74   20. Endocrinology Unit, S. Antonio Abate Hospital, Gallarate, Milan, Mainini AL, Bazzoni N. (opp UO di

75   Endocrinologia, ospedale Sant'Antonio Abate, Gallarate)

76   21. Endocrinology Unit, Regina Elena National Cancer Institute, Rome, Appetecchia M, Baldelli R.

77   22. Endocrinology, Department of Internal and Specialistic Medicine, University of Catania, Garibaldi-

78   Nesina Hospital, Catania, Vigneri R, Tita P.

3

79 23. Endocrinology Unit. Department of Internal Medicine & Medical Specialties (DiMI), Center of

80 Excellence for Biomedical Research (CEBR) IRCCS, AOU San Martino-IST , S Martino Hospital,

81 University of Genova, Genova Minuto F, Nazzari E, Ferone D

82 24. Division of Endocrinology and Metabolic Diseases, IRCCS San Luca Hospital, Istituto Auxologico

83 Italiano, University of Milan, Cavagnini F , Fatti L, Persani L

84

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88

89 *Correspondig author*

90 Giuseppe Reimondo, MD, PhD

91 Internal Medicine 1 - Department of Clinical and Biological Sciences, University of Turin, San Luigi

92 Gonzaga Hospital

93 Regione Gonzole 10 - 10043 Orbassano (TO), Italy

94 Phone: +39 0119026292

95 Fax: +39 0116705456

96 e-mail: giuseppe.reimondo@unito.it

97

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101   **ABSTRACT**

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

103   The aim of the present study was to assess the standardized incidence ratios (SIRs) of different types of

104   cancer in acromegaly on a large series of acromegalic patients managed in the somatostatin analogs era.

105   It was evaluated the incidence of cancer in an Italian nationwide multicenter cohort study of 1512

106   acromegalic patients, 624 men and 888 women, mean age at diagnosis 45 +/- 13 years, followed–up for a

107   mean of 10 years (12573 person-years) in respect to the general Italian population.

108   Cancer was diagnosed at 124 patients, 72 women and 52 men. The SIRs for all cancers was significantly

109   increased compared to the general Italian population (expected: 88, SIR 1.41; 95%CI, 1.18-1.68, p<0.001).

110   In the whole series, we found a significantly increased incidence of colorectal cancer (SIR 1.67; 95%

111   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;

112   95% CI, 2.32-6.87, p<0.001). The exclusion of 11 cancers occurring before diagnosis of acromegaly (all in

113   women) did not change remarkably the study outcome. In multivariate analysis, the factors significantly

114   associated with an increased risk of malignancy were age and family history of cancer, with a non-significant

115   trend for the estimated duration of acromegaly before diagnosis.

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

117   risk.

118

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).

146   A recent meta-analysis of case-control studies employing colonoscopy showed that acromegaly is associated

147   with an increased risk of colon neoplasms, both colon adenomas, a premalignant condition that may lead to

148   overt cancer, and colon cancers. Results were consistent among the different studies with no significant

149   heterogeneity and showed an overall excess risk of about two times (Rokkas *et al.* 2008). Another meta-

150   analysis of case-control studies focusing on thyroid cancer showed an increased risk of both nodular thyroid

151   disease and thyroid cancer in acromegaly, and again results were quite homogeneous across studies, although

152   with less precise estimate due to the low number of events (Wolinski *et al.* 2014).

153   Population-based studies addressing cancer incidence in acromegaly produced controversial findings that

154   may be likely explained by difference in methodology and variable sample size (Table 1). Also population-

155   based studies addressing whether cancer mortality may contribute to overall mortality of acromegaly came to

156   mixed conclusions, with some studies showing an association while others did not (Table 2). However, it has

157   been already argued that studies focusing on mortality are less helpful in answering the question whether

158   acromegaly is associated with cancer because the prevalent cardiovascular mortality may have obscured

159   cancer mortality. In the reported series, the median age at death was less than 60 years, thus most patients

160   died before they could develop clinically evident cancer (Loeper & Ezzat 2008, Boguszewski & Ayuk 2016).

161   The aim of the present study was to assess the standardized incidence ratios (SIRs) of different types of

162   cancer in acromegaly in a nationwide multicenter cohort study in Italy on a large series of acromegalic

163   patients who have been treated in the SRL era.

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166   **MATERIALS AND METHODS**

167   *Subjects*

168   We have evaluated the prevalence of neoplasia from an Italian series of 1512 patients who were proactively

169   followed in 24 tertiary referral centers in Italy. Patient characteristics are given in Table 3. Inclusion criteria

170   were age at diagnosis >18 years and diagnosis of acromegaly made between 1 January 1980 and 31

171   December 2002 according to standard biochemical criteria at the time of enrollment, with at least 1-year

172   follow-up after diagnosis. The mean follow-up time from diagnosis to the end of the study was 120 months

173   (median: 90 months; interquartile range [IQR]: 42–170 months). Follow-up was closed at the end of 2012.

174   Data were collected retrospectively by local investigators in a computerized dataform developed using

175   Access 2000 software (Microsoft Corporation 1999) and approved by all participants. All patients gave their

176   informed consent to the collection of data according to the local ethic committee indications. Briefly, we

177   collected for each patients: demographics, estimated date of appearance of typical acromegalic signs, GH

178   and IGF-I levels at diagnosis and last follow-up, novel diagnosis of malignancies during follow-up, data on

179   family history of cancer, smoking, drinking, participation in oncology screening programs. For further details

180   on data capture and assessment see Arosio et al. (Arosio *et al.* 2012).

181

182   *Statistical analysis*

183   Cancer registrations were coded using the International Classification of Diseases ICD-9, and data were

184   compared to the general Italian population using the cancer registry AIRTUM (Associazione Italiana Registri

185   Tumori, www.registri-tumori.it). The expected number of cancers was calculated by multiplying the number

186   of person-years by the appropriate national, gender-, age-, calendar year-, and site-specific cancer incidence

187   rate for each five-year age group and calendar year of observation. Risks of cancer were estimated by

188   computing the SIRs, defined as the observed to expected number of cancers for all acromegaly patients

189   combined, and by gender, age, and years of follow-up. The 95% confidence intervals (CI) were computed

190   assuming that the observed number follows a Poisson distribution (Liddell 1984).

191   Descriptive statistics were worked out. Continuous data were presented as medians and interquartile ranges,

192   or means and standard deviations. Discrete data are given as counts and percentages. Chi-square test was

193   performed to compare categorical data between groups and the Mann-Whitney U test was used to compare

194   continuous data. Levels of significance were set at $p < 0.05$.

195   The individual effect of patient and clinical variables on the risk of cancer was evaluated by a logistic

196   regression model and a univariate estimate of the Odds Ratios (OR) were presented along with their 95%

197   confidence intervals (CI). A multivariable model was then considered. Variables were entered into the model

198   following a variable selection strategy, which was based on clinical judgement and statistical selection

199   procedures. Model fit was considered as significantly improved on the basis of the Akaike Information

200   Criterion (AIC) applied backwards for each model (i.e. starting from a model with all relevant variables,

201   eliminating those that were not significant), at a significance level of 0.05. Interactions among variables were

202   assessed by the Wald's test.

203

204 **RESULTS**

205

206 *Cancer incidence*

207 We found 124 patients with diagnosis of cancer in our study cohort of 1512 acromegalic followed-up for a

208 mean period of 10 years (12573 person-years). Fourteen patients had multiple cancers. Eleven subject

209 registrations occurred before the date of diagnosis of acromegaly (8 breast, 2 colorectal, 1 uterus cancers) but

210 were included in the analysis, since diagnosis of cancer preceded that of acromegaly of less than 5 years,

211 which is within the time lag occurring between onset and clinical diagnosis of acromegaly in our cohort

212 (Arosio *et al.* 2012). Raw data of observed malignancies are given in supplemental table 1. In a separate

213 analysis, we restricted SIR calculation to the malignancies observed only after the clinical diagnosis of

214 acromegaly.

215 Overall, SIR for all cancers was increased compared to the general Italian population (SIR 1.41; 95%CI,

216 1.18-1.68, p<0.001). In the whole series, we found a significantly increased incidence of colorectal cancer

217 (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

218 cancer (SIR 3.99; 95% CI, 2.32-6.87, p<0.001). We assessed the SIRs of different cancer types in the female

219 and male gender, respectively (Table 4). In female patients, incidence of all malignancies was increased (SIR

220 1.51; 95% CI, 1.20-1.91, p<0.001), as it was incidence of thyroid cancer, colorectal cancer, and breast

221 cancer. In male patients, incidence of all malignancies was increased (SIR 1.29; 95% CI, 1.0-1.7, p=0.06), as

222 it was incidence of thyroid cancer, kidney cancer, and colorectal cancer.

223 The analysis of the malignancies observed only after the clinical diagnosis of acromegaly confirmed an

224 increased SIR for all cancer in the overall population (SIR 1.28; 95%CI, 1.07-1.55, p=0.007). All the

225 prevalent malignancies were observed in female patients; however, the incidence of all malignancies was

226 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,

227 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

228 general female population.

229 A comparable number of patients with or without cancer were submitted to proactive oncologic screening as

230 part of their management (65% in patients with cancer vs. 60% in patients without cancer).

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231   Predictive factors of cancer were analyzed in univariate analysis (age, gender, duration of acromegaly before

232   diagnosis, presence of diabetes, active disease at last follow-up, GH/IGF-I at baseline and last follow-up,

233   pituitary radiotherapy, family history of cancer). Factors significantly associated with an increased risk of

234   cancer were age, family history of cancer, disease duration before diagnosis, presence of diabetes and

235   previous pituitary radiotherapy. Pertinently, we observed only 3 cases of brain cancer. In multivariable

236   analysis, factors significantly associated with an increased risk of cancer were age and family history of

237   cancer, while there was a non-significant trend for duration of acromegaly (Table 5).

238

239 **DISCUSSION**

240

241 Whether acromegaly is associated with increased risk of cancer remains an endless debate. In general, case-

242 control studies focusing on a specific tumor type produced more homogeneous figures, as demonstrated by a

243 meta-analysis of colonoscopy-based studies (Rokkas *et al.* 2008). Since case-control studies may lead to

244 overestimation of risk due to ascertainment bias and problems related to matching with specific patient

245 groups, the "well-worried" bias, it has been suggested that population-based studies are more appropriate for

246 assessing cancer risk (Renehan & Brennan 2008).

247 However, population-based studies produced discrepant data for a number of reasons. First, due to the rarity

248 of acromegaly only nationwide surveys may have adequate statistical power. Second, coverage and accuracy

249 of national cancer registries, as well as duration and completeness of follow-up, are keys for an adequate

250 comparison with the general population. Third, the retrospective nature of these studies is an obvious

251 limitation, particularly when considering that some studies date back to the sixties (Wright *et al.* 1970,

252 Alexander *et al.* 1980), when treatment of acromegaly was far less effective. As a consequence, patients with

253 uncontrolled acromegaly may have died before entering the age when cancer usually occurs; thus,

254 competitive cardiovascular morbidity may have hindered cancer incidence and, particularly, cancer mortality

255 (Loeper & Ezzat 2008, Boguszewski & Ayuk 2016).

256 The aim of the present study was to evaluate the incidence of cancer in a series of 1512 acromegalic patients

257 followed up for 10 years at 24 tertiary referral centers in Italy. Most patients were treated after the

258 introduction of SRL in clinical practice, thus representing a modern series. We found that the overall

259 incidence of cancer was increased compared to the general population with a SIR of 1.41 (95%CI, 1.18-

260 1.68). The excess risk is only moderate and this may explain why less powered studies produced

261 controversial findings. Since acromegaly is usually recognized many years after its biological onset, we

262 included in the analysis the malignancies diagnosed within a period of 5 years prior to the clinical diagnosis

263 of acromegaly, to account for the long period of exposure to excess GH and IGF-I preceding the diagnosis.

264 Even if malignancies detected during this time span are considered formally as prevalent, they occur under

265 the influence of hormone excess that is present albeit undiagnosed. Pertinently, a recent survey in Denmark

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266   identified increased morbidity over the 3 years preceding diagnosis of acromegaly (Dal et al., 2016).

267   However, we also did a separate analysis including only the malignancies diagnosed after the clinical

268   diagnosis of acromegaly to provide a more conservative estimate of the risk. The results of this analysis

269   overall confirmed an excess cancer risk with the exception of breast cancer.

270   Only three studies in the literature have a size comparable to the present one, but only two were nationwide

271   surveys. Ron et al. (Ron *et al.* 1991) analyzed a cohort of 1041 male inpatients with acromegaly in the US

272   and found an increased incidence compared to non-acromegalic hospitalized patients, who served as controls

273   (SIR, 1.6; 95% CI, 1.3-1.9). This increased risk was mainly attributable to gastrointestinal cancers, in

274   particular colon cancer. However, the study may be criticized for the inclusion of only male patients

275   admitted to hospital and for not having used tumor incidence rates of the general population as reference

276   (Loeper & Ezzat 2008). Orme et al. (Orme *et al.* 1998) made a large epidemiological study in the UK,

277   analyzing a cohort of 1239 subjects with acromegaly, and found that the risk for all malignancies was

278   reduced compared to the general population (SIR, 0.76; 95% CI, 0.60-0.95), although there was a non-

279   significant increase in the incidence of colon cancer (SIR, 1.68; P=0.06). However, they excluded

280   approximately 17% of cancer registrations that occurred before the diagnosis of acromegaly. Since the

281   diagnosis of acromegaly is usually made years after its biological onset, excluding such cases may cause an

282   underestimation of the phenomenon (Loeper & Ezzat 2008, Boguszewski & Ayuk 2016). Baris et al. (Baris

283   *et al.* 2002) made an epidemiological study in Sweden and Denmark, analyzing a cohort of 1634 patients,

284   and found an increased risk for all malignancies (SIR, 1.5; 95% CI, 1.3-1.8), in particular of the digestive

285   tract.

286   More recently, three smaller studies have been published that provided controversial results. Kauppinen-

287   Makelin et al. (Kauppinen-Makelin *et al.* 2005), in a nation-wide survey in Finland, analyzed 334 patients

288   and found an increased cancer incidence (SIR, 1.5; 95% CI, 1.1-1.9). Due to the low number of events, it

289   was impossible to make stratification per cancer type, but colon and thyroid cancer were the most frequently

290   observed. Petroff et al. (Petroff *et al.* 2015) analyzed 446 patients from the German Acromegaly Registry

291   and found that cancer incidence was non-significantly lower than the general population (SIR, 0.75; 95% CI,

292   0.55-1.00). They found a two times higher incidence of thyroid cancer in acromegalic patients that was not

293   significant due to the low number of events. However, the study has limits in representing only a sample of

13

294 the German Acromegaly Registry and in the methodology used to ascertain cancer registration, which was

295 not always based on referring to medical records but included also phone interview. Moreover, 16% of

296 patients were lost to follow-up. Cheng et al. (Cheng *et al.* 2015) reported on 408 acromegalic patients

297 followed at 3 referral centers in Canada and found that cancer incidence was higher than in the general

298 population (OR, 2.87; 95% CI, 1.57-5.25). In this cohort, diabetes was associated to the risk of malignancy.

299 The present study has strengths in the large population sample and long follow-up with all cancer

300 registrations confirmed by the physicians who proactively managed the patients. Our study cohort was

301 collected in many referral centers; thus it is representative of the acromegalic population in Italy. It is also

302 representative of a cohort treated in a modern way as demonstrated by the overall mortality data (Arosio *et*

303 *al.* 2012) in a range comparable to those observed in more recent studies (Katznelson *et al.* 2014, Sherlock *et*

304 *al.* 2010, Mercado *et al.* 2014). Our findings on cancer incidence are in close agreement with the nationwide

305 survey in Finland (Kauppinen-Makelin *et al.* 2005) that was done in the same time period (SIR of the present

306 study, 1.41; SIR of the Finnish study, 1.5). The outcome of the German study (Petroff *et al.* 2015), which is

307 also a contemporary series, is at variance but the above-mentioned differences in study methodology may

308 explain the discrepancy.

309 Due to our large sample size, we were able to consider separately cancer incidence between sexes and make

310 a meaningful stratification of different cancer types. Risk of cancer was higher in women (SIR 1.51; 95% CI,

311 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

312 older in our series. Cancers found to be more consistently increased were thyroid cancer, kidney cancer and

313 colorectal cancer. These findings are consistent with abundant evidence linking the IGF system with

314 development and progression of all these cancers (Loeper & Ezzat 2008, Pollak 2008, Weroha & Haluska

315 2012, Brahmkhatri *et al.* 2015, Renehan *et al.* 2004, Clayton *et al.* 2011, Giovannucci *et al.* 2000, Pekic &

316 Popovic 2013).

317 The increased risk of colon neoplasia in acromegaly is the most widely agreed; thus, the Endocrine Society

318 Guidelines suggested incorporating colonoscopy at diagnosis in the management of acromegaly-related

319 comorbidities (Katznelson *et al.* 2014). Higher risk of breast cancer has been reported in an old study

320 (Nabarro 1987), while recent studies found only non-significant increase in risk (Baris *et al.* 2002,

321 Kauppinen-Makelin *et al.* 2005, Petroff *et al.* 2015). However, assessing the prevalence in acromegaly of

322   breast cancer is particularly challenging since it may be looked at only in women, thus substantially halving

323   the sample size. In addition, IGF-I excess could have different effects depending on the menopausal state,

324   and on the levels of other sex and growth hormones, further increasing complexity (Renehan *et al.* 2004,

325   Tworoger *et al.* 2011). In recent reports, there is increasing evidence that thyroid cancer is more frequent in

326   patients with acromegaly than in control groups (Wolinski *et al.* 2014). A recent cross-sectional prospective

327   study in Spain found that either benign nodular thyroid disease or thyroid cancer were more frequent in 123

328   patients with acromegaly than in 50 matched controls applying highly sensitive ultrasound methodology and

329   standardized use of FNA cytology (Reverter *et al.* 2014). Conversely, the association between acromegaly

330   and kidney cancer has been less frequently reported (Cheung & Boyages 1997, Baris *et al.* 2002, Kauppinen-

331   Makelin *et al.* 2005). Interestingly, expression of the IGF-I receptor has been associated with poor survival in

332   patients with early-stage renal cancer (Parker *et al.* 2004).

333   The present study is the first to provide a multivariate analysis aiming at identifying predictors of cancer in

334   acromegaly. We found that age and family history of cancer were significant independent factors associated

335   to cancer risk, and these findings are biologically plausible. Moreover, a non-significant trend between

336   cancer risk and delay in acromegaly diagnosis was apparent, but it is known that the estimate of duration of

337   acromegaly is admittedly imprecise and operator dependent. We did not find evidence of an association

338   between values of GH and IGF-I, or both, and cancer risk. Orme et al. (Orme *et al.* 1998) found a higher

339   cancer-related mortality in patients with elevated post-treatment GH but no clear link between GH and IGF-I

340   levels and cancer incidence in acromegaly has been definitively proven. This does not discredit the view that

341   GH and IGF-I are implicated in cancer development in acromegaly. It has to be pointed out that the

342   hormonal evaluation at diagnosis or at the last follow-up may give only a poor estimate of patient's exposure

343   to GH and IGF-I in the course of a chronic disease such as acromegaly. Moreover, other factors may play

344   important roles in determining the risk of neoplasia in acromegaly, such as insulin, insulin resistance, IGF-

345   BP1 and BP3, obesity, body composition and leptin levels (Melmed 2001, Boguszewski & Ayuk 2016,

346   Giovannucci *et al.* 2000, Pekic & Popovic 2013, Tworoger *et al.* 2011). In this line, it is interesting the

347   finding of Cheng et al. (Cheng *et al.* 2015) that acromegalic patients with diabetes had more malignant

348   tumors than non-diabetic patients. In our cohort, diabetes was associated with cancer risk only in univariate

349   analysis. The alternative hypothesis that cancer risk in acromegaly is due to common underlining genetic

350   factors should be also considered (Loeper & Ezzat 2008, Boguszewski & Ayuk 2016, Renehan & Brennan

351   2008).

352   Limitations of our study are its retrospective nature, as for previous epidemiological studies, the consequent

353   lack of data on the cumulative GH exposure, that has been recently suggested as a very important

354   determinant of morbidity and mortality (Varadhan *et al.* 2016), and the fact that patients have been submitted

355   in many centers to proactive oncologic screening, since previous studies conducted in Italy have suggested

356   an association between acromegaly and colon neoplasia (Terzolo *et al.* 2005) or thyroid cancer (Gasperi *et*

357   *al.* 2002, Tita *et al.* 2005). However, the rate of patients who underwent cancer screening was alike between

358   patients with and without cancer; thus, it is unlikely that our findings are explained by an ascertainment bias.

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

360   nation-wide survey in Italy.

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REFERENCES

373

Alexander L, Appleton D, Hall R, RossWM & Wilkinson R 1980 Epidemiology of acromegaly in the Newcastle region. *Clin Endocrinol (Oxf)* **12** 71–79.

Arosio M, Reimondo G, Malchiodi E, Berchialla P, Borraccino A, De Marinis L, Pivonello R, Grottoli S, Losa M, Cannavo` S, *et al.* 2012 Predictors of morbidity and mortality in acromegaly: an Italian survey. *Eur J Endocrinol.* **167** 189–198.

Ayuk J, Clayton RN, Holder G, Sheppard MC, Stewart PM & Bates AS 2004 Growth hormone and pituitary radiotherapy, but not serum insulin-like growth factor-1 concentrations, predict excess mortality in patients with acromegaly. *J Clin Endocrinol Metab.* **89** 1613–1617.

Bałdys-Waligórska A, Krzentowska A, Gołkowski F, Sokołowski G & Hubalewska-Dydejczyk A 2010 The prevalence of benign and malignant neoplasms in acromegalic patients. *Endokrynol Pol.* **61** 29-34.

Baris D, Gridley G, Ron E, Weiderpass E, Mellemkjaer L, Ekbom A, Olsen JH, Baron JA & Fraumeni JF Jr. 2002 Acromegaly and cancer risk: a cohort study in Sweden and Denmark. *Cancer Causes Control* **13** 395–400.

Barzilay J, Heatley GJ & Cushing GW 1991 Benign and malignant tumors in patiens with acromegaly. *Arch Intern Med* **151** 1629–1632

Bengtsson BA, Eden S, Ernest I, Oden A & Sjogren B 1988. Epidemiology and long-term survival in acromegaly. A study of 166 cases diagnosed between 1955 and 1984. *Acta Med Scand* **223** 327–335

Biermasz NR 2014 Pituitary gland: mortality in acromegaly reduced with multimodal therapy. *Nat Rev Endocrinol.* **10** 708-710.

393   Bogazzi F, Colao A, Rossi G, Lombardi M, Urbani C, Sardella C, Cannelli A, Scattina I, Manetti L, Del

394   Sarto S, *et al.* 2013 Comparison of the effects of primary somatostatin analogue therapy and pituitary

395   adenomectomy on survival in patients with acromegaly: a retrospective cohort study. *Eur J Endocrinol.*

396   **169** 367–376.

397   Boguszewski CL & Ayuk J 2016 Acromegaly and cancer risk: an old debate revisited. *Eur J*

398   *Endocrinol.* 175 147-156

399   Brahmkhatri VP, Prasanna C & Atreya HS 2015 Insulin-like growth factor system in cancer: novel

400   targeted therapies. *Biomed Res Int.* **2015** 538019.

401   Cheng S, Gomez K, Serri O, Chik C & Ezzat S 2015The role of diabetes in Acromegaly Associated

402   Neoplasia *PLoS One*; **10** e0127276.

403   Cheung NW & Boyages SC 1997 Increased incidence of neoplasia in females with acromegaly. *Clin*

404   *Endocrinol (Oxf)* **47** 323–327.

405   Clayton PE, Banerjee I, Murray PG & Renehan AG 2011 Growth hormone, the insulin-like growth

406   factor axis, insulin and cancer risk. *Nat Rev Endocrinol.* **7** 11-24.

407   Dagdelen S, Cinar N & Erbas T 2014 Increased thyroid cancer risk in acromegaly. *Pituitary*. **17** 299–

408   306.

409   Dal J, Feldt-Rasmussen U, Andersen M, Kristensen LØ, Laurberg P, Pedersen L, Dekkers OM, Sørensen

410   HT, Jørgensen JO. *Eur J Endocrinol.* 2016 **175** 181–190

411   Gasperi M, Martino E, Manetti L, Arosio M, Porretti S, Faglia G, Mariotti S, Colao AM, Lombardi G,

412   Baldelli R, *et al.* 2002 Prevalence of thyroid diseases in patients with acromegaly: results of an Italian

413   multi-center study. *J Endocrinol Invest* **25** 240–245.

414   Giovannucci E, Pollak MN, Platz EA, Willett WC, Stampfer MJ, Majeed N, Colditz GA, Speizer FE &

415   Hankinson SE 2000 A prospective study of plasma insulin-like growth factor-1 and binding protein-3

416   and risk of colorectal neoplasia in women. *Cancer Epidemiol Biomarkers Prev.* **9** 345–349.

417   Gullu BE, Celik O, Gazioglu N & Kadioglu P 2010 Thyroid cancer is the most common cancer

418   associated with acromegaly. *Pituitary*. **13** 242–248.

419   Higuchi Y, Saeki N, Iuchi T, Uchino Y, Tatsuno I, Uchida D, Tanaka T, Noguchi Y, Nakamura S,

420   Yasuda T, *et al.* 2000 Incidence of malignant tumors in patients with acromegaly. *Endocr J* **47** (Suppl)

421   57–60.

422   Holdaway IM, Rajasoorya RC & Gamble GD 2004. Factors influencing mortality in acromegaly. *J Clin*

423   *Endocrinol Metab*. **89** 667–674.

424   Katznelson L, Laws ER Jr, Melmed S, Molitch ME, Murad MH, Utz A & Wass J 2014 Acromegaly: an

425   Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* **99** 3933-3951.

426   Kauppinen-Mäkelin R, Sane T, Välimäki MJ, Markkanen H, Niskanen L, Ebeling T, Jaatinen P, Juonala

427   M; Finnish Acromegaly Study Group, Pukkala 2010 Increased cancer incidence in acromegaly--a

428   nationwide survey. *Clin Endocrinol*. **72** 278–279.

429   Kurimoto M, Fukuda I, Hizuka N & Takano K 2008 The prevalence of benign and malignant tumors in

430   patients with acromegaly at a single institute. *Endocr J*. **55** 67–71.

431   Liddell FD 1984 Simple exact analysis of the standardised mortality ratio. *J Epidemiol Community*

432   *Health*. **38** 85-8.

433   Loeper S & Ezzat S 2008 Acromegaly: re-thinking the cancer risk. *Rev Endocr Metab Disord*. **9** 41–58.

434   Maione L, Brue T, Beckers A, Delemer B, Petrossians P, Borson-Chazot F, Chabre O, François P,

435   Bertherat J, Cortet-Rudelli C, Chanson P; French Acromegaly Registry Group. Changes in the

436   management and comorbidities of acromegaly over three decades: the French Acromegaly Registry. *Eur*

437   *J Endocrinol*. 2017 **176** 645-655

438   Melmed S 2001 Acromegaly and cancer: not a problem? *J Clin Endocrinol Metab*. **86** 2929-2934.

439   Melmed S 2009 Acromegaly pathogenesis and treatment. *J Clin Invest*. **119** 3189-3202.

440   Mercado M, Gonzalez B, Vargas G, Ramirez C, De los Monteros AL, Sosa E, Jervis P, Roldan P,

441   Mendoza V, Lopez-Félix B, *et al*. 2014 Successful mortality reduction and control of comorbidities in

442   patients with acromegaly followed at a highly specialized multidisciplinary clinic. *J Clin Endocrinol*

443   *Metab*. **99** 4438-4446.

444   Mustacchi P & Shimkin MB 1957 Occurrence of cancer in acromegaly and in hypopituitarism. *Cancer*

445   **10** 100–104.

446   Nabarro JD 1987 Acromegaly. *Clin Endocrinol. (Oxf)* **26** 481–512.

447   Orme SM, McNally RJ, Cartwright RA & Belchetz PE 1998 Mortality and cancer incidence in

448   acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. *J Clin Endocrinol*

449   *Metab*. **83** 2730–2734.

450   Parker AS, Cheville JC, Blute ML, Igel T, Lohse CM & Cerhan JR 2004 Pathologic T1 Clear Cell Renal

451   Cell Carcinoma: Insulin-Like Growth Factor-I Receptor Expression and Disease-Specific Survival.

452   *Cancer* **100** 2577–82.

453   Pekic S & Popovic V 2013 GH therapy and cancer risk in hypopituitarism: what we know from human

454   studies. *Eur J Endocrinol.* **169** R89–R97.

455   Petroff D, Tönjes A, Grussendorf M, Droste M, Dimopoulou C, Stalla G, Jaursch-Hancke C, Mai M,

456   Schopohl J & Schöfl C 2015 The Incidence of Cancer Among Acromegaly Patients: Results From the

457   German Acromegaly Registry. *J Clin Endocrinol Metab*. **100** 3894-902.

458   Pines A, Rozen P, Ron E & Gilat T 1985 Gastrointestinal tumors in acromegalic patients. *Am J*

459   *Gastroenterol*. **80** 266–269.

460   Pollak M 2008 Insulin and insulin-like growth factor signalling in neoplasia. *Nat Rev Cancer* **8** 915-928.

461   Popovic V, Damjanovic S, Micic D, Nesovic M, Djurovic M, Petakov M, Obradovic S, Zoric S, Simic

462   M, Penezic, *et al.* 1998 Increased incidence of neoplasia in patients with pituitary adenoma. The

463   Pituitary Study Group. *Clin Endocrinol* (*Oxf)* **49** 441–445.

464   Rajasoorya C, Holdaway IM, Wrightson P, Scott DJ & Ibbertson HK 1994 Determinants of clinical

465   outcome and survivial in acromegaly. *Clin Endocrinol (Oxf)* **41** 95–102.

466   Renehan AG & Brennan BM 2008 Acromegaly, growth hormone and cancer risk. Best practice,

467   research. *Clinical endocrinology, metabolism* **22** 639–657.

468   Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM & Egger M 2004 Insulin-like growth

469   factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis.

470   *Lancet* **363** 1346-1353.

471   Reverter JL, Fajardo C, Resmini E, Salinas I, Mora M, Llatjós M, Sesmilo G, Rius F, Halperin I, Webb

472   SM, *et al.* 2014 Benign and malignant nodular thyroid disease in acromegaly. Is a routine thyroid

473   ultrasound evaluation advisable? *PlosOne* **9** e104174.

474   Rokkas T, Pistiolas D, Sechopoulos P, Margantinis G & Koukoulis G 2008 Risk of colorectal neoplasm

475   in patients with acromegaly: a meta-analysis. *World J Gastroenterol.* **14** 3484–3489.

476   Ron E, Gridley G, Hrubec Z, Page W, Arora S & Fraumeni Jr JF 1991 Acromegaly and gastrointestinal

477   cancer. *Cancer* **68** 1673–1677.

478   Sherlock M, Ayuk J, Tomlinson J, Toogood AA, Aragon-Alonso A, Sheppard MC, Bates AS & Stewart

479   PM 2010 Mortality in patients with pituitary disease. *Endo Rev* **31** 301-342.

480   Terzolo M, Reimondo G, Gasperi M, Cozzi R, Pivonello R, Vitale G, Scillitani A, Attanasio R, Cecconi

481   E, Daffara F *et al.* 2005 Colonoscopic screening and follow-up in patients with acromegaly: a

482   multicenter study in Italy. *J Clin Endocrinol Metab.* **90** 84-90.

483   Tita P, Ambrosio MR, Scollo C, Carta A, Gangemi P, Bondanelli M, Vigneri R, degli Uberti EC &

484   Pezzino V 2005 High prevalence of differentiated thyroid carcinoma in acromegaly. *Clin Endocrinol*

485   *(Oxf).* **63(2)** 161-167.

486   Tworoger SS, Rosner BA, Willett WC & Hankinson SE 2011 The combined influence of multiple sex

487   and growth hormones on risk of postmenopausal breast cancer: a nested case-control study. *Breast*

488   *Cancer Res.* **13** R99.

489   Varadhan L, Reulen RC, Brown M & Clayton RN 2016 The role of cumulative growth hormone

490   exposure in determining mortality and morbidity in acromegaly: a single centre study. *Pituitary* **19** 251-

491   261.

492   Weroha SJ & Haluska P 2012 The insulin-like growth factor system in cancer. *Endocrinol Metab Clin*

493   *North Am.* **41** 335–350.

494   Wolinski K, Czarnywojtek A & Ruchala M 2014 Risk of Thyroid Nodular Disease and Thyroid Cancer

495   in Patients with Acromegaly – Meta-Analysis and Systematic Review. *PlosOne* **9** e8878.

496   Wright AD, Hill DM, Lowy C & Fraser TR 1970 Mortality in acromegaly. *Quarterly Journal of*

497   *Medicine* **39** 1–16.

1   **FIGURE LEGENDS**

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

Table 1 – Cancer incidence data in studies with more than 200 patients.

Author, year	Study Period	Patients (n°)	Follow-up (years or person years)	Age at diagnosis	CANCER n°, (%)	SIR 95% CI	P value
Ron, 1991	1969-1985	1041*	8619	NA	89 (8.5)	1.6 1.3-1.9	NA
Orme, 1998	1958-1995	1239	16778	NA	79 (6.4)	0.76 0.60-0.95	1
Popovic, 1998	1992-1998	220	4.5	49.5	23 (10.5)	3.39 2.12-5.12	<0.01
Baris, 2002	1965-1993	1634*	14724	50.4	177 (10.8)	1.5 1.3-1.8	NA
Kauppien-Makelin, 2010	1980-2006	333	10.7	47.5	48 (14.4)	1.5 1.1-1.9	NA
Petroff, 2015	NA	374	6656	45.7	44 (11.8)	0.75 0.55-1.00	0.051
Cheng, 2015	NA	408	10.2	43.2	55 (13.4)	2.87 1.57-5.25	NA
Dal, 2016	1991-2010	405	10.6	48.7	NA	1.4 0.9-2.2	NA
Maione, 2017	1977-2012	999	6728	43 men 48.5 women	94 (10.1%)	1.34 (0.94–1.87) men 1.24 (0.77–1.73) women	NA

*Hospitalized patients

NA=Not Available

Table 2 – Cancer mortality data in studies with more than 150 patients

Author, year	N.	Follow-up Duration (years or person/years)	Age at death	Overall SMR	Cancer-related SMR (95% CI)	P value
Nabarro 1987	256	20	NA	1.26	0.96 (NA)	NA
Bengtsson 1988	166	30	NA	NA	Overall: 2.68 Female: 3.3 (NA)	<0.01
Rajasoorya 1994	151	12	57	NA	1 (NA)	NA
Orme 1998	1362	NA	NA	1.6	1.16 (0.92–1.44)	0.1
Ayuk 2004	419	13	NA	1.26	0.91 (0.59-1.39)	0.65
Holdaway 2004	208	13 ± 9	62 ± 2	1.87	0.92 (NA)	NA
Dal, 2016	405	10.6	NA	1.3	1.1 (0.7-1.9)	NA

NA=Not Available, SMR=Standard Mortality Ratio, CI=Confidence Interval

Table 3 – Characteristics of the study population

	Sex		Overall	P value
	Male	**Female**		
Patient number	624	888	1512	
Age, yrs (median [IQR])	42.3 [33.0, 51.7]	47.2 [37.1, 55.2]	46.0 [35.3, 54.0]	<0.001
Disease duration, yrs (median [IQR])	5.0 [2.0, 9.0]	4.5 [2.0, 8.0]	5.0 [3.0, 8.0]	NS
IGF-I at diagnosis, SDS (median [IQR])	8.8 [6.1, 12.5]	8.3 [5.7, 12.0]	8.5 [5.8, 12.3]	NS
IGF-I at FU, SDS (median [IQR])	1.95 [0.33, 4.39]	1.11 [0.04, 2.80]	1.34 [0.11, 3.50]	<0.001
GH at diagnosis, ng/mL (median [IQR])	20.0 [11.0, 40.0]	18.9 [9.25, 35.0]	20.0 [10.0, 36.0]	NS
GH at FU, ng/mL (median [IQR])	2.0 [1.0, 3.7]	2.0 [1.0, 3.8]	2.0[1.0, 3.8]	NS
Disease remission, n. (%)	360 (62.1)	572 (67.5)	932 (65.3)	0.038
Cancer familiarity, n. (%)	136 (29.9)	216 (33.9)	352 (32.2)	NS
Diabetes, n. (%)	106 (17.0)	139 (15.6)	245 (16.2)	NS
Radiotherapy, n. (%)	103 (16.5)	166 (18.7)	269 (17.8)	NS
Cancer, n. (%)	52 (8.3%)	72 (8.1%)	124 (8.2%)	NS

IQR=Interquartile range, SDS=Standard Deviation Score, NS=Not Significant

Table 4 – Cancer incidence data broken down by gender

Cancer type	Observed	Expected	SIR	95% CI	p-value
Female					
All malignancies	72	47.6	1.51	1.2-1.91	<0.001
Breast cancer	22	16.8	1.31	0.86-1.99	0.21
Colorectal cancer	12	6.4	1.86	1.06-3.28	0.03
Thyroid cancer	8	2.5	3.22	1.61-6.44	0.01
Male					
All malignancies	52	40.2	1.29	1.0-1.7	0.06
Colorectal cancer	8	5.6	1.44	0.72-2.88	0.31
Kidney cancer	7	1.9	3.73	1.78-7.83	<0.001
Thyroid cancer	5	0.8	6.51	2.71-15.65	<0.001
Overall					
Colorectal cancer	20	12	1.67	1.07-2.58	0.022
Kidney cancer	10	3.5	2.87	1.55-5.34	<0.001
Thyroid cancer	13	3.3	3.99	2.32-6.87	<0.001

SIR=Standard Incidence Ratio, CI=Confidence Interval

Table 5 – Predictive factors of cancer in multivariable analysis.

Factor	OR	P value
Age	5.39 CI 95%: 2.08 – 13.9	< 0.001
Family history of cancer	1.73 CI 95%: 1.03 – 2.92	0.04
Disease duration	1.27 CI 95%: 0.97 – 1.64	0.08
Pituitary radiotherapy	1.76 CI 95%: 0.89 – 3.45	0.10
Diabetes	1.39 CI 95%: 0.76 – 2.57	0.28
Gender	1.19 CI 95%: 0.69 – 2.05	0.51
IGF-I at last visit	1.03 CI 95%: 0.76 – 1.38	0.87

OR=Odds Ratio, CI=Confidence Interval

For continuous variables, OR are reported for an interquartile range increase, i.e. 19 years of difference for age and 1.5 SDS for IGF-I

Figure 1
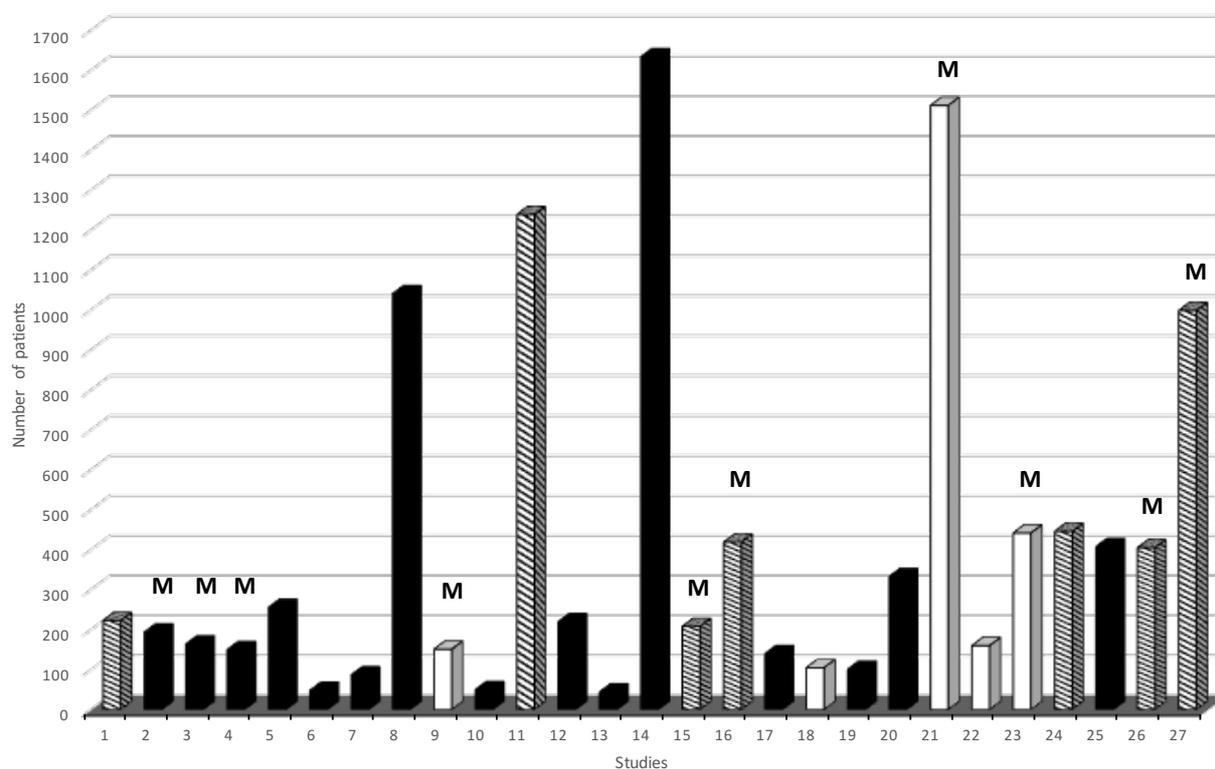
Black bars indicate studies showing a positive association between acromegaly and cancer, striped bars negative studies, and white bars studies that do not conclude whether an association is either present or not. Studies focusing on mortality only are marked by the letter M.

References for the studies are as follows: 1= (Mustacchi & Shimkin 1957), 2= (Wright et al. 1970), 3= (Alexander et al. 1980), 4 = (Bengtsson et al. 1988), 5= (Nabarro 1987), 6= (Pines et al 1985), 7= (Barzilay et al 1991), 8= (Ron et al 1991), 9= (Rajasoorya et al 1994), 10= (Cheung & Boyages 1997), 11= (Orme et al 1998), 12= (Popovic et al 1998), 13= (Higuchi et al 2000), 14= (Baris et al 2002), 15= (Holdaway et al 2004), 16= (Ayuk et al 2004), 17= (Kurimoto et al 2008), 18= (Gullu et al 2010), 19= (Bałdys-Waligórska et al 2010), 20= (Kauppinen-Makelin et al 2010), 21= (Arosio et al 2012), 22= (Dagdelen et al 2014), 23= (Mercado et al 2014), 24= (Petroff et al 2015), 25= (Cheng et al 2015), 26= (Dal et al 2016), 27= (Maione et al. 2017)