

Strategies for Detecting Colorectal Cancer in Patients with Inflammatory Bowel Disease: A Cochrane Systematic Review and Meta-Analysis

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Abbreviations:

AE (adverse event), CD (Crohn's disease), CI (confidence interval), CRC (colorectal cancer), GRADE (The Grading of Recommendations Assessment, Development, and Evaluation), HD-WLE (high definition white light endoscopy), IBD (inflammatory bowel disease), NOS (Newcastle-Ottawa Quality Assessment Scale), OR (odds ratio), SCENIC (Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease), RCT (randomized controlled trial), RR (risk ratio), SIR (standardized incidence ratio), TNM (Tumor Node Metastasis), UC (ulcerative colitis)

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ABSTRACT

Objectives:

Patients with longstanding ulcerative colitis (UC) and colonic Crohn's disease (CD) have an increased risk of colorectal cancer (CRC). We assess the effectiveness of endoscopic surveillance in patients with inflammatory bowel disease (IBD) for diagnosing CRC and reducing CRC-related mortality.

Methods:

MEDLINE, EMBASE, and CENTRAL were searched from inception to September 19, 2016. Randomized controlled trials (RCTs), observational cohorts, or case-control studies assessing any form of endoscopic surveillance for early CRC detection were eligible for inclusion; studies without a comparison non-surveillance group were excluded. The primary outcome was rate of CRC detection. Secondary outcomes were rate of early (Duke stage A & B) versus late (Duke stage C & D) CRC detection and rate of CRC-related death. Data was pooled using fixed or random effects models based on the degree of heterogeneity; pooled odds ratios (OR) with 95% confidence intervals (CI) were calculated using the Mantel-Haenszel method.

Results:

Five observational studies evaluating 7199 IBD patients were included; no RCTs met criteria for inclusion. There are limited new studies evaluating this clinical question (last included study published 2014). There was a significantly higher rate of cancer detection in the non-surveillance group (3.2%, 135/4256) compared to the surveillance group (1.8%, 53/2895) (OR 0.58 [95% CI: 0.42–0.80], $p < 0.001$). In four pooled studies, there was a significantly lower rate of CRC-associated death in the surveillance group (8.5%, 15/176) compared to the non-surveillance group (22.3%, 79/354) (OR 0.36 [95% CI: 0.19–0.69], $p = 0.002$). In two pooled studies, there was a significantly higher rate of early stage CRC detection in the surveillance

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group (15.5%, 17/110) compared to the non-surveillance group (7.7%, 9/117) (OR 5.40 [95% CI: 1.51–19.30], $p=0.009$).

Conclusions:

Colonoscopic surveillance in IBD is associated with a reduction in CRC development and CRC-associated death, as well as increased detection of early stage CRC.

Keywords:

Ulcerative colitis, Crohn's disease, colorectal cancer, colonoscopy, surveillance

STUDY HIGHLIGHTS

1. WHAT IS CURRENT KNOWLEDGE

- Patients with ulcerative colitis and colonic Crohn's disease have an increased risk of colorectal cancer.
- Surveillance colonoscopy for dysplasia and early CRC detection is recommended by multiple international societies for patients with chronic colonic inflammation
- In a previous Cochrane review (Collins 2006), there was no definitive evidence that surveillance colonoscopy prolonged survival in IBD patients

2. WHAT IS NEW HERE

- In this contemporary systematic review and meta-analysis, we identified five relevant observational studies enrolling 7199 IBD patients, but no randomized controlled trials.
- On pooled analysis, a 42% reduction in the odds of CRC with surveillance colonoscopy was observed
- On pooled analysis, a 64% reduction in the odds of CRC-related death with surveillance colonoscopy was observed
- A greater than 5-fold increase in the odds of early stage CRC detection with surveillance colonoscopy

INTRODUCTION

Patients with longstanding ulcerative colitis (UC) and colonic Crohn's disease (CD) are at increased risk of developing colorectal cancer (CRC), likely as sequelae of chronic inflammation (1). Inflammatory bowel disease (IBD)-associated CRC has a unique phenotype compared to sporadic CRC: it typically occurs at a younger age (2, 3), in more proximal locations (4), with aggressive mucinous or signet ring cell histology (5), and frequently with multiple synchronous malignancies (5). In a meta-analysis of population-based studies, the risk of CRC in IBD patients was increased over two-fold (standardized incidence ratio (SIR) 2.4 [95% confidence interval (CI): 2.1–2.7]) compared to the general population (6). Furthermore, CRC is estimated to account for approximately 15% of all deaths in IBD patients (2).

The goal of endoscopic surveillance is to detect and intervene on precursor dysplasia either through endoscopic or surgical therapy, or to detect CRC at an early, curative stage, which may lead to an improved prognosis and survival (7, 8). Multiple international societies have endorsed endoscopic surveillance for patients with chronic UC or colonic CD (9-15) and it has become a cornerstone of IBD-related care, despite paucity of direct evidence for mortality reduction. Understanding the effectiveness of surveillance is crucial: with the increasing incidence of IBD, the costs associated with ongoing surveillance will also continue to rise (16). Not only are surveillance programs expensive, they result in invasive and recurrent patient interventions that are not without risk.

In a previous meta-analysis, Collins *et al.* did not demonstrate a statistically significant reduction in CRC-related death in IBD patients undergoing colonoscopy surveillance (pooled relative risk RR 0.81 [95% CI: 0.17–3.83]) (7). However, this study was published over a decade ago. Strategies for both IBD management and surveillance have evolved since that time and the introduction of highly effective biologic therapies capable of inducing clinical, endoscopic, and

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histologic remission in IBD may have altered the natural history of the disease (17). Currently, the optimal strategy for endoscopic surveillance with respect to timing of colonoscopy, interval between colonoscopies, management of complex lesions using advanced endoscopic resection techniques, and use of chromoendoscopy versus high-definition white light endoscopy (HD-WLE) remains controversial.

In this systematic review and meta-analysis, we update the previous study by Collins *et al* (7). We evaluate the literature with respect to the efficacy of colonoscopy surveillance for CRC detection, stage of CRC diagnosis, and CRC-related mortality in IBD patients with chronic colonic inflammation.

METHODS

Search Strategy

We searched MEDLINE (1948-2016), EMBASE (1947-2016), the Cochrane Central Register of Controlled Trials (1994-2016), and the Cochrane IBD Group Specialized Register from inception to September 19, 2016. This was supplemented with hand-searches of reference lists of potentially relevant papers and conference proceedings from Digestive Disease Week, United European Gastroenterology Week, and the European Crohn's and Colitis Organization Congress. The search strategy is detailed in [Supplemental Materials and Methods](#).

Study Eligibility Criteria

Randomized controlled trials (RCTs) and observational (cohort or case-control) studies evaluating any form of endoscopic surveillance aimed at early detection of CRC in patients of any age with a diagnosis of UC or colonic CD defined by conventional clinical, endoscopic, and histologic criteria selected for surveillance based solely on the duration and extent of disease were eligible for inclusion. Studies without a non-surveillance comparison group were excluded.

Outcomes

The primary outcome was the comparative rate of CRC diagnosis between the surveillance and non-surveillance group. Comparative rates of the following secondary outcomes between the surveillance and non-surveillance group were also evaluated: 1) early stage (Duke stage (18) A & B) CRC diagnosis; 2) late stage (Duke stage C & D) CRC diagnosis; 3) colectomy for CRC; and 4) death from CRC. In the original study protocol, time to cancer detection, time to death, and proportion of patients with adverse events (AEs), serious AEs, and study withdrawal due to AEs were *a priori* defined secondary outcomes; however, the included studies did not sufficiently report these outcomes for inclusion in meta-analysis (19).

Data Extraction

Potentially relevant articles were reviewed independently by three authors (WAB, TMN, CEP) to determine eligibility; disagreements were resolved by consensus. Results from the included studies were then extracted independently by two authors (WAB and TMN) into a standardized extraction form. The proportion of patients dying from CRC in the surveillance and control groups of each study was derived from life tables, survival curves, or where possible, by calculating life tables from the data provided.

Assessment Risk of Bias and Quality of Evidence

Methodological quality of each included study was independently evaluated by two authors (WAB and TMN) using the Newcastle-Ottawa Quality Assessment Scale (NOS) (20). The NOS uses a star system to assess quality of cohort and case-control studies, with a maximum score of nine stars. For cohort studies, quality is evaluated on three domains: selection of study groups, comparability between the study and control group, and ascertainment of exposure or outcome of interest. For case-control studies, study quality is assessed on selection of study groups, comparability between cases and controls, and ascertainment of exposure.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to evaluate the overall quality of evidence supporting the primary and secondary outcomes (21). Evidence from RCTs is considered high quality and evidence from observational studies is considered low quality; quality of evidence can be downgraded due to risk of bias, indirect evidence, inconsistency/unexplained heterogeneity, imprecision, and publication bias. Overall evidence quality is classified as high, moderate, low, and very low quality. Potential reporting bias was assessed by comparison of outcomes listed in protocols to published manuscripts; if protocols were not available, outcomes listed in the methods section were compared to those reported in the results section of published manuscripts. Funnel plots

for evaluation of potential publication bias were not constructed due to the small number of included studies ($n < 10$).

Data Synthesis and Analysis

For dichotomous outcomes, we calculated the odds ratio (OR) and corresponding 95% confidence interval (CI). Data from individual studies were combined for meta-analysis and the pooled OR and 95% CI was calculated using the Mantel-Haenzel method. Heterogeneity was assessed among studies using the χ^2 test (p -value > 0.10 was considered statistically significant) and the I^2 statistic. An I^2 value of 25% indicates low heterogeneity, 50% indicates moderate heterogeneity, and 75% indicates high heterogeneity (22). A fixed effects model was used to pool data unless significant heterogeneity existed between studies; a random-effects model was used if heterogeneity existed (I^2 50-75%). Data was not pooled in meta-analysis if a high degree of heterogeneity ($I^2 > 75\%$) existed. Data analysis was conducted using Review Manager (RevMan 5.3.5).

RESULTS

Search Results and Study Characteristics

The literature search identified 12,896 records; 9499 records were screened after removal of duplicates ([Figure 1](#)). 41 full-text articles were evaluated; most were excluded due to the absence of a non-surveillance control cohort. No RCTs met criteria for inclusion. Seven reports of five observational studies from 1993-2014 were included (23-27). Of these five studies, four (23, 25-27) were cohort studies and one (24) was a case-control design. Four studies (24-27) were retrospective and one study (23) was prospectively performed. In total, 7199 patients with UC or colonic CD were evaluated. Characteristics of the included studies is summarized in [Table 1](#) and patient characteristics from the included studies are reported in [Table 2](#).

Cancer Detection

Three studies had available data for rates of CRC detection (24, 25, 27), enrolling 7151 patients (2895 in the surveillance group vs. 4256 in the non-surveillance group). CRC was detected in 53/2895 (1.8%) patients in the surveillance group compared to 135/4256 (3.2%) patients in the non-surveillance group. Using a fixed effects model, surveillance was associated with a 42% reduction in the odds of CRC detection, which was statistically significant (OR 0.58 [95% CI: 0.42–0.80], $p<0.001$) ([Figure 2A](#)). In a sensitivity analysis excluding the most heavily weighted study (Ananthakrishnan *et al.* (27)), the magnitude and direction of effect of surveillance colonoscopy on CRC detection was similar, however the results were no longer statistically significant (OR 0.67 [95% CI: 0.30–1.50]).

CRC-Related Death

Death due to CRC was reported in four studies (23, 25-27), enrolling 530 patients (176 in the surveillance group vs. 354 in the non-surveillance group). CRC-related death occurred in 8.5% (15/176) of patients in the surveillance group compared to 22.3% (79/354) of patients in the

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non-surveillance group. Using a fixed effects model, surveillance was associated with a 64% reduction in the odds of CRC-related death, which was statistically significant (OR 0.36 [95% CI: 0.19–0.69], $p=0.002$) ([Figure 2B](#)). This effect was maintained even in sensitivity analysis excluding the study by Ananthakrishnan *et al.* (27) (OR 0.40 [95% CI: 0.17–0.95]).

Tumor Stage

Two studies had available data to examine detection of early and late stage CRC (23, 25). A higher rate of early stage CRC was detected in the surveillance group (15.5%, 17/110) compared to the non-surveillance group (7.7%, 9/117) using a fixed effects model (OR 5.40 [95% CI: 1.51–19.30], $p=0.009$) ([Figure 2C](#)), which was statistically significant. In comparison, there was a nominally but not statistically significant lower rate of detection of late stage CRC in patients undergoing surveillance (9.1%, 10/110) compared to patients not undergoing surveillance (16.2%, 19/117) (OR 0.46 [95% CI: 0.08–2.51], $p=0.37$); a random-effects model was used for this analysis due to significant heterogeneity ($I^2 = 71\%$) ([Figure 2D](#)). One study (26) described CRC stage at diagnosis using the American Joint Committee on Cancer 6th Edition Tumor Node Metastasis (TNM) staging system: surveillance was associated with a higher rate of diagnosing stage 1 CRC compared to non-surveillance (43.5%, 10/23 vs. 15.7%, 19/121, $p=0.008$).

Colectomy

In one study, surveillance was associated with a lower risk of colectomy (36.3%, 33/91) compared to non-surveillance (53.7%, 51/95) (OR 0.49 [95% CI: 0.27–0.88]) (25).

Risk of Bias and Quality of Evidence

The risk of bias in the five included non-randomized trials was assessed using the NOS; all studies scored well based on selection of study groups, comparability between intervention and

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276 control group, and outcome and exposure ascertainment ([Supplemental Table 1](#)). A GRADE
277 analysis indicated that the quality of evidence supporting the outcomes of cancer detection,
278 CRC-related death, and tumor stage was very low due to the observational nature of the
279 included studies and imprecision of the effect estimates. No potential reporting bias was
280 detected.
281

DISCUSSION

As the incidence of IBD increases worldwide, a greater resource burden will be placed on endoscopic surveillance programs for CRC detection (16). A prospective, long-term, RCT directly assessing survival benefit with endoscopic surveillance in IBD patients would be challenging to perform due to low event rates; thus the best available evidence arises from observational data. Recognizing the inherent limitations of observational studies for drawing conclusions regarding causality, we updated a previous Cochrane systematic review and meta-analysis to evaluate the impact of surveillance colonoscopy on detection of CRC and death attributable to CRC in IBD patients. This updated review suggests that the ongoing use of colonoscopy surveillance may reduce both CRC development and CRC-associated death through detection of early stage cancers. Although the quality of evidence is very low, an RCT that answers these questions is unlikely to be performed, particularly given the ethical considerations precluding randomization of IBD patients to a non-surveillance arm. Thus, we consider this pooled analysis to be the best available evidence at present to inform the benefit of colonoscopic surveillance.

Drawing conclusions regarding causality are limited by potential confounding bias in the included observational studies. Most authors attempted to control for confounders such as patient age and disease duration in multivariable logistic or Cox regression models ([Table 1](#)). However, important covariates such as concomitant therapy, disease phenotype, and frequency of assessments were not always adjusted for ([Table 2](#)). The largest study in this meta-analysis by Ananthakrishnan *et al.* (27) included 6823 IBD patients: the authors retrospectively examined the effect of colonoscopy within 6-36 months of CRC diagnosis (for cases) or end of follow-up (for controls) in a well-validated electronic IBD database capturing two tertiary care referral centers. In sensitivity analyses excluding this study, our conclusions of a significant benefit to surveillance colonoscopy on mortality were unchanged and surveillance was associated with a

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33% non-statistically significant reduction in CRC detection. Ananthakrishnan *et al.* further demonstrated the beneficial effect of surveillance colonoscopy, which was robust even after adjusting for disease phenotype, extent, primary sclerosing cholangitis, erythrocyte sedimentation rate, follow-up duration, and intensity of health care utilization (27).

Since IBD-associated CRC is postulated to arise from precursor dysplasia (28), the theoretical benefit of surveillance colonoscopy is to detect and remove dysplasia, either endoscopically or surgically, prior to the development of CRC. Screening programs for sporadic CRC leverage the therapeutic window between the onset of dysplasia and development of CRC as an opportunity for endoscopic removal of pre-cancerous lesions (29). Carcinogenesis in sporadic CRC typically results from the “adenoma-carcinoma sequence”, with the progressive accumulation of somatic mutations in a dysplastic focus; this process can take years and can be arrested by endoscopic polypectomy (30).

This surveillance model may not translate to the IBD population. First, strategies and tools for dysplasia detection in IBD patients have evolved substantially. Previous recommendations for random four-quadrant biopsies every 10 cm have come under scrutiny with multiple studies demonstrating that targeted biopsies may be more effective for dysplasia detection than random biopsies (31-33). Second, chromoendoscopy may be superior to white light endoscopy for dysplasia detection (15). However, this was informed by studies conducted before widespread use of HD-WLE and a recent RCT of HD-WLE versus chromoendoscopy demonstrated no significant difference in dysplasia or neoplasia detection (34). Three studies included in our meta-analysis specified the use of random four-quadrant biopsy surveillance and none identified the use of either HD-WLE or chromoendoscopy. Updated studies evaluating the efficacy of these different strategies on CRC detection and mortality are required.

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Although dysplasia detection is an important surrogate for future CRC risk, it does not necessarily confer improved quality of life or increased survival in patients with IBD. While resecting polypoid dysplasia is associated with low future CRC risk (35), it does not obviate the high risk of CRC associated with invisible dysplasia or non-polypoid dysplasia (36). This highlights the difference in tumorigenesis in patients with IBD compared to sporadic CRC. In IBD, chronic inflammation with repeated epithelial wounding and repair results in selection for mutant clones resistant to apoptosis and with accelerated growth better suited to a hostile microenvironment (37). Not only does this predispose to synchronous lesions but it also renders large areas of the colonic mucosa genetically unstable ("field cancerization") (38). Resection of circumscribed focal dysplastic lesions does not address the underlying predisposition to cancer development in histologically inflamed tissue and may not mitigate future CRC risk (39, 40).

Despite these challenges, we demonstrate in this meta-analysis that surveillance colonoscopy is associated with a decrease in both CRC development and death secondary to CRC. This mirrors epidemiologic data that suggests the incidence of IBD-associated CRC is decreasing, although this cannot be causally attributed to surveillance programs since other factors may influence this, such as better treatments to control inflammation. Initial estimates of cumulative CRC risk in UC patients were as high as 2% at 10 years, 8% at 20 years, and 18% at 30 years of disease (1). This risk has been recently downgraded: in a meta-analysis of nine population-based studies, Lutgens *et al.* report a SIR for IBD-associated CRC of 1.7 [95% CI: 1.2–2.2] (41). Advances in endoscopic surveillance and dysplasia detection are postulated mechanisms contributing to this decrease in CRC incidence. However, enhanced medical therapies for control of active inflammation and possible chemoprophylaxis protection from 5-aminosalicylates are potential confounders (42).

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Although the incidence of IBD-associated CRC may be decreasing, the number of patients undergoing surveillance is increasing due to the rising incidence of IBD (16). Given the substantial financial and resource costs associated with colonoscopy, identifying IBD patients at highest risk for CRC development for targeting screening is critical. Current guidelines for the timing of surveillance colonoscopy are primarily based on disease extent and duration, which are demonstrated risk factors for IBD-associated CRC (37). Other risk factors for IBD-associated CRC include increasing age, male sex, and strong family history (43). However, these are relatively crude predictors for identifying specific patients that would benefit from surveillance. Future research should focus on improving the precision of CRC risk estimation, potentially through incorporation of less invasive tests such as fecal DNA testing or rectal mucosal fluorescence in situ hybridization analysis for chromosomal instability (44). Fecal immunochemical testing has been adopted for sporadic CRC screening in average risk populations; however, its application to IBD patients is limited by false positives due to detection of fecal hemoglobin from mucosal ulcerations in active inflammation (45).

The effect of surveillance colonoscopy on colectomy was investigated by Lashner *et al.*, who reported significantly lower rates of colectomy for CRC, dysplasia, or active disease (OR 0.49 [95% CI: 0.27–0.88], $p=0.02$) in patients receiving surveillance colonoscopy compared to those in the non-surveillance group (25). However, these results should be re-examined given that endoscopic techniques for both lesion identification and excision have advanced significantly since this study. Furthermore, a finding of dysplasia no longer absolutely necessitates colectomy. Indeed, in patients with invisible low grade dysplasia, the decision for ongoing surveillance colonoscopy versus colectomy as the most cost-effective management strategy is dependent on multiple factors including age, comorbidity, and expected postoperative morbidity (46).

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Our study has several limitations. First and most importantly, no RCTs were eligible for inclusion, which limited the quality of evidence synthesis in GRADE analysis. However, RCTs that directly evaluate the effect of colonoscopy surveillance on CRC in IBD patients are unlikely to ever be performed due to ethical and logistical considerations. Even retrospective studies that evaluate this question are difficult to perform because the pool of IBD patients not undergoing surveillance is limited. Second, limitations of the included studies need to be considered when interpreting pooled results from meta-analysis. Such limitations include: 1) the potential for volunteer bias among patients seeking out surveillance colonoscopy; 2) possible referral bias when data is derived from tertiary care centers that treat a higher prevalence of patients with refractory or severe disease; and 3) heterogeneous surveillance practices with respect to interval of repeat surveillance colonoscopy and biopsy strategy. Although we included all studies evaluating endoscopic surveillance, there was insufficient data to compare different surveillance strategies and comparative studies of HD-WLE, chromoendoscopy, and digital image enhancement colonoscopy are needed. Third, we evaluated the effect of surveillance on stage of CRC diagnosis by the Duke staging system; this has largely been replaced by the American Joint Committee on Cancer TNM staging system (47). However, many of the included studies were published before the TNM system was widely adopted and both classifications have distinct similarities with respect to depth of tumor penetration. Fourth, we did not evaluate the effect of polypectomy on mortality as it was outside the scope of this review. However, additional data linking dysplasia detection and endoscopic resection to reduction in IBD-associated CRC outcomes is needed.

In conclusion, in this Cochrane systematic review and meta-analysis, we demonstrate in pooled analysis from observational studies that colonoscopy surveillance results in a reduction in IBD-associated CRC development by 42% and CRC-associated death by 64% compared to patients who do not undergo surveillance. We speculate that this reduction in CRC-associated death is

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411 due to increased detection of early stage cancers associated with better prognosis. Updated
412 studies are required to evaluate the benefits of modern surveillance techniques, including
413 advancements in endoscopic technology and dysplasia resection. We further hypothesize that
414 additional benefits may be derived from surveillance: as therapeutic targets for both UC and CD
415 shift from symptom resolution towards normalization of histologic and endoscopic endpoints,
416 surveillance colonoscopy offers a further opportunity to tailor treatment towards targeting more
417 robust objective outcomes and improve long-term disease prognosis.
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GUARANTOR OF THE ARTICLE

JEE is the guarantor of the article and accepts full responsibility for the conduct of the study.

SPECIFIC AUTHOR CONTRIBUTIONS

WAB, VJ and JEE conceived and designed the study. WAB, TMN, and CEP were involved in data collection and analysis. WAB and CM drafted the initial manuscript. VJ and JEE contributed to manuscript editing. All authors approve the final draft.

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567 **TABLES AND FIGURES LEGEND**

568 **Figure 1.** Study flow diagram

569 **Figure 2.** Forest plots for effect of surveillance compared to non-surveillance for detection of
570 colorectal cancer (A), death from colorectal cancer (B), early stage colorectal cancer diagnosis
571 (C), and late stage colorectal cancer diagnosis (D) in patients with inflammatory bowel disease
572

573 **Table 1.** Characteristics of included studies

574 **Table 2.** Baseline reported patient characteristics

575 **Table 3.** Surveillance compared to non-surveillance for detection of colorectal cancer and death
576 from colorectal cancer in patients with inflammatory bowel disease
577

578 **Supplemental Materials and Methods.** Search Strategy

579 **Supplemental Table 1.** Risk of Bias Assessment using the Newcastle-Ottawa Scale

Study	Sample size (n)		Study population	Study design	Outcomes	Statistical Methods
	Surveillance (n)	Non-surveillance (n)				
Lashner 1990 (25)	186		UC (disease duration ≥ 9 years)	Retrospective cohort study (1984-1986), annual colonoscopy with q10cm biopsies	Survival, death CRC detection Colectomy rate	Kaplan-Meier survival analysis (log-rank test) Multivariate Cox regression analysis
	91	95				
Choi 1993 (23)	41		UC (disease duration ≥ 8 years)	Prospective cohort study (1974-1991), UC patients who developed CRC, colonoscopy q2 years with biopsies	5-year survival Tumor stage Death	Kaplan-Meier survival analysis (Tarone-Ware test)
	19	22				
Karlen 1998 (24)	142		UC (disease duration ≥ 5 years)	Nested population-based case-control study (1958-1988), 40 patients with UC and 102 controls, colonoscopy with multiple biopsies	Exposure to surveillance colonoscopy	Conditional logistic regression analysis (matched analysis)
	20	122				
Lutgens 2009 (26)	149		IBD (UC and CD)	Retrospective, pathology-database derived cohort study of IBD patients with CRC (1990-2006), colonoscopy q<3 years with q10cm biopsies	CRC-related death Tumor stage	Kaplan-Meier survival analysis (Tarone-Ware test) Multivariate Cox regression analysis
	23	126				
Ananthakrishnan 2014 (27)	6823		IBD (UC and CD)	Retrospective, population-based cohort study (1994-2014)	Diagnosis of CRC (by diagnostic coding for colon or rectal cancer)	Univariate and multivariate logistic regression modeling
	2754	4509				

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582 CD Crohn's disease, CRC colorectal cancer, UC ulcerative colitis

Study	Baseline Covariates	Surveillance	Non-Surveillance
Lashner 1990 (25)	Sex (n, male:female)	53:38	43:52
	Mean age at symptom onset (years, \pm SD)	25.5 (\pm 11.3)	26.5 (\pm 13.1)
	Family history of CRC	1	4
Choi 1993 (23)	Mean age at UC onset (years, \pm SD)	24.9 (\pm 11.9)	30.2 (\pm 12.1)
	Mean disease duration (years, \pm SD)	18.5 (\pm 5.8)	17.6 (\pm 8.6)
	Pancolitis disease extent (%)	16 (84.2)	11 (50.0)
	Mean follow-up (years, \pm SD)	4.5 (\pm 2.9)	2.6 (\pm 3.2)
Karlen 1998 [†] (24)	Sex (n, male:female)	NR	NR
	Age at UC diagnosis (years)	NR	NR
	UC disease extent at diagnosis	NR	NR
Lutgens 2009 (26)	IBD (n, UC:CD)	18:5	71:54
	Sex (n, male:female)	17:6	72:54
	Median age at IBD diagnosis (years, range)	26 (9-50)	30 (6-83)
	Median age at CRC diagnosis (years, range)	48 (38-71)	49 (21-85)
	Primary sclerosing cholangitis (%)	2 (9%)	17 (14%)
	Mean follow-up (months, range)	57 (0-188)	51 (0-235)
Ananthakrishnan 2014 (27)	Median age (years, IQR)	47 (32-61)	49 (35-63)
	Median age at IBD diagnosis (years, IQR)	37 (24-51)	39 (27-54)
	Mean follow-up (years, IQR)	8 (5-12)	8 (5-11)
	Sex (% , male:female)	48:52	43:57
	Race (% , white:non-white)	87:13	87:13
	IBD (% , UC:CD)	49:51	54:46
	PSC (%)	3	2
	Any immunomodulator use (%)	40	21
	Any biologic use (%)	21	9
	Median C-reactive protein (mg/dL, IQR)	3.7 (1.4-10.4)	4.8 (1.6-16.7)

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584 † For Karlen *et al.* 1998 (24), baseline characteristics reported between cases and controls, not
585 surveillance vs. non-surveillance
586 CD Crohn's disease, CRC colorectal cancer, IBD inflammatory bowel disease, IQR interquartile
587 range, SD standard deviation, UC ulcerative colitis
588

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Table 3. Surveillance compared to non-surveillance for detection of colorectal cancer and death from colorectal cancer in patients with inflammatory bowel disease.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect OR (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Risk with non-surveillance*	Risk with surveillance			
Cancer detection (per patient)	32 per 1,000 ¹	19 per 1,000 (14 to 26)	0.58 (0.42 to 0.80)	7151 (3 studies)	⊕⊕⊕⊕ VERY LOW ¹
Death from colorectal cancer (per cancer)	223 per 1,000 ¹	94 per 1,000 (52 to 165)	0.36 (0.19 to 0.69)	530 (4 studies)	⊕⊕⊕⊕ VERY LOW ³
Cancer stage – Duke A or B (per cancer)	77 per 1,000 ¹	310 per 1,000 (112 to 617)	5.40 (1.51 to 19.30)	227 (2 studies)	⊕⊕⊕⊕ VERY LOW ⁴
Cancer stage – Duke C or D (per cancer)	162 per 1,000 ¹	82 per 1,000 (15 to 327)	0.46 (0.08 to 2.51)	227 (2 studies)	⊕⊕⊕⊕ VERY LOW ⁵

CI confidence interval, GRADE Grading of Recommendations Assessment, Development, and Evaluation, OR odds ratio

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

¹ Control group risk comes from control arm of meta-analysis, based on included trials

² Downgraded one level due to sparse data (188 events)

³ Downgraded one level due to sparse data (94 events)

⁴ Downgraded due to very sparse data (26 events)

⁵ Downgraded due to very sparse data (29 events) and heterogeneity ($I^2 = 71\%$)

GRADE Working Group Grades of Evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect