

Meta-analysis of the role of colonoscopy after an episode of left-sided acute diverticulitis

S. J. Rottier^{1,2,4} , S. T. van Dijk², A. A. W. van Geloven⁴, W. H. Schreurs¹, W. A. Draaisma⁵, W. A. van Enst⁶, J. B. C. M. Puylaert⁷, M. G. J. de Boer⁸, B. R. Klarenbeek⁹, J. A. Otte¹⁰, R. J. F. Felt³ and M. A. Boermeester²

¹Department of Surgery, Northwest Clinics, Alkmaar, Departments of ²Surgery and ³Gastroenterology, Amsterdam UMC, Amsterdam, ⁴Department of Surgery, Tergooi Hospital, Hilversum, ⁵Department of Surgery, Jeroen Bosch Hospital, 's-Hertogenbosch, ⁶Knowledge Institute of Medical Specialists, Utrecht, ⁷Department of Radiology, Haaglanden Medical Centre, The Hague, ⁸Department of Infectious Diseases, Leiden University Medical Centre, Leiden, ⁹Department of Surgery, Radboud University Medical Centre, Nijmegen, and ¹⁰Department of Internal Medicine, ZorgSaam Hospital, Terneuzen, the Netherlands

Correspondence to: Professor M. A. Boermeester, Department of Surgery, AMC, Meibergdreef 9, 100 DD, PO Box 22660, Amsterdam, the Netherlands (m.a.boermeester@amc.nl)

Background: Routine colonoscopy was traditionally recommended after acute diverticulitis to exclude coexistent malignancy. Improved CT imaging may make routine colonoscopy less required over time but most guidelines still recommend it. The aim of this review was to assess the role of colonoscopy in patients with CT-proven acute diverticulitis.

Methods: PubMed and Embase were searched for studies reporting the prevalence of advanced colorectal neoplasia (ACN) or colorectal carcinoma in patients who underwent colonoscopy within 1 year after CT-proven left-sided acute diverticulitis. The prevalence was pooled using a random-effects model and, if possible, compared with that among asymptomatic controls.

Results: Seventeen studies with 3296 patients were included. The pooled prevalence of ACN was 6.9 (95 per cent c.i. 5.0 to 9.4) per cent and that of colorectal carcinoma was 2.1 (1.5 to 3.1) per cent. Only two studies reported a comparison with asymptomatic controls, showing comparable risks (risk ratio 1.80, 95 per cent c.i. 0.66 to 4.96). In subgroup analysis of patients with uncomplicated acute diverticulitis, the prevalence of colorectal carcinoma was only 0.5 (0.2 to 1.2) per cent.

Conclusion: Routine colonoscopy may be omitted in patients with uncomplicated diverticulitis if CT imaging is otherwise clear. Patients with complicated disease or ongoing symptoms should undergo colonoscopy.

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Introduction

The incidence rates of acute diverticulitis have been increasing rapidly over recent decades^{1–3}. Acute diverticulitis has traditionally been associated with an increased risk of colorectal malignancy, which has led to routine colonic evaluation by colonoscopy after the episode of acute diverticulitis has resolved. However, a causal association between colonic diverticulitis or diverticulosis and malignancy has never been found. The association is most likely explained by misdiagnosis of colorectal malignancy as acute diverticulitis. The fact that acute diverticulitis used to be diagnosed based on the clinical picture or barium enemas, and later on by ultrasonography, probably increased the number of misdiagnoses and thereby played

a role in establishing the association between acute diverticulitis and colorectal malignancy^{4,5}. CT has a higher accuracy for the detection of an alternative diagnosis such as colorectal carcinoma^{6,7}. If this were accurate enough, colonoscopy would not be needed in every patient, thereby reducing the healthcare burden and colonoscopy-related morbidity^{8–10}.

Even though the risk of colorectal carcinoma in patients with acute diverticulitis has been the topic of debate in multiple studies^{11–18}, there remains a lack of clarity. The majority of guidelines^{11,13–15,17,18} still recommends routine colonoscopy after an episode of acute diverticulitis. The objective of this review was to assess the role of colonoscopy in patients with CT-proven acute diverticulitis in detecting

a colorectal carcinoma that is presenting as acute diverticulitis or is masked by acute diverticulitis.

Methods

Study identification

Two authors searched PubMed and Embase databases independently for studies published up to April 2018, using the following search terms: diverticulitis, diverticular, colonoscopy, colonic evaluation, colon cancer, colon carcinoma, colorectal cancer, colorectal carcinoma, sigmoid cancer and sigmoid carcinoma. The search strategy is shown in *Appendix S1* (supporting information). Additionally, a manual cross-reference search of the reference lists of relevant articles was performed to identify other studies not found in the initial search. No language limits were applied. MOOSE guidelines¹⁹ for reporting were followed. A review protocol for this systematic review was not published or registered before the study was undertaken.

Study selection

Studies eligible for inclusion were: RCTs or observational cohort studies including patients with CT-proven acute colonic diverticulitis and reporting rates of advanced colorectal neoplasia (ACN) or colorectal carcinoma found at colonoscopy. Only patients who underwent colonoscopy within 1 year after the acute diverticulitis diagnosis were included, to enable assessment of the risk of having a colorectal carcinoma at the time of the acute diverticulitis diagnosis rather than the risk of developing a colorectal carcinoma several years later that is unrelated to the acute diverticulitis. Studies of Western origin that did not quantify the number of patients with right-sided diverticulitis were included on the assumption that the vast majority of cases in the Western world (usually above 90 per cent^{20–22}) comprise left-sided diverticulitis. Right-sided diverticulitis was defined as diverticulitis located proximal to the splenic flexure. Reviews, conference abstracts, letters to the editor, animal studies and studies with fewer than ten patients were excluded. For studies with overlapping patient cohorts, the largest study was included. The two reviewers independently considered all studies retrieved from the search for eligibility against these criteria. Any disagreements in any phase of the study selection, quality assessment or data extraction were resolved by discussion.

Quality assessment

The two reviewers appraised each study critically using the Newcastle–Ottawa Scale for cohort studies²³.

Data extraction

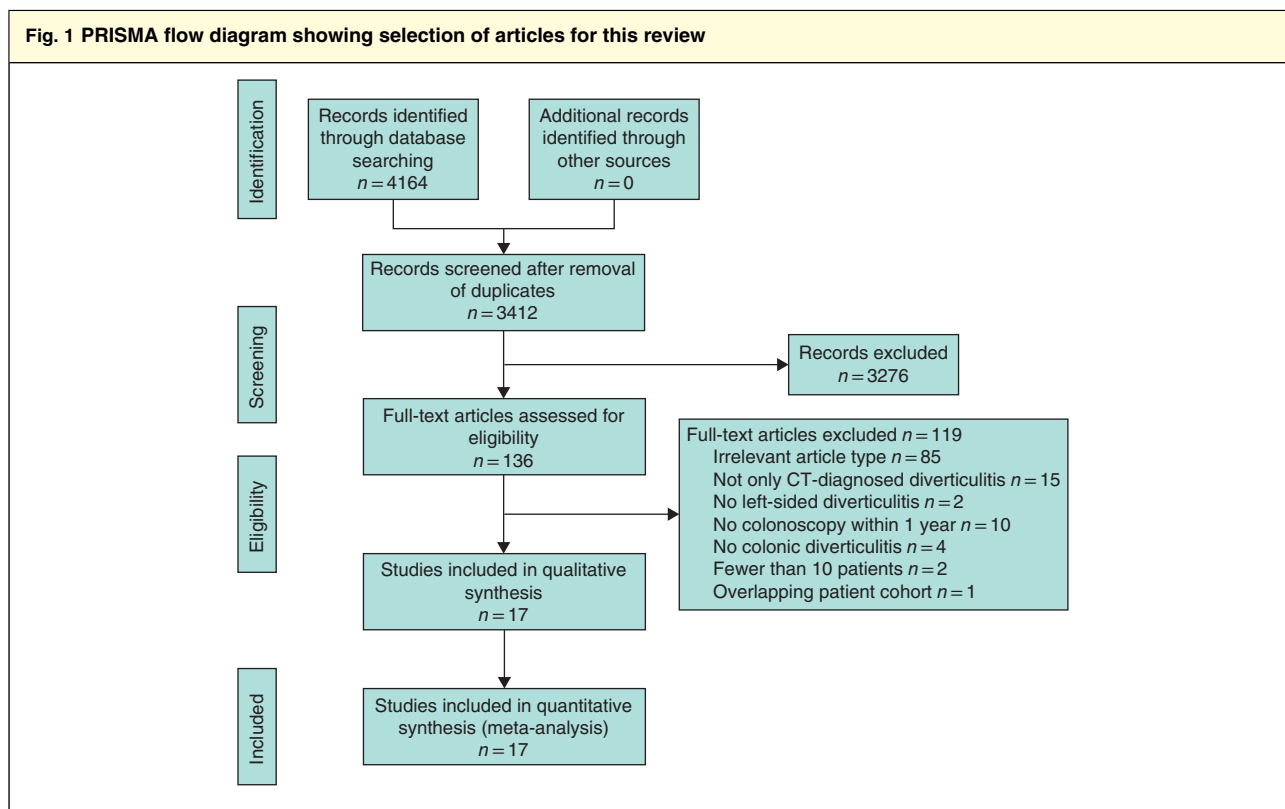
Data from each included study were extracted by two reviewers independently using a predefined extraction table. These data included: study setting, study design (prospective or retrospective data collection), type of patient (uncomplicated *versus* complicated diverticulitis), number of patients, patient age, proportion of complete colonoscopies (caecal intubation), time interval between acute diverticulitis episode and colonoscopy, number of colonoscopy-related complications (complications as reported by the studies), number of patients with ACN, number of patients with colorectal carcinoma and tumour location, and outcome results from logistic regression analyses. For some studies, only a subgroup of patients who fulfilled the inclusion and exclusion criteria for the present systematic review was included in the analysis: only patients who underwent colonoscopy, or only those who had colonoscopy within 1 year after the acute diverticulitis episode.

Outcome measures

Primary outcome measures were the prevalence of colorectal carcinoma and ACN at follow-up colonoscopy. These rates were compared with those in asymptomatic control cohorts, when this information was reported by the studies. A sensitivity analysis was undertaken to assess rates of colorectal carcinoma and ACN in patients with uncomplicated and complicated acute diverticulitis separately, but only for studies that reported these numbers specifically for one or both of these patient subgroups. ACN was defined by colorectal carcinoma or advanced adenoma, according to the most advanced lesion per patient. ACN prevalence was analysed in addition to colorectal carcinoma prevalence only because it is a clinically relevant additional finding, given the potential of advanced adenomas to progress into malignancy²⁴. Advanced adenoma was defined as an adenoma either larger than 10 mm, or with more than 25 per cent villous features (also classified as tubulovillous or villous histology), or with high-grade dysplasia²⁵. Uncomplicated diverticulitis was defined by peridiverticular inflammation, and complicated diverticulitis by diverticular abscess, perforation or fistula. The secondary outcome was colonoscopy-related adverse events.

Statistical analysis

Prevalence rates of colorectal carcinoma and ACN were pooled using a DerSimonian and Laird random-effects model and displayed using forest plots. The result



of comparison between groups of patients with diverticulitis and asymptomatic controls was expressed as a pooled risk ratio with 95 per cent confidence intervals. Statistical heterogeneity was assessed using χ^2 analysis and I^2 values. Funnel plots were used to assess publication bias. Statistical analyses were conducted using RStudio® (RStudio, Boston, Massachusetts, USA).

Results

Study selection

The search retrieved 4164 records (Fig. 1). After removal of 752 duplicates, 3412 records were screened based on title and abstract, and 136 full-text articles were assessed for eligibility. Cross-referencing did not identify additional relevant studies. Seventeen studies fulfilled the inclusion and exclusion criteria, and were included in this systematic review. The reasons for exclusion of full-text articles are available in *Table S1* (supporting information).

Study characteristics

All studies were published after 2003. There were four prospective cohort studies^{26–29} and 13 retrospective cohort

studies^{30–42} (Table 1). Four studies^{26,32,34,36} included only patients with left-sided acute diverticulitis, and only the subgroup of patients with left-sided diverticulitis from one Korean study³³ was included in the present review. Twelve studies^{27–31,35,37–42} did not report the proportion of left-sided diverticulitis, but were conducted in the West. Most studies included all patients with acute diverticulitis; two^{28,30} included only patients with uncomplicated diverticulitis. Eight studies^{26,28,29,32–34,36,37} excluded patients who underwent colonoscopy before (varying from 6 months to 2 years) the diagnosis of acute diverticulitis. Colorectal carcinoma was reported in all 17 studies^{26–42}. Eight studies^{28,31–34,37,38,40} used the correct definition of advanced adenoma and could therefore be used for analysis of ACN (colorectal carcinoma and advanced adenoma combined). Only two studies^{34,37} included a group of asymptomatic controls from a screening colonoscopy cohort; one study³⁷ matched each patient with diverticulitis to a control patient based on sex and age, and the other³⁴ selected patients aged between 50 and 75 years, of similar age to patients with acute diverticulitis. Ten of the 17 studies reported whether patients had undergone a complete colonoscopy. Six studies^{29–31,34,36,37} reported caecal intubation rates above 90 per cent; the caecal intubation

Table 1 Summary of study characteristics

Reference	Setting	Design	Left-sided (%)	Caecal intubation (%)	Age (years)*
Alexandersson <i>et al.</i> ³⁰	Iceland	Retrospective	n.r.	91	58 (50–67)†
Andrade <i>et al.</i> ³¹	Portugal	Retrospective	n.r.	100	55 (11.1)†
Brar <i>et al.</i> ³²	Canada	Retrospective	100	86	55 (27–90)‡
Chabok <i>et al.</i> ²⁶	Sweden	Prospective	100	n.r.	56 (27–84)§
Choi <i>et al.</i> ³³	Korea	Retrospective	100	n.r.	n.r.
Daniels <i>et al.</i> ³⁴	Netherlands	Retrospective	100	91	57 (49–65)†
Elmi <i>et al.</i> ³⁵	USA	Retrospective	n.r.	n.r.	n.r.
Hjern <i>et al.</i> ²⁷	Sweden	Prospective	n.r.	n.r.	56 (29–79)‡
Lahat <i>et al.</i> ²⁸	Israel	Prospective	n.r.	88	60(12.7)
Lau <i>et al.</i> ³⁶	Australia	Retrospective	100	93	n.r.
Leclaire <i>et al.</i> ³⁷	France	Retrospective	n.r.	97	60.9(12.6)
Ou <i>et al.</i> ³⁸	Canada	Retrospective	n.r.	80	59.4(15.1)
Sakhnini <i>et al.</i> ²⁹	Israel	Prospective	n.r.	98	63 (30–89)§
Sallinen <i>et al.</i> ³⁹	Finland	Retrospective	n.r.	76	58.3(13.9)
Schmilovitz-Weiss <i>et al.</i> ⁴⁰	Israel	Retrospective	n.r.	n.r.	61.8(14.3)
Suhardja <i>et al.</i> ⁴¹	Australia	Retrospective	n.r.	n.r.	58.8 (47–71)†
Zaman <i>et al.</i> ⁴²	UK	Retrospective	n.r.	n.r.	n.r.

*Values are mean(s.d.) unless indicated otherwise; values are †median (i.q.r.), ‡mean (range) and §median (range). n.r., Not reported.

rate in the other four studies^{28,32,38,39} ranged from 76 to 88 per cent.

Population characteristics

A total of 3296 patients with acute diverticulitis was included in this review. The subgroup with uncomplicated acute diverticulitis across studies consisted of 959 patients.

Critical appraisal

Results of the risk-of-bias analysis are shown in *Table S2* (supporting information). The quality of studies varied from moderate to good, ranging from four to seven stars on the Newcastle–Ottawa Scale. Most studies were mainly biased by the lack of a control group or the limited comparability between patients with acute diverticulitis and groups of asymptomatic controls. Most studies did not state which patients, among all those diagnosed with acute diverticulitis, eventually underwent colonoscopy. Patients with a deviant clinical course, for example persistent or progressive disease, may have undergone surgery before colonoscopy could be performed, risking selection bias for the patients who did undergo colonoscopy. The risk of publication bias was assessed for two outcomes: prevalence of colorectal carcinoma in all patients with acute diverticulitis and prevalence of colorectal carcinoma in the subgroup with uncomplicated acute diverticulitis (*Fig. S1*, supporting information). The funnel plot of studies assessing all

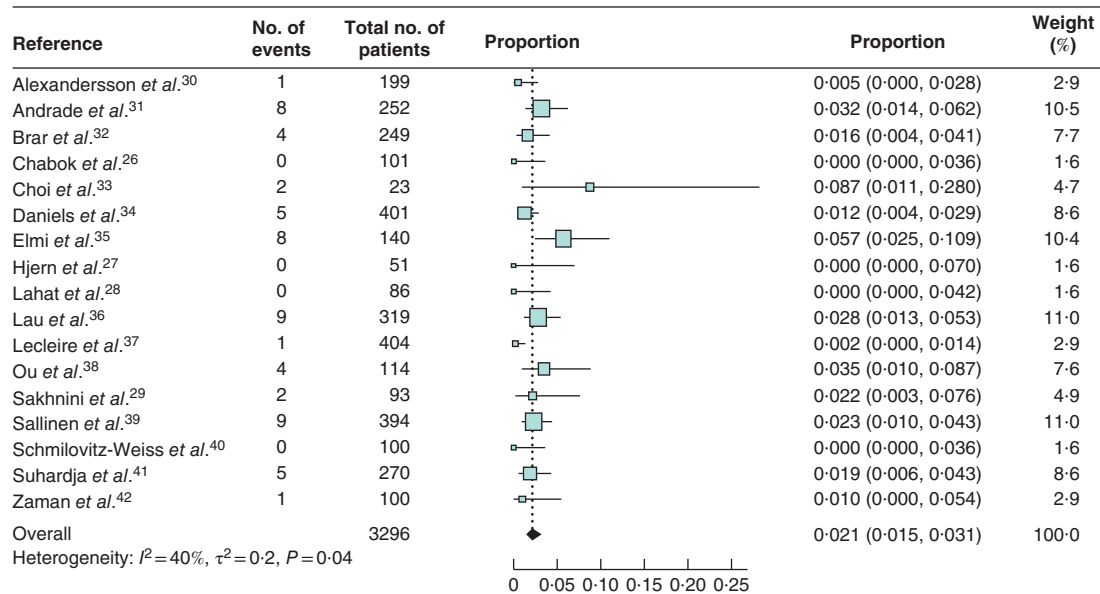
patients with acute diverticulitis was slightly asymmetrical regarding small studies. Some small studies with a higher proportion of colorectal carcinoma may be considered missing. The funnel plot of the subgroup analysis in uncomplicated acute diverticulitis was symmetrical.

Prevalence of colorectal cancer and advanced colorectal neoplasia

The risk of colorectal carcinoma in patients with acute diverticulitis was comparable to that in asymptomatic controls (risk ratio 1.80, 95 per cent c.i. 0.66 to 4.96) in the meta-analysis of data from only two studies^{34,37} with a control group. All 17 studies reported rates of colorectal carcinoma in patients with acute diverticulitis, yielding a pooled colorectal carcinoma prevalence of 2.1 (95 per cent c.i. 1.5 to 3.1) per cent ($I^2 = 40$ per cent) (*Fig. 2*). The pooled prevalence of ACN was 6.9 (5.0 to 9.4) per cent ($I^2 = 61$ per cent) based on eight studies^{28,31–34,37,38,40} (*Fig. 3*). The subgroup analysis of 959 patients with uncomplicated acute diverticulitis from six studies^{28,30–32,40,41} showed a pooled colorectal carcinoma prevalence of 0.5 (0.2 to 1.2) per cent ($I^2 = 0$ per cent) (*Fig. 4a*). Subgroup analysis of 197 patients with complicated acute diverticulitis from four studies^{31,32,40,41} showed a pooled colorectal carcinoma prevalence of 8.3 (4.2 to 15.8) per cent ($I^2 = 40$ per cent) (*Fig. 4b*).

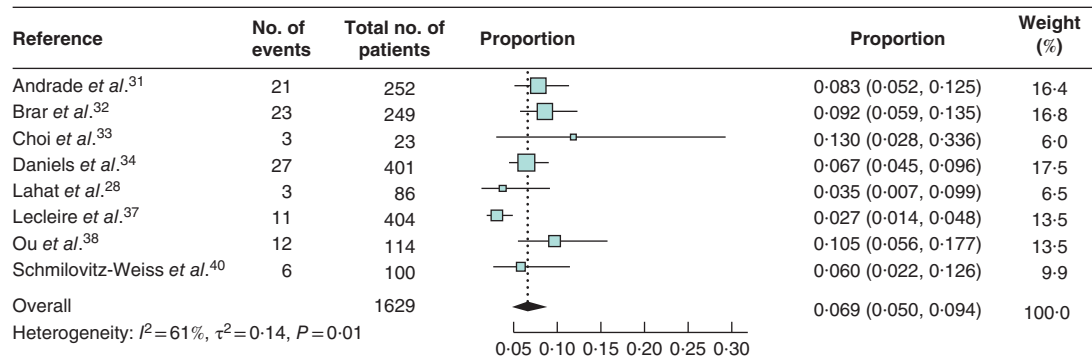
Ten studies^{29,30,32,34–39,42}, including 43 patients with colorectal carcinoma, reported the location of the

Fig. 2 Forest plot of colorectal cancer prevalence in patients with acute diverticulitis



A random-effects model was used for meta-analysis. Proportions are shown with 95 per cent confidence intervals.

Fig. 3 Forest plot of advanced colorectal neoplasia prevalence in patients with acute diverticulitis

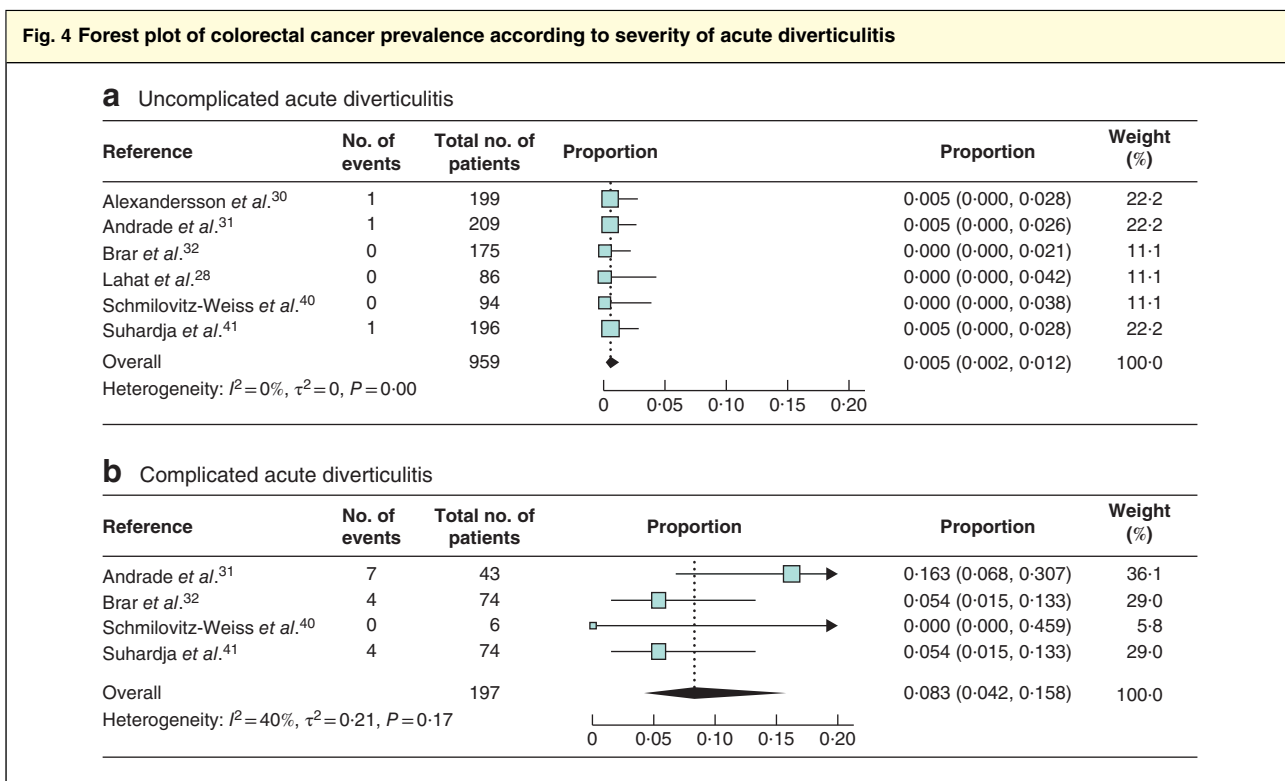


A random-effects model was used for meta-analysis. Proportions are shown with 95 per cent confidence intervals.

carcinoma. Almost all tumours (41 of 43) were found at the site of the presumed acute diverticulitis.

Two studies^{31,32} used logistic regression analyses to assess risk factors for ACN in the groups of patients with acute diverticulitis included in the present systematic review. Both found that patients with an abscess were at significantly higher risk of having ACN than those with uncomplicated acute diverticulitis, with multivariable odds ratios of 3.15 (95 per cent c.i. 1.59 to 11.59) and 4.15 (1.68 to 10.30) respectively. Older age was an independent

predictor of the presence of ACN in both studies. Two other studies^{36,39} used logistic regression, but performed these analyses on a combined group of patients who underwent colonoscopy and, if no colonoscopy had been performed, patients whose follow-up data were collected using a cancer registry. These two studies assessed the risk of colorectal carcinoma instead of ACN. Nevertheless, their results were comparable to those of studies that included only patients who underwent colonoscopy; diverticular abscess was an independent risk



a Uncomplicated and b complicated acute diverticulitis. A random-effects model was used for meta-analysis. Proportions are shown with 95 per cent confidence intervals.

factor for (the presence of) colorectal carcinoma in both studies.

Colonoscopy-related adverse events

Only four studies^{28,29,37,40} reported colonoscopy-related adverse events. In two studies^{28,40} (86 and 100 patients respectively), no complications occurred. In the other two studies^{29,37} (93 and 404 patients respectively), three patients in total developed a perforation after colonoscopy; one was secondary to polypectomy and two were diverticular perforations.

Discussion

The risk of having colorectal carcinoma seemed to be comparable in patients with acute diverticulitis and asymptomatic controls, but only two studies could be included in this comparison, limiting firm conclusions. Three systematic reviews^{24,43,44} on this topic were published in 2014. The selection of studies included varied between these reviews and differed substantially from that in the present systematic review. Few studies in the previous reviews were included in the present systematic review,

mainly because of differences in inclusion and exclusion criteria (Table S3, supporting information). Only one systematic review⁴⁴ assessed the prevalence of colorectal carcinoma in all patients with acute diverticulitis, yielding a prevalence of 1.6 (95 per cent c.i. 0.9 to 2.8) per cent. The slightly lower prevalence compared with the present result may be explained by the fact that the 2014 meta-analysis⁴⁴ included two studies^{45,46} in which some patients were diagnosed by ultrasonography, one study⁴⁷ in which colonic evaluation was performed by barium enema or CT colonography in some patients, one study⁴⁸ that undertook colonoscopies up to 2 years before the episode of acute diverticulitis, two studies^{28,49} with overlapping patients cohorts, and one conference abstract⁵⁰ that was never published as a full paper.

The three previous systematic reviews found a slightly higher prevalence of colorectal carcinoma in patients with uncomplicated acute diverticulitis than the present systematic review: 1.5 (95 per cent c.i. 1.0 to 2.3) per cent²⁴, 1.2 (0.7 to 1.9) per cent⁴³ and 0.7 (0.3 to 1.4 per cent)⁴⁴. Two reviews^{24,44} included studies^{26,29,35,36} of patients with complicated diverticulitis rather than the intended uncomplicated disease only. Furthermore, these previous

systematic reviews included several studies or subgroups of patients specifically excluded from the present review because the diverticulitis diagnoses were made partly using ultrasonography^{45,46,51} and not CT, colonoscopies were performed up to 2 years before⁴⁸ or up to 11 years after³⁵ the acute diverticulitis episode, or studies were only published as a conference abstract^{50,52,53}. Moreover, one of the systematic reviews⁴³ reported a crude mean proportion instead of using a fixed- or random-effects model with a pooled, weighted mean proportion. The prevalence of ACN was reported in only one previous systematic review²⁴, with a prevalence of 5.0 (3.8 to 6.7) per cent, comparable to that in the present review.

To assess the role of colonoscopy after an episode of acute diverticulitis, the prevalence of colorectal carcinoma and ACN needs to be compared with that in healthy individuals without acute diverticulitis, comprising asymptomatic controls. Because studies including such a control group were scarce, the only other way is to compare prevalence in the present systematic review with that in published data from cohorts of asymptomatic individuals^{54–61}. Eight studies assessed the prevalence of colorectal carcinoma and ACN in asymptomatic individuals who underwent screening colonoscopy (not related to diverticulitis). One study⁵⁶ included asymptomatic individuals aged over 40 years, and the other seven^{54,55,57–61} included only those over 50 years of age, comparable to the age of patients with acute diverticulitis included in the present systematic review.

The eight screening colonoscopy studies reported a prevalence of colorectal carcinoma of between 0.4 and 1.0 per cent, compared with 2.1 per cent among all patients with acute diverticulitis in the present systematic review. The prevalence of colorectal carcinoma in patients with acute diverticulitis therefore seems to be higher than that in asymptomatic screening subjects. However, the 0.5 per cent prevalence of colorectal carcinoma in patients with uncomplicated acute diverticulitis is comparable to the prevalence in controls. The prevalence of ACN ranged from 3.8 to 10.3 per cent in the eight studies with asymptomatic controls, and seems comparable to that in patients with acute diverticulitis here (6.9 per cent). However, it is possible that the true ACN prevalence may be slightly higher in patients with acute diverticulitis owing to incomplete colonoscopies. Caecal intubation at colonoscopy may be more difficult after acute diverticulitis as luminal narrowing, spasm, muscular hypertrophy and fixation can cause technical difficulties^{8,9,62}. Of the ten studies in the present review that reported the proportion of complete colonoscopies (caecal intubation), four did not have adequate caecal intubation rates (defined as at least 90 per cent⁶³), which could have led to underestimation

of the ACN prevalence. As almost all colorectal carcinomas are found at the site where acute diverticulitis is diagnosed, the effect of these lower caecal intubation rates is considered to be limited for the prevalence of colorectal carcinoma, but may be important for the prevalence of ACN.

It has been proposed that the association between acute diverticulitis and colorectal malignancy is not causal⁶⁴. It is likely that colorectal carcinomas are sometimes misdiagnosed as acute diverticulitis because they have similar clinical and radiological signs. As the risk of malignancy is increased predominantly in complicated acute diverticulitis, misdiagnosis seems to be an issue particularly in this group. The comparable prevalence of colorectal carcinoma in asymptomatic screening controls and patients with uncomplicated diverticulitis also supports this misdiagnosis hypothesis. Apparently, a colorectal malignancy is not easily missed in a radiological image of uncomplicated diverticulitis, but it can be missed in an image of complicated diverticulitis.

A limitation of this review is the lack of studies including asymptomatic controls. Only two studies included such a control group, so conclusions are based mainly on comparison with the colorectal carcinoma prevalence in asymptomatic controls reported in the literature. Although a direct comparison would have been preferable, the consistency of the published prevalence seems to be a sign of the robustness of this comparison; the colorectal carcinoma prevalence in all screening colonoscopy studies from the literature (0.4–1.0 per cent) is below the 95 per cent confidence interval of the prevalence in patients with acute diverticulitis in the present review (95 per cent *c.i.* 1.5 to 3.1 per cent), but within the 95 per cent confidence interval of the prevalence in patients with uncomplicated acute diverticulitis (0.2 to 1.2 per cent). Another potential limitation is that the group of patients who underwent colonoscopy may have been subject to selection bias. Patients with a protracted clinical course may have undergone surgery before a colonoscopy could have been done, leading to possible underestimation of the prevalence of malignancy. On the other hand, patients with uncomplicated diverticulitis who did not develop persistent complaints are less likely to have undergone colonoscopy owing to doctor or patient preferences, which means that the prevalence of colorectal carcinoma may have been overestimated.

Several national and international guidelines^{11–18} on acute diverticulitis have been published in recent years. The recommendations in these guidelines are conflicting, and the evidence on which they based differs. Most of the guidelines (6 of 8)^{11,13–15,17,18} recommend routine

colonoscopy after an episode of acute diverticulitis to rule out malignancy, although the American Gastroenterological Association (AGA)¹⁷ suggests that previous colonoscopies, co-morbidities, persistent symptoms and patients' preferences may influence the decision. The scientific grounds for the recommendations in these six guidelines are noteworthy. Whereas the AGA¹⁷ and German¹⁵ guidelines are based on a previous systematic review, two other guidelines^{11,18} used only two observational studies, and an Italian guideline¹³ published in 2015 stated that evidence-based data were not available. The American Society of Colon and Rectal Surgeons¹⁴ made strong recommendations based on studies with a low quality of evidence, but based their recommendation for routine colonoscopy mainly on studies that assessed the risk of malignancy in a selected group of patients with signs suggestive of malignancy, such as colonic wall thickening or mass on CT. Two guidelines^{12,16} recommend not performing routine colonoscopy after an episode of acute diverticulitis; of these, the World Society of Emergency Surgery (WSES)¹⁶ recommends omitting colonoscopy only in patients with uncomplicated acute diverticulitis. The fact that the AGA¹⁷ and WSES¹⁶ guidelines make opposite recommendations based on the same systematic reviews from 2014 highlights the interpretational uncertainty of previous evidence. The more robust evidence in the present systematic review may reduce the conflicting interpretation of evidence, and may result in higher levels of consensus on this topic.

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Disclosure: The authors declare no conflict of interest.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.