The risk of colectomy and colorectal cancer after appendectomy in patients with ulcerative colitis

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The risk of colectomy and colorectal cancer after appendectomy in patients with ulcerative colitis: a systematic review and meta-analysis

Short title: Colectomy and colorectal cancer after appendectomy in UC

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Abstract

Background: Appendectomy decreases the risk of developing ulcerative colitis (UC), and is suggested to have a beneficial effect on the clinical course of established UC. However, recent studies showed no significantly decreased colectomy rate, and moreover an apparently increased risk of colorectal cancer (CRC). We aimed to investigate the suggested correlation in a meta-analysis, and analyze possible confounding factors.

Methods: A systematic review and meta-analysis were performed using MEDLINE, EMBASE and the Cochrane library. Data from studies describing the influence of appendectomy on colectomy and CRC were extracted from published reports. Exclusion criteria were patients <18 years, non-UC, and animal studies.

Results: From 891 studies, 13 studies evaluating 73323 UC patients (appendectomy n=2859) were included. All studies, except one, were rated as poor quality. Overall, colectomy rate in appendectomized and non-appendectomized patients was not significantly different (OR 1.25, 95%CI 0.88-1.77, I^2=53%). The proportion of colectomies undertaken for CRC or high grade dysplasia (HGD) was significantly higher after appendectomy (OR 2.85, 95%CI 1.40-5.78, I^2=32%), with 50% of the colectomies indicated for CRC/HGD compared to 9.4% in non-appendectomized patients. Possible additional confounding factors were a longer UC disease duration, less medication use and a higher prevalence of PSC in appendectomized patients.

Conclusions: Appendectomy in established UC is associated with apparently higher rates of subsequent CRC/HGD, but this appears to be due to inequalities in at-risk exposure between groups, presumably secondary to positive clinical effects of appendectomy on disease symptoms. This finding emphasizes the importance of regular endoscopic surveillance in this patient group.

Keywords: Ulcerative Colitis, Appendectomy, Colorectal Cancer, High Grade Dysplasia

Introduction

An appendectomy is a protective factor against the development of ulcerative colitis (UC), and is also suggested to confer beneficial effects on the clinical course of established disease.[1] As early as in 1987, Gilat et al[2] evaluated childhood factors associated with inflammatory bowel disease and reported an inverse relationship between appendectomy and subsequent diagnosis of UC. This observation was regarded as an incidental finding for many years, until another study found an appendectomy prevalence of 0.6% in UC patients compared to 25.4% in controls.[3] Thereafter, more epidemiological and case-control studies reported similar results, and led to an increase in interest over the last decade of the potential therapeutic benefits of an appendectomy in established UC. Various studies exploring this intervention reported lower relapse rates and a decreased risk of colectomy, making this relatively cheap procedure an attractive treatment option for UC patients.[4]

However, more recently published data show contradictory findings after appendectomy in UC patients with an apparently increased colectomy rate, and moreover an increased risk of colorectal cancer (CRC). The retrospective database analysis of Parian et al[5] including 2714 UC patients found a higher risk of colectomy in 48 patients who underwent appendectomy after UC diagnosis and concluded that an appendectomy should not be recommended as a therapy for ulcerative colitis. Harnoy et al[6] also reported an increased risk of colorectal cancer and high grade dysplasia (HGD) in UC patients after appendectomy with an odds ratio of 16.88, although this study only included 15 patients undergoing appendectomy and the timing of appendectomy in relation to their UC diagnosis was unknown. If an appendectomy is indeed associated with the an increased risk of the subsequent development of CRC, this would have considerable implications for ongoing clinical studies and daily clinical practice.

We systematically reviewed the literature and performed a meta-analysis to investigate if an appendectomy is associated with an increased risk of colectomy, and CRC/HGD in UC patients. Additionally, possible confounding factors for the development of CRC or HGD were evaluated

including disease duration, extent and severity of disease, primary sclerosing cholangitis (PSC), and family history for CRC.[7]

Our research questions were: (1) Is an appendectomy in UC patients associated with an increased risk of colectomy and CRC/HGD? (2) Is there a change in the colectomy indication after appendectomy? (3) What possible patient-level confounding factors should be taken into account when interpreting current data?

Methods

Search strategy and selection criteria

A systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[8] All randomized controlled trials, cohort studies, case-control studies and case series describing the influence of an appendectomy on the colectomy rate or risk of CRC or HGD in UC patients were included. Patients with any extent of the disease, and both active and non-active disease, were eligible. There were no limitations concerning timing and reason of appendectomy, nor limitations concerning use of medication. Exclusion criteria were patients <18 years, appendectomy performed in non-UC patients, and animal studies.

An electronic search was performed in MEDLINE (PubMed), EMBASE (Ovid), and the Cochrane library, with the last update on 10 July 2017. The search contained both MeSH and free text terms and was composed with a clinical librarian. Search terms used were 'ulcerative colitis' or 'colitis' or 'proctitis' or 'proctocolitis' or 'UC' or 'pancolitis' and 'appendectomy' or 'appendicectomy'. No restrictions considering the date or type of publication, language, or other methodological filters were used. Further details of the search are provided in Supplementary 1.

Two reviewers (MS and MK) independently screened the titles and abstracts of the studies obtained from the search. Cases of disagreement about inclusion were resolved by joint discussion and when needed the opinion of a third researcher (CB) was sought. The remaining articles were separately reviewed by reading the full-text version (by MS and MK). The reference lists of relevant articles were cross-checked to find any additional studies of interest. Included articles were translated if they were not published in English or Dutch. We used data extracted from published reports and contacted the study authors in cases where data was missing.

Data analysis

The co-primary outcomes of this study were colectomy rate and risk of CRC or HGD after

appendectomy in UC patients. To investigate possible confounding factors for developing CRC or HGD, we specifically looked at UC duration, disease extent and severity, PSC and family history for CRC. Patient characteristics and outcome data were obtained separately for appendectomized and non-appendectomized patients. The collected patient characteristics were: gender, age, age at UC diagnosis, age and timing of appendectomy, UC disease duration, extent and severity of disease (including symptoms, endoscopy results and medication use), PSC, family history of CRC, and duration of follow-up. Outcome data contained: the percentage of colectomies including the age at colectomy, the percentage of CRC and HGD and age at diagnosis, and the indication for colectomy.

Two investigators (MS and MK) independently assessed the risk of bias of the included studies according to The Newcastle Ottawa Quality Assessment Scale.[9] The quality items were adjusted for cohort studies and case-control studies. Studies with less than 5% loss to follow-up and a minimal follow-up duration of eight years were considered acceptable since an increased colorectal cancer risk is only seen after a longer period of time.[10] The Newcastle-Ottawa scale scores were rated following the AHRQ standard as good, fair or poor depending on the number of assigned stars.[11]

A meta-analysis was performed comparing the risk of colectomy, and of CRC and/or HGD in appendectomized and non-appendectomized patients. The influence of timing of appendectomy, before or after the diagnosis of UC, was evaluated in subgroup analyses. A random-effects model was applied and an $I^2 \geq 60\%$ was considered as a substantial heterogeneity. A p-value of <0.05 was statistically significant and the odds ratios and 95% confidence intervals were reported. The statistical analyses were done using Review Manager (version 5.3).

Results

The systematic literature search resulted in 891 studies: 285 in PubMed, 592 in EMBASE and 14 from the Cochrane library. After removal of the duplicates, 573 records were screened on title and abstract. Main reasons for exclusion were: no patients with UC or appendectomy, no data about colectomy or CRC/HGD provided and wrong study designs such as reviews and conference abstracts. In total 81 full-text articles were assessed for eligibility. A further 13 articles were excluded because there was no full text available (most were old and therefore not retrievable), and 55 articles had different outcome parameters, including disease severity, hospitalization or requirement of medical therapy. Qualitative synthesis was done in 13 studies and of these studies, 12 were eligible for the quantitative synthesis. More details can be obtained from figure 1.

There were two prospective cohort studies, ten retrospective cohort studies, and one case-control study. Table 1 shows the study and patient characteristics of the included studies. A total of 73323 UC patients was evaluated of whom 2859 (3.9%) previously had an appendectomy. Patients who had an appendectomy were subdivided in three groups: appendectomy before UC diagnosis (n=1879), appendectomy after UC diagnosis (n=927) and appendectomy with timing unknown (n=53). Of the 13 included studies, two studies did not make a distinction between appendectomy before or after UC diagnosis.[6, 12] The follow-up ranged from a median of 14 months to 193 months, however, 6 studies did not report the follow-up time. All of the included studies, except one, were rated as poor quality studies. The retrospective study of Hallas et al[13] was the only study meeting the criteria of a good quality study (supplementary table 1).

Appendectomy and the risk of colectomy

The risk of colectomy was investigated in 11 studies in 72453 UC patients. Two studies observed a significantly higher colectomy risk in the appendectomy group, and two studies in the non-appendectomy group (table 2). The prospective study of Bolin et al[14] was not included in the final

meta-analyses due to the lack of a control group.

The forest plot of the 10 resulting studies showed no significant difference in colectomy rate between the group with appendectomy and the group without appendectomy (OR 1.25, 95% CI 0.88 to 1.77, I^2=53%; figure 2). Interestingly, patients who underwent an appendectomy after UC diagnosis seemed to have a slightly higher risk of colectomy (OR 1.37, 95% CI 0.61 to 3.07, I^2=63%; supplementary figure 1) compared to an appendectomy before diagnosis (OR 0.99, 95% CI 0.62 to 1.58, I^2=39%; supplementary figure 2), however, this difference was not statistically significant.

Appendectomy and the risk of CRC or HGD

A total of seven studies evaluated the risk of CRC or HGD in 5064 UC patients. Two studies[12, 15] reported cases of CRC including HGD, the other five studies[6, 16-19] separated CRC from HGD (table 2).

Meta-analysis of the risk of having a colectomy for CRC or HGD showed a significant increase after appendectomy (OR 2.85, 95% CI 1.40 to 5.78, I^2=32%; figure 3). Subgroup analysis of the five studies looking at colorectal cancer risk specifically also showed a significant increase after appendectomy with an OR of 3.97 (95% CI 1.35 to 11.70, I^2 =48%; figure 4). Five of the studies evaluated the effect of appendectomy before diagnosis and only one of the studies after diagnosis, therefore no subgroup analysis on timing of appendectomy and the risk of CRC or HGD was performed.

Confounding factors

The indication for colectomy was described in four of the studies, and the pooled weighted percentage of colectomies indicated for (therapy refractory) UC was 40.9% in appendectomized patients, versus 86.3% in non-appendectomized patients. In appendectomized patients, 50% of the colectomies were performed for an indication of CRC or HGD, compared to 9.4% in non-appendectomized patients.

When looking at the patient and disease characteristics, there are some possible confounding factors that might influence the risk of developing CRC or HGD in our included studies. UC disease duration was significantly increased in the appendectomy group in four of seven studies[5, 6, 16, 20](table 3). Furthermore, the average weighted disease duration across the included studies was 133.0 months in the appendectomy group versus 112.3 months in the non-appendectomy group. Also the age at colectomy was significantly higher in the appendectomy group compared to the non-appendectomy group in one out of three studies (median 49.0 versus 38.5 years respectively)(table 2). This same study[6] also reported the age at colectomy for patients with CRC specifically, and the median age was three years older in the appendectomy group (44 versus 41 years), but this difference was not statistically significant. None of the studies reported the exact age at diagnosis of CRC or HGD in appendectomized and non-appendectomized patients separately.

As time to colectomy is related to disease severity, we also scored clinical symptoms, endoscopic severity, and need for medication. Unfortunately, symptoms and endoscopic severity were only reported in the uncontrolled study of Bolin et al.[14] Medication use was presented in seven studies, with a lower pooled weighted percentage of immunomodulators and/or biologicals in the appendectomy group (18.0% versus 28.5%).

When looking at other well-known predictors for the development of CRC we found a significantly higher percentage of patients with PSC in the appendectomy group in three out of seven studies, with a pooled weighted percentage of 12.1% versus 3.9% in the non-appendectomy group. Interestingly, the incidence tended to be higher in patients undergoing appendectomy before UC diagnosis (13.8%) compared to after diagnosis (6.8%). In contrast, there was no significant difference in extent of disease across studies, with extensive colitis in 44.5% of appendectomized patients versus 43.0% in the non-appendectomized patients. One study[17] looked at the extent of disease in CRC patients separately and in this study all patients had extensive colitis irrespective of a previous appendectomy or not. Another study[6] described the location of CRC and interestingly this was more

247 often in the right hemicolon in appendectomized patients compared to non-appendectomized
248 patients (P=0.004). Finally no difference in a positive family history for sporadic colorectal neoplastic
249 changes was found between the appendectomy and non-appendectomy group, although this was
250 only reported in two studies.[6 19]
251
252 **Discussion**
253 We have identified that the previously reported higher rates of CRC and/or HGD after appendectomy
254 in established UC persist in meta-analysis, but are likely to be a result of a marked change in
255 indication for colectomy, alongside unequal risk exposure due to delayed colectomy in those
256 undergoing appendectomy. Significantly less colectomy operations were performed for colitis
257 symptoms in the appendectomy group (40.9%), compared to the non-appendectomy group (86.3%).
258 This has resulted in a denominator shift which produces the aberrant impression of higher rates of
259 malignant transformation in the appendectomy group – when in fact there are just less operations
260 being performed for colitis. This must be interpreted alongside other positive findings which suggest
261 a clinical benefit from appendectomy in terms of both decreasing relapse rates and postponing
262 colectomy.
263 We demonstrated a significantly longer duration of UC in the appendectomy group in four
264 out of seven studies, accompanied by a decreased use of immunomodulators and/or biologicals. If an
265 appendectomy results in decreased disease activity but does not lead to mucosal healing, this might
266 result in a situation where the need for colectomy can be postponed or avoided on the grounds of
267 clinical symptoms. However, leaving a (subclinical) inflammatory colon in situ might promote tumor
268 development as the production of chemokines and cytokines facilitate tumor growth, genomic
269 instability and angiogenesis.[21] Therefore, a postponed colectomy might produce an apparently
270 increased CRC risk over the long term, due to a disparity in at-risk exposure for appendectomized
271 patients compared to the normal UC population.

This hypothesis is further supported by results of the only two prospective series so far describing clinical results in therapy-refractory UC patients undergoing appendectomy. The study of Bolin et al[14] showed an improvement in the clinical activity index score in 27/30 (90%) patients, but after one year only 12 (40%) patients had a complete resolution of symptoms. There was no description of the number of patients in endoscopic remission in this study. The long-term results of 28 patients reported in the abstract of another prospective cohort series showed clinical response in 12 (46%) patients and remission in 5 (18%) patients 12 months after appendectomy for therapy refractory UC.[22] After a median of 4 years, 13 (46%) had lasting clinical response and 6 (21%) were in endoscopic remission. Although the results were considered to be promising as this patient group was originally referred for colectomy, it also demonstrates that only a minority of patients achieve complete remission.

These studies do suggest that an appendectomy can result in a beneficial clinical effect; a substantial proportion of patients appear to experience a reduction in inflammation and disease activity , thereby waiving the need for colectomy. In contrast, in our study we found no overall significant decrease in the risk of colectomy in appendectomized patients although we identified a shift in the indication for colectomy from (therapy refractory) disease activity to (pre)malignant degeneration. In the study of Harnoy et al[6], the prevalence of CRC in appendectomized UC patients was 33%, while the overall prevalence of CRC in any UC patient is estimated to be around 4%.[23] The shift in indication might, over time, result in comparable colectomy rates in both groups.

Another well-known risk factor which is associated with the development of CRC in UC patients is PSC. The prevalence of PSC was significantly higher in the appendectomy group in three out of seven studies. The relation between appendectomy and the development of PSC has been analyzed previously in several studies and a recently published meta-analysis found a significant association with an OR of 1.37.[24] However, this meta-analysis included both PSC (without UC) and PSC-UC patients, and perhaps only the UC patients are at risk after appendectomy due to a distinct

297 IBD phenotype with more frequent involvement of the right hemicolon.[25] In addition to this, the only
298 study in our meta-analysis describing the location of CRC found significantly more cancers located in
299 the right hemicolon in appendectomized patients. A Swiss nationwide cohort study including 2744
300 patients (which was not included in the aforementioned meta-analysis) builds upon this hypothesis
301 as the authors indicated an appendectomy as independent risk factor for developing PSC in UC
302 patients (OR 4.11, P = 0.019).[26] Further research is required to investigate this possible association
303 and possible underlying immunological mechanisms.

304 Unfortunately, we cannot comment on other important risk factors for CRC like severity and
305 a history of CRC in the family.[7] Due to the retrospective character of most of the included studies in
306 this systematic review, data on these variables was often lacking.

307 There are several limitations to this study. As only two prospective studies could be included,
308 the conclusions of our meta-analysis are merely based on retrospective data with its inherent
309 shortcomings. Pooling data of these different study designs is generally not preferred as this poses
310 substantial heterogeneity. Even though the heterogeneity in our main analyses was low, it should be
311 kept in mind that this might be due to simplification of the analytical model (from adjusted
312 regression to non-adjusted regression). Also, several studies did not present all relevant outcome
313 parameters, which could lead to bias. An attempt was made to collect these data from the original
314 author groups, but this was not completely successful. Lastly, it is difficult to clearly extrapolate these
315 findings to clinical practice because in the majority of the studies describing appendectomy and the
316 risk of CRC/HGD the appendectomy was performed prior to the diagnosis of UC. This impacts on the
317 relevance to current UC sufferers. . Compounding this, since we know that appendectomy protects
318 against the development of UC in the first place, if a patient goes on to develop the condition having
319 already had an appendectomy, this may perhaps be viewed as a special high-risk subset of a
320 particularly virulent version of UC – hence the higher subsequent risk of CRC/HGD. If an
321 appendectomy performed after the diagnosis of UC postpones colectomy, when do we call this

clinically relevant? Obviously, if this difference is 10 years, like the data presented by Harnoy et al[6], an appendectomy will be interesting for this generally young patient group (e.g. with respect to fertility), but in our pooled data (including both appendectomies prior to and after the UC diagnosis) the difference was less compelling (112.3 versus 133.0 months). The clinical relevance of postponing colectomy is dependent on the years gained with colon in situ and good quality of life. Unfortunately, it is impossible to comment on this with these retrospective data. A recently published abstract of prospective data demonstrated that quality of life measured by the disease specific (IBDQ) significantly improve after appendectomy, but it should be emphasized that this is a therapy-refractory patient group who were referred for colectomy.[22]

In conclusion, this systematic review and meta-analysis shows that when the data is pooled from previously published reports, the apparently significantly increased risk of CRC and HGD after appendectomy in UC patients persists. The increased risk of CRC and HGD is likely to be secondary to the fact that the colon is longer in situ because of the suggested positive effect of appendectomy on disease severity. With the current findings, discontinuation of ongoing studies on appendectomy in UC is not recommended. In contrast, we feel that this review confirms the clinical interest in the role of an appendectomy as therapy for UC. However, it is clear that there remains an ongoing risk of CRC or HGD in patients who may have clinically improved after appendectomy, and as such this study emphasizes the importance of ongoing regular endoscopic surveillance in appendectomized UC patients. Future studies should aim to address possible confounding factors when analyzing the effect of an appendectomy on UC and CRC related outcomes.

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References

1. Andersson RE, Olaison G, Tysk C, Ekbom A. Appendectomy and protection against ulcerative colitis. N Engl J Med. 2001;344(11):808-14.

2. Gilat T, Hacohen D, Lilos P, Langman MJ. Childhood factors in ulcerative colitis and Crohn's disease. An international cooperative study. Scandinavian journal of gastroenterology. 1987;22(8):1009-24.

3. Rutgeerts P, D'Haens G, Hiele M, Geboes K, Vantrappen G. Appendectomy protects against ulcerative colitis. Gastroenterology. 1994;106(5):1251-3.

4. Sahami S, Kooij IA, Meijer SL, Van den Brink GR, Buskens CJ, Te Velde AA. The Link between the Appendix and Ulcerative Colitis: Clinical Relevance and Potential Immunological Mechanisms. Am J Gastroenterol. 2016;111(2):163-9.

5. Parian A, Limketkai B, Koh J, Brant SR, Bitton A, Cho JH, et al. Appendectomy does not decrease the risk of future colectomy in UC: results from a large cohort and meta-analysis. Gut. 2016.

6. Harnoy Y, Bouhnik Y, Gault N, Maggiori L, Sulpice L, Cazals-Hatem D, et al. Effect of appendicectomy on colonic inflammation and neoplasia in experimental ulcerative colitis. Br J Surg. 2016;103(11):1530-8.

7. Lakatos PL, Lakatos L. Risk for colorectal cancer in ulcerative colitis: changes, causes and management strategies. World J Gastroenterol. 2008;14(25):3937-47.

8. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine. 2009;6(7):e1000097.

9. GA Wells BS DOC, J Peterson, V Welch, M Losos, P Tugwell. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. [Available from: http://wwwohrica/programs/clinical_epidemiology/oxfordasp].

392 10. Van Assche G, Dignass A, Bokemeyer B, Danese S, Gionchetti P, Moser G, et al. Second
393 European evidence-based consensus on the diagnosis and management of ulcerative colitis part 3:
394 special situations. Journal of Crohn's & colitis. 2013;7(1):1-33.
395 11. Penson DF KS JA, et al. Newcastle-Ottawa Quality Assessment Form for Cohort Studies 2012
396 [Available from: https://wwwncbinlmnihgov/books/NBK115843/bin/appe-fm3pdf].
397 12. Picazo-Ferrera K, Bustamante-Quan Y, Santiago-Hernandez J, Yamamoto-Furusho JK. [The
398 role of appendectomy in the ulcerative colitis in Mexico]. Rev Gastroenterol Mex. 2011;76(4):316-21.
399 13. Hallas J, Gaist D, Vach W, Sorensen HT. Appendicectomy has no beneficial effect on
400 admission rates in patients with ulcerative colitis. Gut. 2004;53(3):351-4.
401 14. Bolin TD, Wong S, Crouch R, Engelman JL, Riordan SM. Appendicectomy as a therapy for
402 ulcerative proctitis. Am J Gastroenterol. 2009;104(10):2476-82.
403 15. Radford-Smith GL, Edwards JE, Purdie DM, Pandeya N, Watson M, Martin NG, et al.
404 Protective role of appendicectomy on onset and severity of ulcerative colitis and Crohn's disease.
405 Gut. 2002;51(6):808-13.
406 16. Cosnes J, Carbonnel F, Beaugerie L, Blain A, Reijasse D, Gendre JP. Effects of appendicectomy
407 on the course of ulcerative colitis. Gut. 2002;51(6):803-7.
408 17. Florin TH, Pandeya N, Radford-Smith GL. Epidemiology of appendicectomy in primary
409 sclerosing cholangitis and ulcerative colitis: its influence on the clinical behaviour of these diseases.
410 Gut. 2004;53(7):973-9.
411 18. Lee HS, Park SH, Yang SK, Kim SO, Soh JS, Lee S, et al. Appendectomy and the clinical course
412 of ulcerative colitis: a retrospective cohort study and a nested case-control study from Korea. J
413 Gastroenterol Hepatol. 2015;30(3):470-7.
414 19. Gordillo J, Cabre E, Garcia-Planella E, Ricart E, Ber-Nieto Y, Marquez L, et al. Thiopurine
415 Therapy Reduces the Incidence of Colorectal Neoplasia in Patients with Ulcerative Colitis. Data from
416 the ENEIDA Registry. Journal of Crohn's & colitis. 2015;9(12):1063-70.

20. Selby WS, Griffin S, Abraham N, Solomon MJ. Appendectomy protects against the development of ulcerative colitis but does not affect its course. Am J Gastroenterol. 2002;97(11):2834-8.

21. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002;420(6917):860-7.

22. Stellingwerf ME SS, Winter DC, Mulcahy HE, Doherty G, Cullen G, Martin S, D'Haens GR, Bemelman WA, Buskens CJ. P578 Therapy refractory ulcerative colitis patients may benefit from appendectomy: long-term clinical results from a multicentre prospective cohort series. Journal of Crohn's and Colitis.Volume 12, Issue supplement_1, 16 January 2018, Pages S399–S400, https://doi.org/10.1093/ecco-jcc/jjx180.705.

23. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut. 2001;48(4):526-35.

24. Wijarnpreecha K, Panjawatanan P, Mousa OY, Cheungpasitporn W, Pungpapong S, Ungprasert P. Association between appendectomy and risk of primary sclerosing cholangitis: A systematic review and meta-analysis. Clinics and research in hepatology and gastroenterology. 2018.

25. Boonstra K, van Erpecum KJ, van Nieuwkerk KM, Drenth JP, Poen AC, Witteman BJ, et al. Primary sclerosing cholangitis is associated with a distinct phenotype of inflammatory bowel disease. Inflammatory bowel diseases. 2012;18(12):2270-6.

26. Fraga M, Fournier N, Safroneeva E, Pittet V, Godat S, Straumann A, et al. Primary sclerosing cholangitis in the Swiss Inflammatory Bowel Disease Cohort Study: prevalence, risk factors, and long-term follow-up. European journal of gastroenterology & hepatology. 2017;29(1):91-7.

27. Manguso F, Sanges M, Staiano T, Gargiulo S, Nastro P, Gargano D, et al. Cigarette smoking and appendectomy are risk factors for extraintestinal manifestations in ulcerative colitis. Am J Gastroenterol. 2004;99(2):327-34.

28. Myrelid P, Landerholm K, Nordenvall C, Pinkney TD, Andersson RE. Appendectomy and the Risk of Colectomy in Ulcerative Colitis: A National Cohort Study. Am J Gastroenterol. 2017.

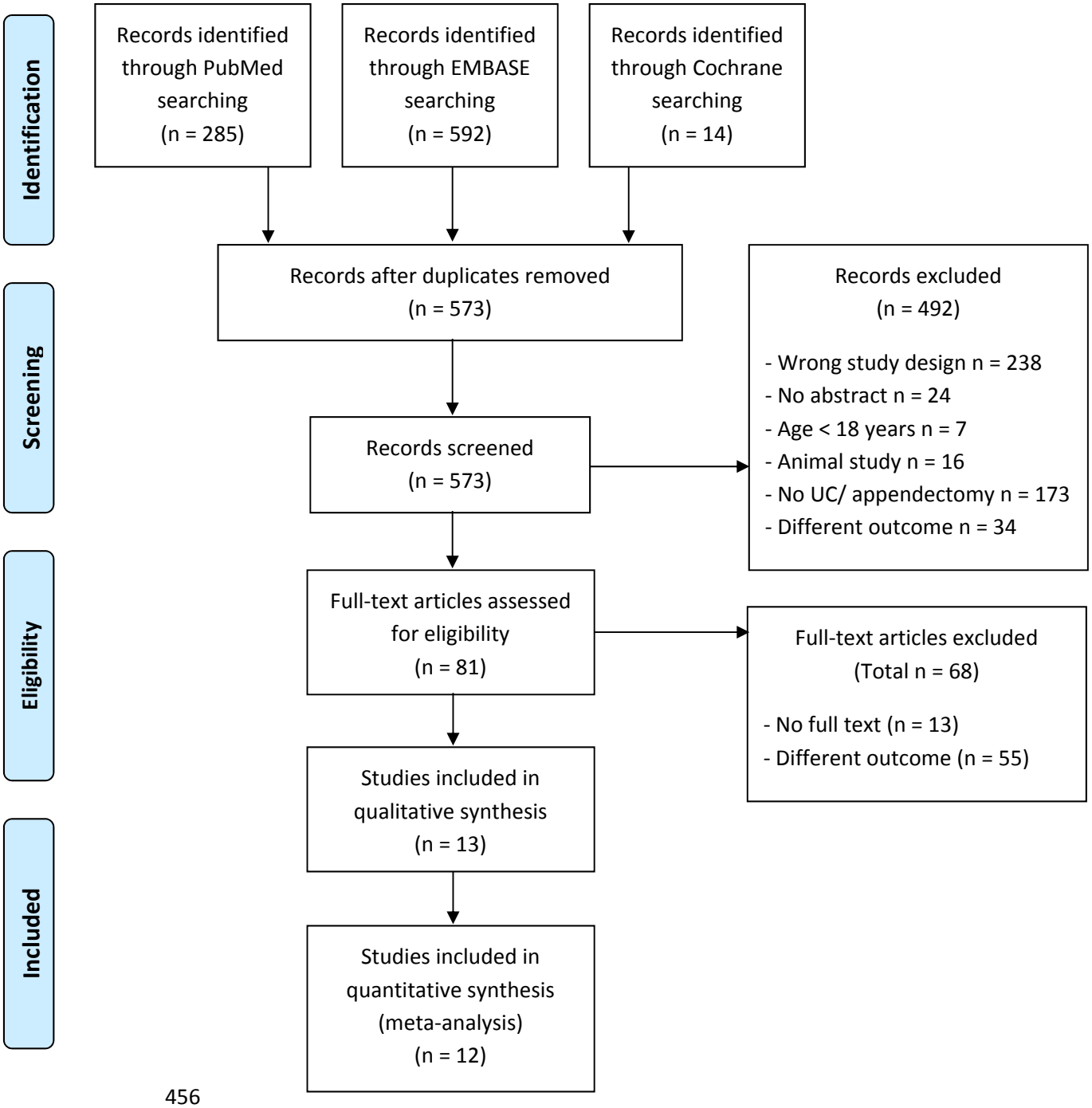

Figure 1: Study selection

Author	Journal	Country	Study design	Inclusion period	Intervention	No. of patients	Female	Age (yrs)	Age at UC diagnosis	Age at appen-dectomy (yrs)	Fami ly	PSC	Subtotal/ pan-colitis	Corticoster oid use	Immunomodulato rs/ biologicals	Follow-up (mo) until study
Cosnes et al (2002)[16]	Gut	France	R	Jan 1997 - Dec 2000	A-	589 (92.3%)	51.6%	-	Mean 32.9	-	-	-	40.6%	412 (70%)	112 (19%)	-
					A+ (< UC)	49 (7.7%)	73.5%	-	Mean 35.7	<20: 35	-	-	38.8%	33 (67%)	13 (27%)	-
Selby et al (2002)[20]	The American Journal of Gastroenterology	Australia	R	-	A-	239 (92.3%)	48.6%	Mean 41.8	Mean 32.1	-	-	7.5%*	37.7%	-	43 (18.0%)	-
					A+ (< UC)	12 (4.6%)		Mean 62.6	Mean 42.5	Mean 26.6	-	25%*	50%	-	4 (33.3%)	-
					A+ (> UC)	8 (3.1%)		Mean 53.8	Mean 24.6	Mean 31.8	-	25%*	25%	-	1 (12.5%)	-
Radford-Smith et al (2002)[15]	Gut	Australia	R	1995-1999	A-	286 (93.2%)	48.9%	Mean 32.7	Mean 31.3	-	-	-	42.1%	-	71 (24.8%)*	-
					A+ (< UC)	21 (6.8%)		(0.85)	Mean 37.8	<20: 10, >20:	-	-	61.9%	-	1 (4.8%)*	-
Florin et al (2004)[17]	Gut	Australia	R	1995-2002	A-	275 (93.5%)	48.2%	Mean 32.7	Mean 32.4	-	-	17.4*	40%	-	74 (27%)*	-
					A+ (< UC)	19 (6.9%)		(0.86)	Mean 37.9	<20: 8, >20:	-	50*	58%	-	1 (5.6%)*	-
Hallas et al (2004)[13]	Gut	Denmark	R	Jan 1977 - Dec 1999	A-	808	-	-	Mean 38.7	-	-	-	-	-	-	Mean 131.9 (61.2)
					A+ (> UC)	202 (1.7%)	58.4%	-	Mean 38.6	Mean 43.3	-	-	-	-	-	Mean 129.2 (62.4)
Manguso et al (2004)[27]	The American Journal of	Italy	P	Jan 1984 - Jan 2002	A-	485 (90.7%)	37.5%*	-	Median 28	-	-	1%	44%	-	-	Median 132 (96)
					A+ (< UC)	50 (9.4%)	68%*	-	Median 31	-	-	8%	36%	-	-	
Bolin et al	The American	Australia	P	Jul 2006 -	A+ (> UC)	30 (100%)	63.3%	Median 35	-	Median 35	-	-	0%	1 (3.3%)	7 (23.3%)	Median 14 (9-32)
Picazo-Ferrera et al (2011)[12]	Revista de gastrenterologia	Mexico	R	Jan 2007 - Jun 2010	A-	76 (66.7%)	43.7%	-	<40: 71%	-	-	1.3%*	48.6%	-	-	-
					A+	38 (33.35)	47.3%	-	<40: 63.2%	25.1	-	10.5%*	50%	-	-	-
Lee et al (2014)[18]	Journal of gastroenterology and hepatology	South Korea	R	Jul 1989 - Dec 2013	A-	2544 (96.1%)	45.7%*	Mean 45.3	Mean 37.0	-	-	1.1%	22%	1427	646 (25.4%)	Mean 100.4 (73.4)
					A+ (< UC)	68 (2.6)	66.2%*	Mean 49.1	Mean 40.7	Mean 31.1	-	1.5%	27.9%	40 (58.8%)	15 (22.1%)	Mean 100.3 (84)
					A+ (> UC)	36 (1.4%)	47.2%*	Mean 49.9	Mean 36.3	Mean 42.5	-	2.8%	16.7%	4 (26.7%)	8 (24.4%)	Mean 162.6 (98)
Gordillo et al (2015)[19]	Journal of Crohn's and Colitis	Spain	CC	Jan 2006 - Jan 2010	A-	771 (92.8%)	46%	Mean 56.1	Mean 37.6	-	15%	3%	6.6%	555 (72%)	393 (51%)	Mean 188 (103.1)
					A+ (< UC)	60 (7.2%)	55%	Mean 58.9	Mean 40.1	-	18%	5%	6.7%	41 (68%)	6 (10%)	Mean 193 (119.1)
Harnoy et al (2016)[6]	British Journal of Surgery	France	R	Jan 2001 - Dec 2011	A-	217 (93.5%)	49.8%	Median 38.5	-	-	4.6%	21.7%	87.1%	204 (94%)	-	Median 41 (14-107)*
					A+	15 (6.5%)	40%	Median 49.0	-	-	0%	6.7%	86.7%	11 (73.3%)	-	Median 151 (113-242)*
Parian et al (2016)[5]	Gut	USA	R	Jan 2003 - Nov 2013	A-	2603 (95.9)	49.3%	-	Mean 30.8	-	-	-	64.9%	-	-	-
					A+ (< UC)	63 (2.4%)	55.9%	-	Mean 41.8	<20: 28	-	-	63.4%	-	-	-
					A+ (> UC)	48 (1.8%)		-	-		-	-		-	-	-
Myrelid et al (2017)[28]	The American Journal of Gastroenterology	Sweden	R	Jan 1964 - Dec 2010	A- (< UC)	62174	47.6%	-	Mean 44.6	-	-	-	-	-	-	603462 person years
					A+(< UC)	1537 (2.4%)	48.2%	-	Mean 45.9	Mean 32.2	-	-	-	-	-	15047 person years
					A+ (> UC)	603 (1.0%)	50.2%	-	Mean 33.6	Mean 40.6	-	-	-	-	-	7598 person years

Table 1: Study and patient characteristics

*significantly different. Mean values are accompanied by SDs and medians by IQRs. R=retrospective. P=prospective. CC=case-control. A-=no appendectomy.

A+=appendectomy. <UC=before the diagnosis of UC. >UC=after the diagnosis of UC.

Author	Intervention	No. of patients	Colectomy	Colectomy indicated for UC	Duration of UC (mo)	Age at colectomy	CRC	HGD
Cosnes et al (2002)[16]	A-	589	-	-	Mean 86.4 (99.6)*	-	11 (1.9%)	-
	A+ (< UC)	49	-	-	Mean 121.2 (97.2)*	-	0 (0%)	-
Selby et al (2002)[20]	A-	239	21 (8.8%)	-	Mean 9.7 (1.2)*	-	-	-
	A+ (< UC)	12*	2 (16.7%)	1 (8.3%)	Mean 20.1 (7.9)*	-	1 (8.3%)	-
	A+ (> UC)	8*	1 (12.5%)	0 (0%)	Mean 29.2 (8.0)*		0 (0%)	-
Radford-Smith et al (2002)[15]	A-	286	65 (22.7%)*	60 (21.0%)	-	-	5 (1.8%) (+HGD)	-
	A+ (< UC)	21	1 (4.8%)*	0 (0%)	-	-	1 (4.8%) (+HGD)	-
Florin et al (2004)[17]	A-	275	68 (24.7%)	67 (24.4%)	-	-	2 (0.7%)	5 (1.8%)
	A+ (< UC)	19	3 (16%)	1 (5.3%)	-	-	2 (10.5%)	0 (0%)
Hallas et al (2004)[13]	A-	808	42 (5.2%)	-	Mean 131.9 (61.2)	-	-	-
	A+ (> UC)	202	9 (4.5%)	-	Mean 129.2 (62.4)	-	-	-
Manguso et al (2004)[27]	A-	485	6 (1.2%)	-	-	-	-	-
	A+ (< UC)	50	2 (4%)	-	-	-	-	-
Bolin et al (2009)[14]	A+ (> UC)	30	0 (0%)	-	Median 60 (8-360)	-	-	-
Picazo-Ferrera et al (2011)[12]	A-	76	12 (15.7%)*	-	-	-	3 (4.0%) (+HGD)	-
	A+	38	16 (42.1%)*	-	-	-	3 (7.9%) (+HGD)	-
Lee et al (2014)[18]	A-	2544	207 (8.1%)	-	Mean 100.4 (73.4)	Mean 42.3 (14.8)	19 (0.7%)	21 (0.8%)
	A+ (< UC)	68	6 (8.8%)	-	Mean 100.3 (84)	Mean 45.5 (17.9)	0 (0%)	0 (0%)
	A+ (> UC)	36	0 (0%)	-	Mean 162.6 (98)	-	0 (0%)	1 (2.8%)
Gordillo et al (2015)[19]	A-	771	3.7%	-	Mean 223.2	-	19 (2.5%)*	19 (2.5%)
	A+ (< UC)	60	6.7%	-	Mean 224.4	-	5 (8.3%)*	2 (3.3%)
Harnoy et al (2016)[6]	A-	217	(217 (100%))	175 (80.7%)	Median 41 (14-107)*	Median 38.5 (27-50)*	12 (5.5%)*	18 (8.3%)*
	A+	15	(15 (100%))	7 (46.7%)	Median 151 (113-242)*	Median 49.0 (35-64)*	5 (33.3%)*	4 (26.7%)*
Parian et al (2016)[5]	A-	2603	424 (16.4%)*	-	Mean 104.5 (109.2)*	-	-	-
	A+ (< UC)	63	26 (23.6%)*	-	Mean 128.9 (116.4)*	-	-	-
	A+ (> UC)	48		-		-	-	-
Myrelid et al (2017)[28]	A- (< UC)	62174	7541 (12.1%)*	-	-	Mean 43.5 (17.2)	-	-
	A+(< UC)	1537	149 (9.7%)*	-	-	Mean 44.1 (14.7)	-	-
	A+ (> UC)	603	70 (11.6%)*	-		Mean 38.4 (14.1)	-	-

Table 2: Outcome data of the included studies

*significantly different. Mean values are accompanied by SDs and medians by IQRs. A-=no appendicectomy. A+=appendicectomy. <UC=before the diagnosis of UC. >UC=after the diagnosis of UC. PSC=primary sclerosing cholangitis

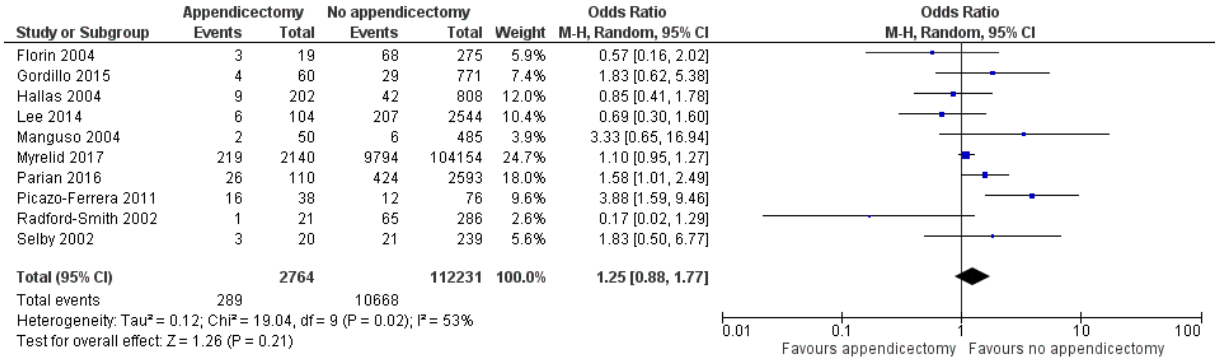

Figure 2: Forest plot of appendectomy and risk of colectomy

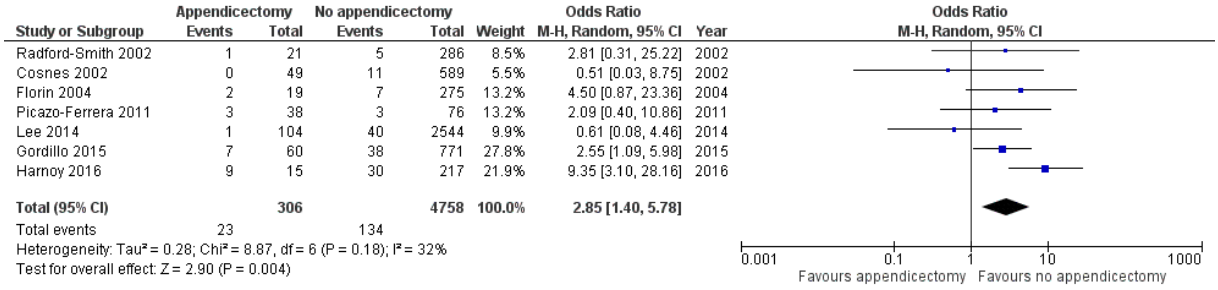

Figure 3: Forest plot of appendectomy and CRC or HGD

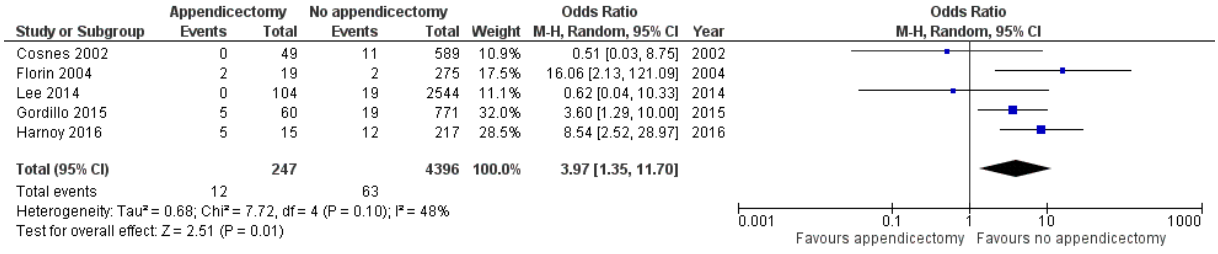

Figure 4: Forest plot of appendectomy and CRC

Author	Disease duration			Extensive disease spread (%)			PSC (%)		
	A-	A+ (< UC)	A+ (> UC)	A-	A+ (< UC)	A+ (> UC)	A-	A+ (< UC)	A+ (> UC)
Cosnes et al[14]	Mean 86.4 (99.6)*	Mean 121.2 (97.2)*		239/589 (40.6)	19/49 (38.8)				
Selby et al[15]	Mean 9.7 (1.2)*	Mean 20.1 (7.9)*	Mean 29.2 (8.0)*	90/239 (37.7)	6/12 (50)	2/8 (25)	18/239 (7.5)*	3/12 (25)*	2/8 (25)*
Radford-Smith et al[16]				120/286 (42.0)	13/21 (61.9)				
Florin et al[17]				110/275 (40.0)	11/19 (57.9)		58/333 (17.4)*	19/28 (50)*	
Hallas et al[13]	Mean 131.9 (61.2)		Mean 129.2 (62.4)						
Manguso et al[18]				213/485 (44.0)	18/50 (36)		5/485 (1)	4/50 (8)	
Picazo-Ferrera et al[12]				37/76 (48.6)	19/38 (50)		1/76 (1.3)*	4/38 (10.5)*	
Lee et al[20]	Mean 100.4 (73.4)	Mean 100.3 (84.0)	Mean 162.6 (98.0)	560/2544 (22.0)	19/68 (27.9)	6/36 (16.7)	29/2544 (1.1)	1/68 (1.5)	1/36 (2.8)
Gordillo et al[21]	Mean 223.3	Mean 224.4					23/771 (3)	3/60 (5)	
Harnov et al[6]	Median 41 (14-107)*	Median 151 (113-242)*		189/217 (87.1)	13/15 (86.7)		47/217 (21.7)	1/15 (6.7)	
Parian et al[5]	Mean 104.5 (109.2)*	Mean 128.9 (116.4)*		1584/2603 (60.9)	64/111 (57.7)				
Myrelid et al[22]									
Weighted total	112.3 mths	93.2 mths	150.7 mths	3142/7314 = 43.0%	86/219 = 39.3%	8/44 = 18.2%	181/4665 =3.9%	30/218 = 13.8%	3/44 = 6.8%
		133.0 mths			190/427 = 44.5%			38/315 = 12.1%	

Table 3: Confounding factors

*significantly different. Mean values are accompanied by SDs and medians by IQRs. A-=no appendectomy. A+=appendectomy. <UC=before the diagnosis of UC. >UC=after the diagnosis of UC. PSC=primary sclerosing cholangitis