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COLORECTAL CANCER

Risk of colorectal neoplasm in patients with acromegaly: A meta-analysis

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Abstract

AIM: To examine the risk of colorectal neoplasm in acromegalic patients by meta-analyzing all relevant controlled studies.

METHODS: Extensive English language medical literature searches for human studies, up to December 2007, were performed using suitable keywords. Pooled estimates [odds ratio (OR) with 95% confidence intervals (CI)] were obtained using either the fixed or random-effects model as appropriate. Heterogeneity between studies was evaluated with the Cochran *Q* test whereas the likelihood of publication bias was assessed by constructing funnel plots. Their symmetry was estimated by the adjusted rank correlation test.

RESULTS: For hyperplastic polyps the pooled ORs with 95% CI were 3.557 (2.587-4.891) by fixed effects model and 3.703 (2.565-5.347) by random effects model. The *Z* test values for overall effect were 7.81 and 6.984, respectively ($P < 0.0001$). For colon adenomas the pooled ORs with 95% CI were 2.486 (1.908-3.238) (fixed effects model) and 2.537 (1.914-3.364) (random effects model). The *Z* test values were 6.747 and 6.472, respectively ($P < 0.0001$). For colon cancer the pooled OR with 95% CI was identical for both fixed and random effects model (OR, 4.351; 95% CI, 1.533-12.354; $Z = 2.762$, $P = 0.006$). There was no significant heterogeneity and no publication bias in all the above meta-analyses.

CONCLUSION: Acromegaly is associated with an increased risk of colorectal neoplasm.

Key words: Acromegaly; Colon cancer; Colon polyps; Colon neoplasia; Meta-analysis

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INTRODUCTION

Acromegaly is a disease caused by excess secretion of growth hormone (GH), which is characterized by enlarged acral parts, coarse facial features, and visceromegaly. Acromegalic patients have a reduced life expectancy primarily due to cardiovascular, respiratory or cerebrovascular disease[1-5]. Acromegalics may also be at an increased risk for malignancies in several systems including the digestive tract, brain, kidney, breast and prostate[6-10]. Colon cancer incidence[6,7,10] and mortality rates[9] have been reported to be higher in acromegalics than expected. However, reported relative risks of colorectal cancer vary significantly depending on the study population and the study design. Moreover, the reported higher indices of colorectal neoplasia in acromegalics have not been a universal finding[11-13]. The main aim of this meta-analysis, therefore, was to examine the pooled risk of colorectal neoplasia (polyps and cancer) in acromegalic patients by meta-analyzing all relevant controlled studies. Secondary aims were to explore the possibility of heterogeneity between studies and to look for the existence of publication bias. This study is justified by the fact that, so far, no meta-analysis has been published examining the relationship between acromegaly and colorectal neoplasia.

MATERIALS AND METHODS

Data identification and extraction

We searched the MEDLINE/PUBMED and EMBASE databases up to December 2007 to identify all relevant English language medical literature for human studies under the search text terms; acromegaly AND (colon cancer OR colon polyps OR colorectal cancer OR colorectal polyps). We also performed a full manual search of all review articles, published editorials and of retrieved original studies. Data from each study were extracted independently by two authors (T.R and D.P) by using a predefined form, and disagreements were resolved by discussion and consensus.

Selection criteria

Inclusion and exclusion criteria were delineated before the commencement of the literature search. Thus, eligible studies published as full articles were included in this meta-analysis if they met all of the following criteria: (1) written in the English language, (2) published as full articles and (3) a simultaneous control group was included.

Studies not meeting the aforementioned criteria, and in addition studies without data for retrieval, studies using historical control patients or autopsy data and duplicate publications were excluded. When two papers reported the same study the publication that was more informative was selected.

Statistical analysis

Agreement in the selection of studies between the 2 reviewers was evaluated by the κ coefficient. We calculated the pooled odds ratios (ORs) and 95% confidence intervals (CI) and compared outcomes of individual studies by using the fixed[14] or the random effects model[15] as appropriate. Forest plots were constructed for visual display of OR (95% CI) of individual studies and pooled data. Heterogeneity between studies was evaluated with the Cochran Q test[16] and it was considered to be present if the Q test provided a P value of less than 0.10[16,17]. In the presence of significant statistical heterogeneity, sensitivity analyses were performed to search for the possible sources, such as sample size of each study, *etc*. These analyses were achieved by repeating the meta-analyses with exclusion of each individual study one at a time, in order to assess the overall effect of each study on the pooled ORs[18]. This indicates which particular studies are most influential and might help in the evaluation of the possibility that the conclusions result from the influence of a particular study. The likelihood of publication bias was assessed by constructing funnel plots[18] and their symmetry was estimated by the Begg and Mazumdar adjusted rank correlation test[19].

All meta-analyses, sensitivity and meta-regression analyses in this study were performed by using suitable meta-analysis software (Comprehensive Meta Analysis-Version 2, Biostat Inc, Englewood, NJ, USA).

Role of funding source

This was an investigator-initiated unfunded study. All authors had access to the data and the statistical analysis report. Each author approved the final article and attests to the validity of the results.

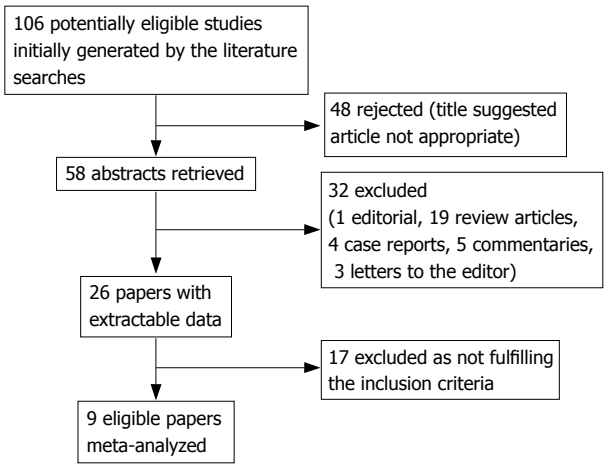

Figure 1 Flow diagram of the studies identified in this meta-analysis.

RESULTS

Descriptive assessment and study characteristics

A flow chart describing the process of study selection is shown in Figure 1. Out of 106 titles initially generated by the literature searches, 48 were rejected as the title suggested that the articles were not appropriate. Of the remaining 58 abstracts, 32 were excluded for not having extractable data (editorials, review articles, case reports, commentaries and letters to the editor). Therefore, 26 papers remained candidates for eligibility. Of these, 17[6,8,9,11-13,20-30] were rejected on the basis of not fulfilling the inclusion criteria. Therefore 9 controlled studies remained eligible for meta-analysis[31-39]. Initial agreement between the reviewers for the selection of relevant articles was high (κ = 0.924, 95% CI, 0.851-0.997).

The main characteristics of the papers eligible for meta-analysis are shown in Table 1. The studies were conducted in different parts of the world; most were single centre studies and included 701 acromegaly patients and 1573 controls.

Colon adenomas

Eight of the nine meta-analyzed studies[31-35,37-39] provided data concerning the frequency of colon adenomas in acromegaly patients and controls [149/641 (23.2%) *vs* 176/1,413 (12.45%)]. The pooled ORs (95%CI), by both the fixed and random effects model, were 2.486 (1.908-3.238) and 2.537 (1.914-3.364), respectively with Z test values for overall effect 6.747 and 6.472, respectively and $P < 0.0001$ for both models (Figure 2). There was no significant heterogeneity ($P = 0.371$) among these trials (Table 2). In addition there was no publication bias (P two tailed value 0.711, Table 2) as shown in the respective funnel plot (Figure 3).

Colon hyperplastic polyps

Seven studies[31,33-38] provided data concerning the

Table 1 The main characteristics of studies selected for meta-analysis

Ref.	1st author, year, country	Acromegaly patients		Control subjects		Type of the study	Control group composition
		n (M/F)	Mean age (range or SD yr)	*n* (M/F)	Mean age (range or SD, yr)		
31	Terzolo, 1994, Italy	31 (11/20)	52.2 (27-85)	236 (127/109)	50.1 (23-84)	Hospital based control study	Patients with rectal bright-red bleeding from hemorrhoids
32	Vasen, 1994, Germany and Holland	49 (30/19)	54 (30-75)	57 (28/29)	54 (34-72)	Hospital based control study	Patients with irritable bowel syndrome
33	Delhougne, 1995, Belgium and France	103 (49/54)	5 (12, SD)	138 (55/83)	53 (15, SD)	Hospital based control study	Patients with irritable bowel syndrome
34	Colao, 1997, Italy	50 (25/25)	20-70	318 (Sex matched)[1]	Age matched[1]	Hospital based control study	Patients with irritable bowel syndrome
35	Martino, 2004, Italy	75 (33/42)	54 (11, SD)	75 (33/42)	55 (10, SD)	Hospital based control study	Patients with irritable bowel syndrome
36	Bhansali, 2004, India	60 (35/25)	37.4 (13.2, SD)	160 (88/72)	38.2 (14, SD)	Hospital based control study	Patients with irritable bowel syndrome
37	Matano, 2005, Japan	19 (11/8)	46.7 (16.3, SD)	76 (44/32)	47.3 (16.5, SD)	Hospital based control study	Randomly selected from subjects referred for colonoscopy
38	Terzolo, 2005, Italy	235 (115/120)	49.1 (12.6, SD)	233 (156/77)	50.8 (12, SD)	Hospital based control study	Consecutive patients with nonspecific abdominal symptoms
39	Bogazzi, 2006, Italy	79 (33/46)	55.0 (11.1, SD)	280 (166/114)	50.9 (10.8, SD)	Hospital based control study	Consecutive donors for kidney or liver transplantation
	Total	701		1573			

[1]Paper did not provide detailed data on patients mean age, control subjects, sex distribution and control subjects age.

Table 2 Heterogeneity and publication bias results of meta-analyzed studies, concerning the three types of colonic lesion examined, i.e. colon adenomas, hyperplastic polyps and colon cancer

Type of colonic lesion	Heterogeneity					Publication bias	
	Number of studies	*Q*-value	df (Q)	I^2	*P* value	Kendall's tau	*P* value (two-tailed)
Adenomatous polyps	8	7.584	7	7.700	0.371	0.143	0.711
Hyperplastic polyps	7	7.447	6	19.433	0.281	0.143	0.764
Cancer	3	1.068	2	0.000	0.586	-0.333	1.000

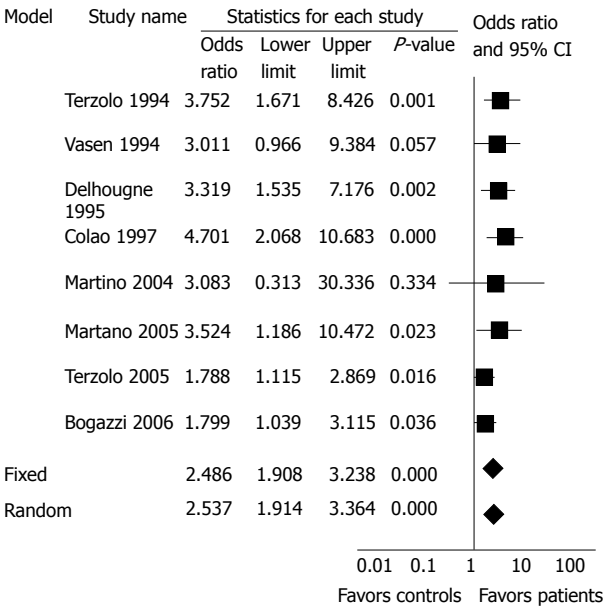

Figure 2 Forest plot showing individual and pooled ORs (95% CIs) and *P* values in studies comparing the colon adenoma prevalence in acromegaly patients and controls.

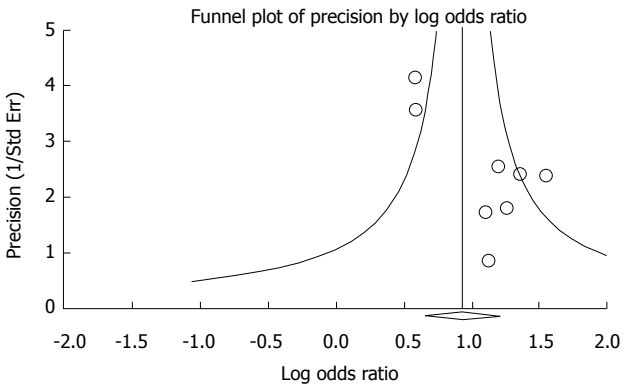

Figure 3 Funnel plot of selected studies examining colon adenoma prevalence in acromegaly patients and controls. No evidence of publication bias found (*P* = 0.711, by adjusted rank correlation test). Similarly no evidence of publication bias was found for the other colon neoplasias studied, i.e. colon hyperplastic polyps and colon cancer (see results, Table 2).

frequency of colon hyperplastic polyps in acromegaly patients and controls [128/573 (22.3%) *vs* 91/1236 (7.36%)]. The pooled OR (95% CI), by both the fixed and random effects model, were 3.557 (2.587-4.891) and 3.703 (2.565-5.347), respectively, with *Z* test values for overall effect 7.81 and 6.984, respectively and $P < 0.0001$ for both models (Figure 4A). There was no significant

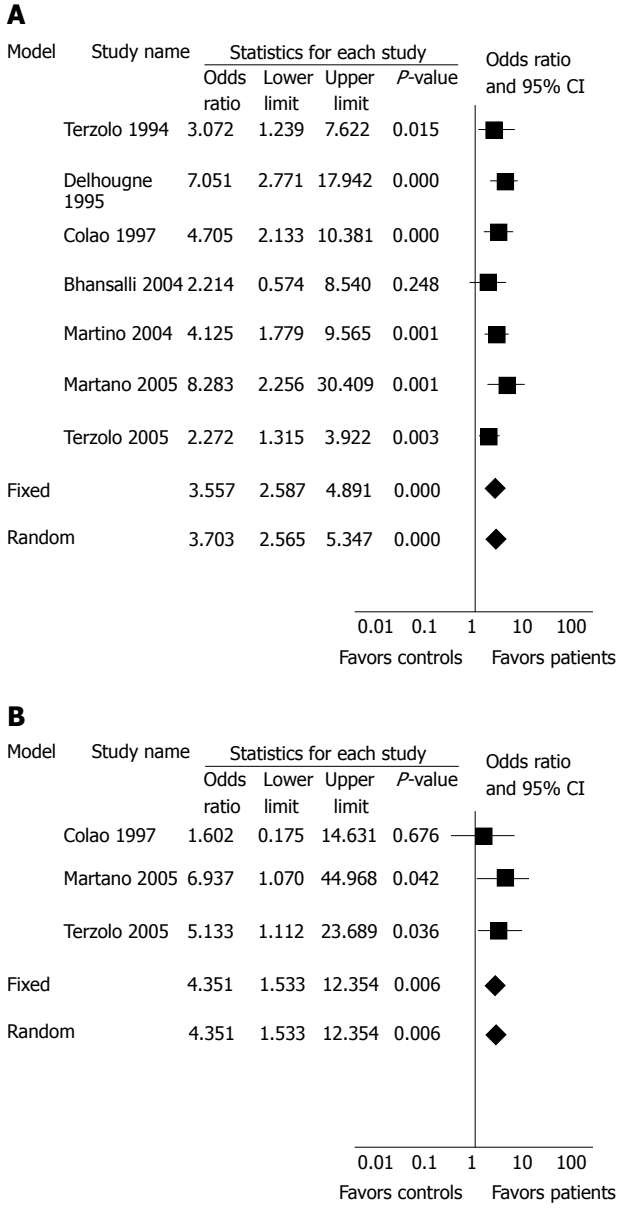

Figure 4 Forest plot showing individual and pooled ORs (95% CIs) and *P* values in studies comparing the colon hyperplastic polyp prevalence (**A**) and the colon cancer prevalence (**B**) in acromegaly patients and controls.

heterogeneity among these trials (P = 0.281) and no publication bias (P = 0.764, Table 2).

Colon cancer

Three studies[34,37,38] provided data concerning the frequency of colon cancer in acromegaly patients and controls [14/304 (4.6%) *vs* 8/627 (1.2%), respectively]. The pooled ORs (95%CI), by both the fixed and random effects model, were identical [4.351 (1.533-12.354) for both] with Z test for overall effect = 2.762 and P = 0.006 (Figure 4B). There was no significant heterogeneity among these trials (P = 0.586) and no publication bias (P = 1).

DISCUSSION

The study on the association between acromegaly and cancer risk has focused primarily on colorectal cancer, but the findings of previous studies are far from conclusive and the matter of colorectal cancer in acromegaly has been debated in the literature[40-44].

The discrepant results in the literature prompted us to undertake a meta-analysis on control trials in order to assess whether patients with acromegaly are at an increased risk of developing colorectal neoplasia, because if this is the case, then in these patients an aggressive approach to endoscopic management should be applied. In addition, our study is justified by the fact that, so far, no meta-analysis has been published examining the relationship between acromegaly and colorectal neoplasia.

The pooled results in this study clearly showed that acromegalic patients are at a significantly increased risk of developing colorectal adenomatous and hyperplastic polyps as well as colorectal cancer compared with controls. This estimate is in agreement with the results of three larger epidemiological studies assessing the risk of colonic cancer in acromegaly[7,9,10]. According to these findings, therefore, it is beyond doubt that a suitable endoscopic approach, with early large bowel endoscopic screening and regular surveillance, is fully justified in acromegaly patients. Needless to say total colonoscopy is essential in acromegaly, as in several studies proximal colon pathology was found[13,33,34]. This requirement is made more difficult by the increased length and capacity of the acromegalic colon[13,42]. To overcome this and the prolonged colonic transit time in acromegalic patients, rigorous bowel preparation, in excess of that usually used, is needed[42].

One possible weakness of this meta-analysis might be the inclusion of underpowered studies of small sizes. Another weakness might be the fact that five of the nine meta-analysed studies come from the same country, i.e. Italy. However, all possible weaknesses are compensated by the lack of heterogeneity among the meta-analysed studies and also by the lack of publication bias.

Why should acromegaly patients be at an increased risk of colorectal neoplasia? The answer to this question is difficult, but it seems that the increased risk for several cancers among acromegaly patients may be due to the elevated proliferative and anti-apoptotic activity associated with increased circulating levels of insulin-like growth factor- I (IGF- I). There is an increasing body of evidence suggesting that adults with high concentrations of IGF- I are at increased risk of colorectal cancer[45-47]. In some of these studies, high IGF binding protein-3 (IGFBP-3) levels were associated with a lower risk of cancer[45,46]. In acromegaly, GH excess increases serum IGF- I and, to a lesser extent, IGFBP-3 concentrations, with the IGF- I to IGFBP-3 ratio being greater as GH concentrations increase[48,49]. Thus, an elevated IGF- I to IGFBP-3 ratio is expected to increase cancer risk in acromegaly[45,50]. On the other hand, IGF- I receptors and mRNAs for IGF- I have been identified in human colorectal cells[51]. IGF- I is a known mitogen that may stimulate, by autocrine and paracrine actions, the proliferation of intestinal epithelial cells and their

migration[52]. In fact, increased proliferation of colonic epithelium, proportional to circulating IGF- I levels, has been demonstrated in acromegaly[53]. Moreover, IGF-I is able to stimulate the growth of colorectal cancer cells *in vitro*, whereas blockade of IGF- I receptors inhibits cell growth in the same model[51,54,55].

In conclusion, this study showed that acromegalic patients are at an increased risk of colorectal adenomatous and hyperplastic polyps as well as colorectal cancer. Therefore, acromegaly should be characterized as a disorder carrying a high risk for the development of colorectal neoplasia where an aggressive approach to endoscopic management with early screening and regular surveillance is justified.

COMMENTS

Background

Patients with acromegaly may be at an increased risk for malignancies in several systems including the digestive tract. However, the reported higher indices of colorectal neoplasia in acromegalics have not been a universal finding.

Research frontiers

We evaluated the risk of colorectal neoplasm in acromegalic patients by meta-analyzing all relevant controlled studies.

Innovations and breakthroughs

We made a comprehensive search of studies dealing with colorectal neoplasm in acromegalic patients. The studies were analyzed to determine the risk of colorectal neoplasm in these patients.

Applications

Based on this evaluation, we concluded that acromegalic patients are at an increased risk of colorectal adenomatous and hyperplastic polyps as well as colorectal cancer. Therefore, acromegaly should be characterized as a disorder carrying a high risk for the development of colorectal neoplasia where an aggressive approach to endoscopic management with early screening and regular surveillance is justified.

Peer review

The authors explored the risk of colorectal neoplasm in acromegalic patients. It was concluded that acromegalic patients are at an increased risk of colorectal adenomatous and hyperplastic polyps as well as colorectal cancer.

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