

Open

# Inflammatory Bowel Disease-Associated Colorectal Cancer Epidemiology and Outcomes: An English Population-Based Study

Rebecca J. Birch, PhD<sup>1,\*</sup>, Nicholas Burr, BSc, MBBS, MRCP, MD<sup>1,2,3,\*</sup>, Venkataraman Subramanian, MRCP, MD<sup>1,4</sup>, Jim P. Tiernan, PhD, FRCS<sup>4</sup>, Mark A. Hull, PhD, FRCP<sup>1,4</sup>, Paul Finan, MBChB, MD, FRCS<sup>1</sup>, Azmina Rose, BSc Hons, ATT PG Cert/Dip<sup>5</sup>, Matthew Rutter, MBBS, MD, FRCP<sup>6,7</sup>, Roland Valori, MD, FRCP, MSc (Oxon)<sup>8</sup>, Amy Downing, PhD<sup>1</sup> and Eva J.A. Morris, PhD<sup>2</sup>

**INTRODUCTION:** Patients with inflammatory bowel diseases (IBDs) of the colon are at an increased risk of colorectal cancer (CRC). This study investigates the epidemiology of IBD-CRC and its outcomes.

**METHODS:** Using population data from the English National Health Service held in the CRC data repository, all CRCs with and without prior diagnosis of IBD (Crohn's, ulcerative colitis, IBD unclassified, and IBD with cholangitis) between 2005 and 2018 were identified. Descriptive analyses and logistic regression models were used to compare the characteristics of the 2 groups and their outcomes up to 2 years.

## IBD-associated CRC epidemiology and outcomes

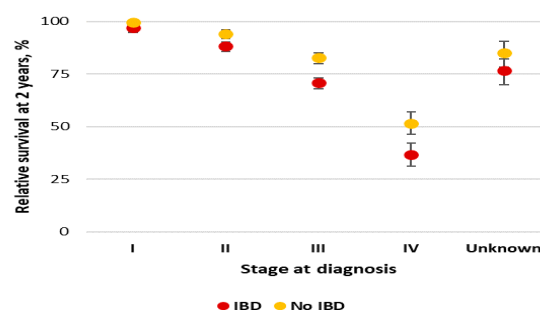
English population data 2005 to 2018  
~390,000 CRC cases, ~5000 with IBD

### IBD cases are:

- Younger, 66 yrs vs 72 yrs
- More diagnosed as emergencies, 25% vs 17%
- More right colonic CRC, 37% vs 34%
- More synchronous CRC, 3.2% vs 1.6%
- More metachronous CRC, 1.7% vs 0.9% at 3 yrs

### Total colectomy performed:

- 44% ulcerative colitis
- 15% Crohn's
- 67% IBD and cholangitis



### Implications

- Need to explore variation in practice
- Improvement required:
  - Screening and surveillance
  - Outcomes
  - Personalized care

Birch et al. *Am J Gastroenterol.* [2022]. [doi:10.14309/ajg.0000000000001941]

**AJG** The American Journal of GASTROENTEROLOGY

<sup>1</sup>Leeds Institute of Medical Research at St James's, University of Leeds, Leeds, UK; <sup>2</sup>Mid Yorkshire Hospitals NHS Trust, Wakefield, UK; <sup>3</sup>Nuffield Department of Population Health, University of Oxford, Oxford, UK; <sup>4</sup>Leeds Teaching Hospitals NHS Trust, Leeds, UK; <sup>5</sup>Independent Patient Representative, London, United Kingdom; <sup>6</sup>University Hospital of North Tees, Stockton-on-Tees, UK; <sup>7</sup>Faculty of Medical Sciences, Newcastle University, Newcastle, UK; <sup>8</sup>Gloucestershire Hospitals NHS Foundation Trust, Cheltenham, UK. **Correspondence:** Nicholas Burr, BSc, MBBS, MRCP, MD. E-mail: nick.burr@nhs.net.

\*Rebecca J. Birch and Nicholas Burr contributed equally to this work.

Received April 28, 2022; accepted July 29, 2022; published online August 12, 2022

- RESULTS:** Three hundred ninety thousand six hundred fourteen patients diagnosed with CRC were included, of whom 5,141 (1.3%) also had a previous diagnosis of IBD. IBD-CRC cases were younger (median age at CRC diagnosis [interquartile range] 66 [54–76] vs 72 [63–79] years [ $P < 0.01$ ]), more likely to be diagnosed with CRC as an emergency (25.1% vs 16.7% [ $P < 0.01$ ]), and more likely to have a right-sided colonic tumor (37.4% vs 31.5% [ $P < 0.01$ ]). Total colectomy was performed in 36.3% of those with IBD (15.4% of Crohn's, 44.1% of ulcerative colitis, 44.5% of IBD unclassified, and 67.7% of IBD with cholangitis). Synchronous (3.2% vs 1.6%  $P < 0.01$ ) and metachronous tumors (1.7% vs 0.9%  $P < 0.01$ ) occurred twice as frequently in patients with IBD compared with those without IBD. Stage-specific survival up to 2 years was worse for IBD-associated cancers.
- DISCUSSION:** IBD-associated CRCs occur in younger patients and have worse outcomes than sporadic CRCs. There is an urgent need to find reasons for these differences to inform screening, surveillance, and treatment strategies for CRC and its precursors in this high-risk group.

**SUPPLEMENTARY MATERIAL** accompanies this paper at <http://links.lww.com/AJG/C626>

*Am J Gastroenterol* 2022;117:1858–1870. <https://doi.org/10.14309/ajg.0000000000001941>

## BACKGROUND

Inflammatory bowel diseases (IBDs) affecting the colon are associated with an increased risk of developing colorectal cancer (CRC) (1–4). Although IBD accounts for only a relatively small proportion of the total burden of CRC, it accounts for a disproportionate number of CRC-related deaths (1).

IBD-related CRC (IBD-CRC) has distinct tumor and patient-related factors when compared with sporadic CRC (3–5). IBD-CRC often develops along an inflammation-dysplasia-CRC pathway rather than an adenomatous polyp-CRC pathway. Early detection and surveillance is challenging because dysplastic inflammatory lesions can be difficult to detect (6). Although large-scale population data are sparse, there is some evidence to suggest that IBD-CRC cases tend to be younger, tend to be more frequently seen in the right colon, and are associated with poorer prognosis (3,5,7). There is a higher rate of emergency surgery for CRC among patients with IBD-CRC than is seen among sporadic cases (8), which may reflect rapidly growing, aggressive tumors or missed opportunities for earlier diagnosis. There is a lack of population data on treatments, in particular surgical resection and related outcomes, for IBD-CRC. This study aimed to examine the characteristics, surgical treatment, and outcomes for Patients with IBD-CRC within the English National Health Service (NHS).

## METHODS

### Study population and data sources

Information was extracted for patients diagnosed with a first, primary colorectal adenocarcinoma tumor (CRC) (*International Classification of Diseases version 10 [ICD-10]* code (9) C18-20) between January 1, 2005, and December 31, 2018, from the CRC data repository (CORECT-R) (10). CORECT-R is a population-based repository, which contains linked cancer registration and Hospital Episode Statistics (HES) data for all patients diagnosed with CRC within England. The use of population data means that most of the cases are likely to be included, and patients can be tracked wherever they receive care within England. Registrations based on death certification only were excluded as were tumors of the appendix (*ICD-10* code C18.1).

### Variables

Variables included age at diagnosis of CRC, sex, stage of disease at diagnosis, tumor site (right colon, left colon [including rectosigmoid], colon unspecified, and rectum), socioeconomic status

(based on the income domain of the Index of Multiple Deprivation score) (11), route to diagnosis (RtD) (12,13), and survival time. An emergency diagnosis is defined elsewhere using the RtD information but briefly includes those after presentation to accident and emergency departments, GP emergency referrals, and emergency pathways for inpatients and outpatients (13). RtD codes also include those diagnosed by the UK Bowel Cancer Screening Programme and urgent 2-week wait pathway for those with red-flag symptoms of CRC.

Comorbidity was estimated with the Charlson comorbidity score (14), excluding CRC. The score was derived from diagnoses recorded during inpatient hospital admissions during the year preceding the diagnosis of CRC.

Multiple CRCs in the same individual were classified as synchronous if they occurred within 6 months of the first CRC diagnosis. Any CRC diagnosed beyond that point was classified as metachronous.

IBD status was determined using *ICD-10* codes reported in HES data from any inpatient admission to hospital in the 6 years preceding CRC diagnosis. Patients were classified into one of 4 categories according to *ICD-10* codes: Crohn's (*ICD-10* K50), ulcerative colitis (UC) (*ICD-10* K51), IBD unclassified (IBD-U) (*ICD-10* K50 and K51 both reported), and IBD and cholangitis (IBD-C) (*ICD-10* K50/K51 with K83.0). Primary sclerosing cholangitis (PSC) is an important risk factor for the development of IBD-CRC (15). There is no dedicated disease code for PSC in *ICD-10*, but K83.0 pertains to either acute (bacterial) or chronic bile duct inflammation, including PSC. Emergency diagnosis was identified from the RtD information, and patients were classified as having either an emergency or nonemergency CRC diagnosis (13).

### Inflammatory bowel disease management

Colonoscopies were identified from linked HES data. Frequency of colonoscopic investigation was defined based on the number of colonoscopies recorded in each year that an individual was present within the data set. Based on this, patients were allocated to one of 7 groups: none, single, annual, alternate years, every 3 years, every 5 years, or other interval. Patients were allocated to the none or single group if they were only present in the data for a single year or less. Investigations occurring within 30 days of CRC diagnosis were excluded.

### Colorectal cancer surgery

Details of the surgical management of patients were obtained from HES data (16,17). Surgical procedures for CRC are grouped into predefined categories in CORECT-R (18) using OPCS Classification of Interventions and Procedures version 4 (OPCS-4) (19). The categories are major resection, minor resection, bypass, stoma/stent, and no NHS surgery (see Supplementary Table 1, <http://links.lww.com/AJG/C626>). Patients are classified as having undergone a major surgical resection or no major surgical resection (including minor resections, bypass, stoma and stent procedures, and no NHS surgery) to differentiate between those treated with potentially curative intent and those who were not. Major colorectal surgical procedures were categorized into broad groups based on the OPCS code (see Supplementary Table 2, <http://links.lww.com/AJG/C626>). Total excision of the colon and rectum, total excision of the colon, and other colectomy were classified as total colectomy; all other major surgical resections were classified as segmental resections (see Supplementary Table 2, <http://links.lww.com/AJG/C626>). For patients who underwent a major surgical resection of their colorectal tumor, 90-day postoperative mortality was obtained from the date of surgery and date of death.

### Statistical analysis

Descriptive analysis was performed to examine differences between the IBD and non-IBD groups. Subanalysis was performed to assess the characteristics of those with and without IBD who were diagnosed with CRC through an emergency route.

The Kaplan-Meier method was used to analyze the time to metachronous tumor after a major surgical resection, with patients grouped by IBD status and type of major surgical resection (total colectomy or segmental resection). This analysis was restricted to include only those who underwent surgery which resulted in residual colorectal tissue where endoscopic surveillance may be indicated (20,21). In this instance, OPCS codes H041, H048, and H049 were excluded from the total colectomy group; 15 patients with IBD and 2,267 of those without were also excluded.

Adjusted logistic regression models were used to calculate the odds of diagnostic (late-stage disease [stages III and IV] and emergency presentation) and 90-day postoperative mortality outcomes in relation to an individual's IBD status (no IBD, Crohn's, UC, IBD-U, and IBD-C). Each outcome was modeled separately and adjusted for age, sex, socioeconomic status, comorbidity score, tumor site (right colon, left colon [including rectosigmoid], colon not otherwise classified, or rectum), and year of diagnosis. Late stage of disease was also adjusted for RtD while emergency diagnosis was adjusted for the stage of disease. The emergency diagnosis model was restricted to include only patients diagnosed between 2005 and 2017 because the RtD information was not available for diagnoses occurring in 2018. The postsurgical outcome models were restricted only to those who had undergone a major surgical resection and were also adjusted for RtD, stage of disease, and type of operation. Multivariable Cox proportional hazards modeling was performed to determine the 2-year hazard of death associated with IBD-CRC (adjusted for age, sex, socioeconomic status, tumor site, Charlson comorbidity score, stage of CRC, surgical procedure [major resection, minor resection, bypass, stoma, stent, or no NHS surgery], route to CRC diagnosis, and type of IBD).

Unadjusted relative survival estimates were calculated in Stata using the Pohar Perme estimator (strs command) (22); estimates

were calculated at 2 years from CRC diagnosis. Analyses were restricted to those who had undergone a major surgical resection, stratified by IBD status and stage of disease. Analyses were performed in Stata 16.0.

## RESULTS

### Characteristics

Of the 390,614 patients diagnosed with CRC over the study period, 5,141 (1.3%) were identified as having IBD. Most of these patients had UC accounting for 60.7% of this population ( $n = 3,123$ ), with Crohn's accounting for 29.4% ( $n = 1,512$ ), IBD-U for 6.9% ( $n = 354$ ), and IBD with cholangitis for 3.0% ( $n = 152$ ) (Table 1).

Patients with IBD were younger than those without (median age at CRC diagnosis 66 years [interquartile range 54–76] vs 72 years [interquartile range 63–79], respectively [ $P < 0.01$ ]) (Table 1). Those with IBD-U and IBD with cholangitis were younger than those with either Crohn's or UC ( $P < 0.01$ ) (Table 1). A higher proportion of those with IBD were diagnosed with CRC by an emergency route compared with those without (25.1% vs 16.7% [ $P < 0.01$ ]) (Table 1). In patients with IBD, emergency diagnosis rates were highest among those with Crohn's (32.6%) and lowest for those with IBD-C (17.1%) ( $P < 0.01$ ) (Table 1). Patients with IBD had a higher proportion of right-sided colonic tumors than those without (37.4% vs 31.4%  $P < 0.01$ ) (Table 1). A higher proportion of those with IBD had synchronous tumors than observed in patients without IBD (3.2% vs 1.6%  $P < 0.01$ ). Synchronous tumors were most common in those with IBD-C (8.6%), followed by UC (3.5%), IBD-U (3.4%), and Crohn's (2.2%) ( $P < 0.01$ ) (Table 1).

### Investigations before diagnosis of colorectal cancer

In total, 3,483 of the 5,141 patients with IBD (67.7%) were identified as having at least 1 colonoscopy more than 30 days before their CRC diagnosis. Of these 1,216 (34.9%) only had 1 colonoscopy recorded in 6 years before their CRC diagnosis. The proportion of patients undergoing colonoscopies on alternate years increased with time, from 17.1% in 2005–2011 to 22.1% 2012–2018. Over the same period, the proportion undergoing no colonoscopies or a single colonoscopy fell from 47.7% to 33.3% (see Supplementary Table 5, <http://links.lww.com/AJG/C626>). Of those with IBD-C, 44% underwent annual colonoscopy before diagnosis of CRC.

Those with annual and alternate year tests had the highest proportion of stage I disease (stage I–20.4% and 18.8%, respectively); among those with tests every 3 years, 15.9% were diagnosed at stage I, and for those with tests every 5 years, this fell to 11.1% (Table 2). Emergency diagnosis of CRC was more common among those with tests every 3 or 5 years (21.3% and 23.5%, respectively), compared with those with annual or alternate year tests (16.5% and 17.9%, respectively) (Table 2).

### Colorectal cancer surgery

Overall, a significantly higher proportion of patients with IBD underwent total colectomy rather than a segmental procedure (the details of the specific segmental procedures used in these cases are listed in Supplementary Digital Content [see Supplementary Table 4, <http://links.lww.com/AJG/C626>]) for the treatment of their cancer than was observed among patients without IBD (36.3% vs 2.9%  $P < 0.01$ ) (Table 1). Total

**Table 1.** Characteristics of the study population

	IBD		No IBD		P value	Crohn's		UC		IBD-U		IBD & cholangitis		P value
	n	%	n	%		n	%	n	%	n	%	n	%	
Median age at CRC diagnosis (IQR), yr	66 (54–76)		72 (63–79)			65 (52–76)		68 (56–77)		60 (47–71)		54–5 (43–65.5)		
Sex														
Male	3,091	60.1	220,472	57.2	<0.01	818	54.1	1,948	62.4	211	59.6	114	75	<0.01
Female	2,050	39.9	165,473	42.9		694	45.9	1,175	37.6	143	40.4	38	25	
Socioeconomic status														
1—most affluent	1,143	22.2	83,813	21.7	0.4	318	21	699	22.4	85	24	41	27	0.18
2	1,126	21.9	87,319	22.7		320	21.2	716	22.9	60	16.9	30	19.7	
3	1,107	21.5	80,615	20.9		326	21.6	681	21.8	74	20.9	26	17.1	
4	948	18.4	70,476	18.3		287	19	554	17.7	77	21.8	30	19.7	
5—most deprived	817	15.9	63,722	16.5		261	17.3	473	15.1	58	16.4	25	16.4	
Charlson comorbidity score														
0	3,520	68.5	295,816	76.7	<0.01	1,021	67.5	2,167	69.4	232	65.5	100	65.8	<0.01
1	944	18.4	51,634	13.4		291	19.2	553	17.7	72	20.3	28	18.4	
2	389	7.6	22,414	5.8		113	7.5	235	7.5	27	7.6	14	9.2	
≥3	288	5.6	16,081	4.2		87	5.8	168	5.4	23	6.5	10	6.6	
Stage of CRC														
I	782	15.2	56,097	14.6	0.13	168	11.1	529	16.9	53	15	32	21.1	<0.01
II	1,295	25.2	102,457	26.6		437	28.9	736	23.6	87	24.6	35	23	
III	1,502	29.2	109,496	28.4		456	30.2	902	28.9	93	26.3	51	33.6	
IV	863	16.8	63,937	16.6		251	16.6	511	16.4	82	23.2	19	12.5	
Unknown	699	13.6	53,958	14		200	13.2	445	14.2	39	11	15	9.9	
Tumor site														
Right colon	1923	37.4	121,309	31.4	<0.01	690	45.6	1,023	32.8	134	37.9	76	50	<0.01
Left colon	1,403	27.3	134,564	34.9		330	21.8	942	30.2	94	26.6	37	24.3	
Colon, unspecified	341	6.6	15,002	3.9		111	7.3	183	5.9	25	7.1	22	14.5	
Rectum	1,474	28.7	115,070	29.8		381	25.2	975	31.2	101	28.5	17	11.2	
Route to CRC diagnosis <sup>b</sup>														
Emergency	1,291	25.11	64,520	16.7	<0.01	493	32.6	672	21.5	100	28.3	26	17.1	<0.01
Nonemergency	3,850	74.9	321,425	83.3		1,019	67.4	2,451	78.5	254	71.8	126	82.9	
Synchronous tumors														
Yes	166	3.2	6,192	1.6	<0.01	33	2.2	108	3.5	12	3.4	13	8.6	<0.01
No	4,975	96.8	379,753	98.5		1,479	97.8	3,015	96.5	342	96.6	139	91.4	
Metachronous tumors														
Yes	87	1.7	3,533	0.9	<0.01	22	1.5	54	1.7	9	2.5	<sup>a</sup>		<0.01
No	5,054	98.3	382,412	99.2		1,490	98.5	3,069	98.3	345	97.5	<sup>a</sup>		
Primary procedure for CRC														
Major resection	3,703	72	269,332	69.9	<0.01	1,108	73.3	2,217	71.0	254	71.8	124	81.6	<0.01
Minor resection	236	4.6	24,855	6.4		73	4.8	144	4.6	14	4.0	5	3.3	
Bypass, stoma, or stent	320	6.2	18,795	4.9		90	6.0	203	6.5	20	5.7	7	4.6	
No NHS surgery	882	17.2	73,963	19.2		241	15.9	559	17.9	66	18.6	16	10.5	

Table 1. (continued)

	IBD		No IBD		P value	Crohn's		UC		IBD-U		IBD & cholangitis		P value
	n	%	n	%		n	%	n	%	n	%	n	%	
Type of major resection														
Total colectomy	1,345	36.3	7,823	2.9	<0.01	171	15.4	977	44.1	113	44.5	84	67.7	<0.01
Segmental	2,358	68.7	261,059	97.1		937	84.6	1,240	55.9	141	55.5	40	32.3	
Total	385,945		5,141			1,512		3,123		354		152		

CRC, colorectal cancer; IBD, inflammatory bowel diseases; IBD-U, IBD unclassified; NHS, National Health Service.  
<sup>a</sup>Counts <5 are suppressed.  
<sup>b</sup>Full route to diagnosis information presented in Supplementary Digital Content (see Supplementary Table 3, <http://links.lww.com/AJG/C626>).

colectomy was performed in 15.4% of patients with Crohn's, compared with 44.1% of those with UC, 44.5% of those with IBD-U, and 67.7% of those with IBD with cholangitis ( $P < 0.01$ ) (Table 1).

### Outcomes

**Diagnostic.** After adjustment for sociodemographic factors, the relationship between IBD and late-stage CRC at diagnosis varied by type of IBD, with Crohn's and UC having significantly lower odds of late stage (III or IV) at diagnosis than those without IBD (OR 0.84 95% confidence interval [CI] 0.75–0.93 for patients with Crohn's and OR 0.89 95% CI 0.83–0.96 for patients with UC) (Figure 1). There was no significant association between IBD-U or IBD-C and late-stage CRC.

When compared with those without a record of IBD, Crohn's, UC, and IBD-U were all associated with significantly higher adjusted odds of emergency diagnosis (Figure 1). Crohn's, in particular, was associated with a 2-fold increase (OR 2.39 95% CI 2.24–2.37) (Figure 1).

**Metachronous tumors.** The overall rate of metachronous CRC was higher in those with IBD than those without (1.7% vs 0.9%) (Table 1). Within the IBD group, metachronous tumors were

most common in those with IBD-U (2.5%) (Table 1). After a segmental colonic resection for CRC, a higher proportion of those with IBD developed metachronous CRC, with an estimated 1.6% of patients with IBD developing further CRC within 3 years of their initial surgical resection compared with 0.7% of those without (survivor function 0.98 95% CI 0.98–0.99 vs 0.99 95% CI 0.99–0.99). This difference increased over time with an estimated 6.3% of those with IBD developing a metachronous tumor within 15 years of initial segmental resection compared with 2.3% of those without IBD (survivor function 0.94 95% CI 0.92–0.95 vs 0.98 95% CI 0.98–0.98) (Figure 2).

After a colectomy with the potential for retained rectal or colonic mucosa, a similar proportion of those with IBD developed a metachronous tumor within 3 years compared with those without (1.0% vs 0.8%) (Figure 2). The incidence of metachronous cancer in those with ileorectal anastomosis, ileal pouch-anal anastomosis, or ileostomy and a rectal stump procedure was <2%. We were unable to report the precise risk in these groups because of the small number ( $n < 5$ ) and the potential for reidentification of patients.

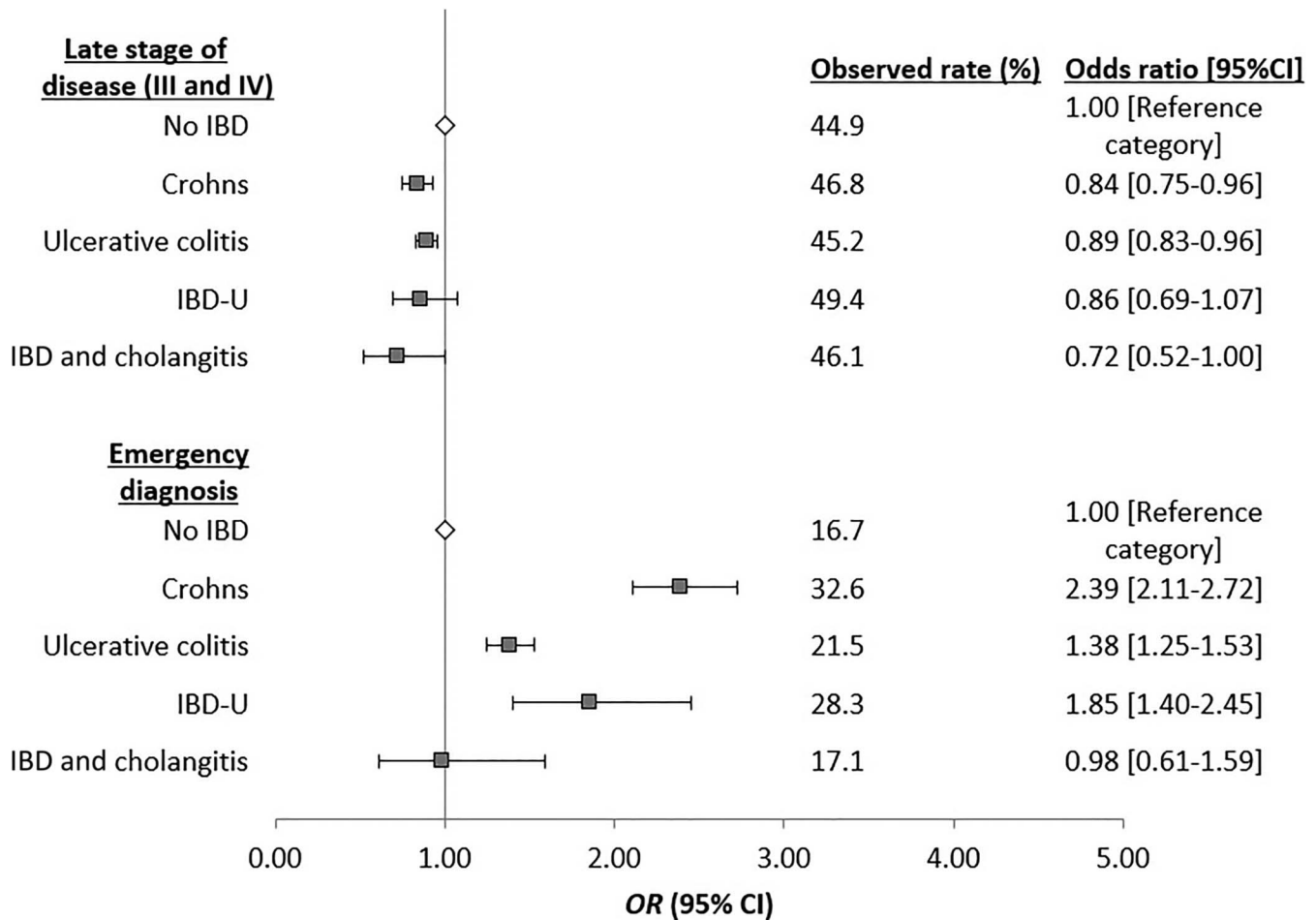
**Postoperative mortality.** Overall, 5.4% of patients ( $n = 14,648$ ) who underwent a major surgical resection died within 90 days of the procedure. This was higher among patients with Crohn's

Table 2. Stage at diagnosis and route to diagnosis for patients with IBD, by colonoscopy interval

	Colonoscopy interval											
	None or single		Annual		Alternate yr		Every 3 yr		Every 5 yr		Other	
	n	%	n	%	n	%	n	%	n	%	n	%
Stage of CRC												
I	229	11.3	136	20.4	193	18.8	96	15.9	18	11.1	110	16.8
II	496	24.4	178	26.7	263	25.6	149	24.8	50	30.9	159	24.3
III	626	30.9	180	27.0	297	28.9	174	28.9	47	29.0	188	28.7
IV	355	17.5	87	13.1	162	15.8	121	20.1	25	15.4	113	17.3
Unknown	323	15.9	85	12.8	122	11.9	62	10.3	22	13.6	85	13.0
Route to CRC diagnosis												
Emergency	659	32.5	110	16.5	184	17.9	128	21.3	38	23.5	172	26.3
Nonemergency	1,370	67.5	556	83.5	843	82.1	474	78.7	124	76.5	483	73.7
Total	2029		666		1,027		602		162		655	

CRC, colorectal cancer; IBD, inflammatory bowel diseases.





**Figure 1.** Adjusted logistic regression results for diagnostic outcomes. Each outcome modeled separately. Both adjusted for age, sex, Index of Multiple Deprivation, tumor site, year of diagnosis, and comorbidity score. Late diagnosis also adjusted for route to diagnosis. Emergency diagnosis also adjusted for stage of disease. IBD, inflammatory bowel diseases; IBD-U, IBD unclassified.

(7.8%,  $n = 86$ ) than patients without IBD (5.4%,  $n = 4,413$ ) ( $P < 0.01$ ). The rates observed among those with UC, IBD-U, and IBD and cholangitis were comparable with that identified in the population without IBD (5.8%, 6.4%, and 4.0%, respectively).

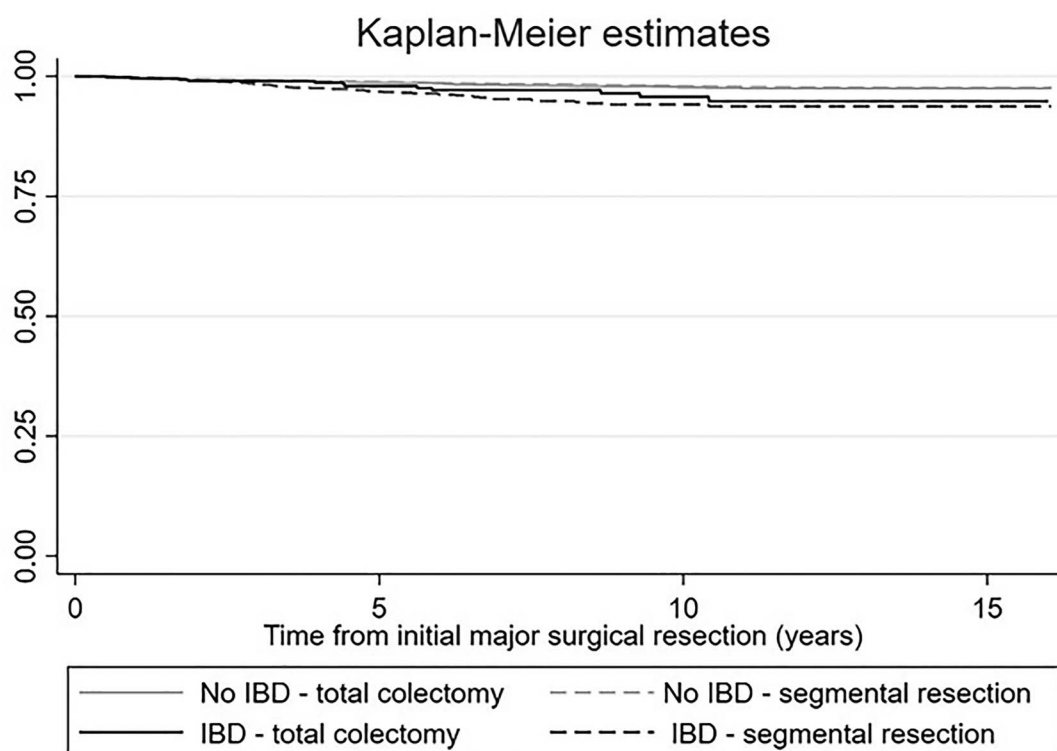
After adjustment for case-mix factors (age, sex, socioeconomic status, Charlson comorbidity score, tumor site, year of CRC diagnosis, route to CRC diagnosis, stage of disease, and type of operation), patients with Crohn's who underwent a major surgical resection had significantly higher odds of 90-day postoperative mortality (OR 1.81 95% CI 1.41–2.34) when compared with those without IBD (Figure 3). IBD-U was associated with a significant increase in 90-day postoperative mortality (OR 1.89 95% CI 1.05–3.42); however, there was no significant association between UC and IBD-C and 90-day postoperative mortality (Figure 3).

**Survival.** In a multivariable Cox regression model, even after adjustment for case-mix factors, Crohn's (hazard ratio [HR] 1.42 95% CI 1.33–1.52), UC (HR 1.20 95% CI 1.14–1.26), IBD-U (HR 1.55 95% CI 1.34–1.79), and IBD with cholangitis (HR 1.68 95% CI 1.34–2.11) were all significantly associated with shorter survival when compared with those without IBD (Table 3). Among the major surgical resection group, a lower proportion of those with IBD survived to 2 years from diagnosis compared with those

without. No significant difference was observed among those with stage I disease in contrast to those with IBD, and stage II to stage IV disease had significantly worse survival than those without. The difference between the 2 groups increased with stage; among those with stage III disease, 70.7% (95% CI 68.1–73.3) of those with IBD survived to 2 years, compared with 82.6% (95% CI 82.4–82.9) without. For stage IV, 36.6% (95% CI 31.3–42.0) of patients with IBD survived to 2 years compared with 51.6% (95% CI 51.0–52.3) of those without (Figure 4).

## DISCUSSION

This English population-based study included over 5,000 CRC cases with a prior diagnosis of IBD and, to the best of our knowledge, is the largest such study to date. 1.3% of all CRC cases in England had a prior recorded diagnosis of IBD, higher than 0.5% of the general population who are believed to have IBD (23). It confirms that there are clinically important differences for IBD-CRC, in that they occur in younger patients, and have worse outcomes. The management of these cancers is different, with over 30% of IBD-CRC undergoing total colectomy procedures for colonic and rectal tumors compared with less than 3% for sporadic CRC. This is not surprising and will reflect clinical decisions to treat IBD and address future risk of metachronous CRC and the extent of oncological resection of CRC being treated. There are



		Time from initial major surgical resection for CRC (years)			
		0	5	10	15
No IBD	Total colectomy*	6390	2656	1146	162
	Segmental resection	261334	128718	47655	4945
IBD	Total colectomy*	501	255	111	15
	Segmental resection	2357	858	262	19

\* Excludes 3 surgery codes where no colonic or rectal mucosa is retained (H041, H048 & H049)

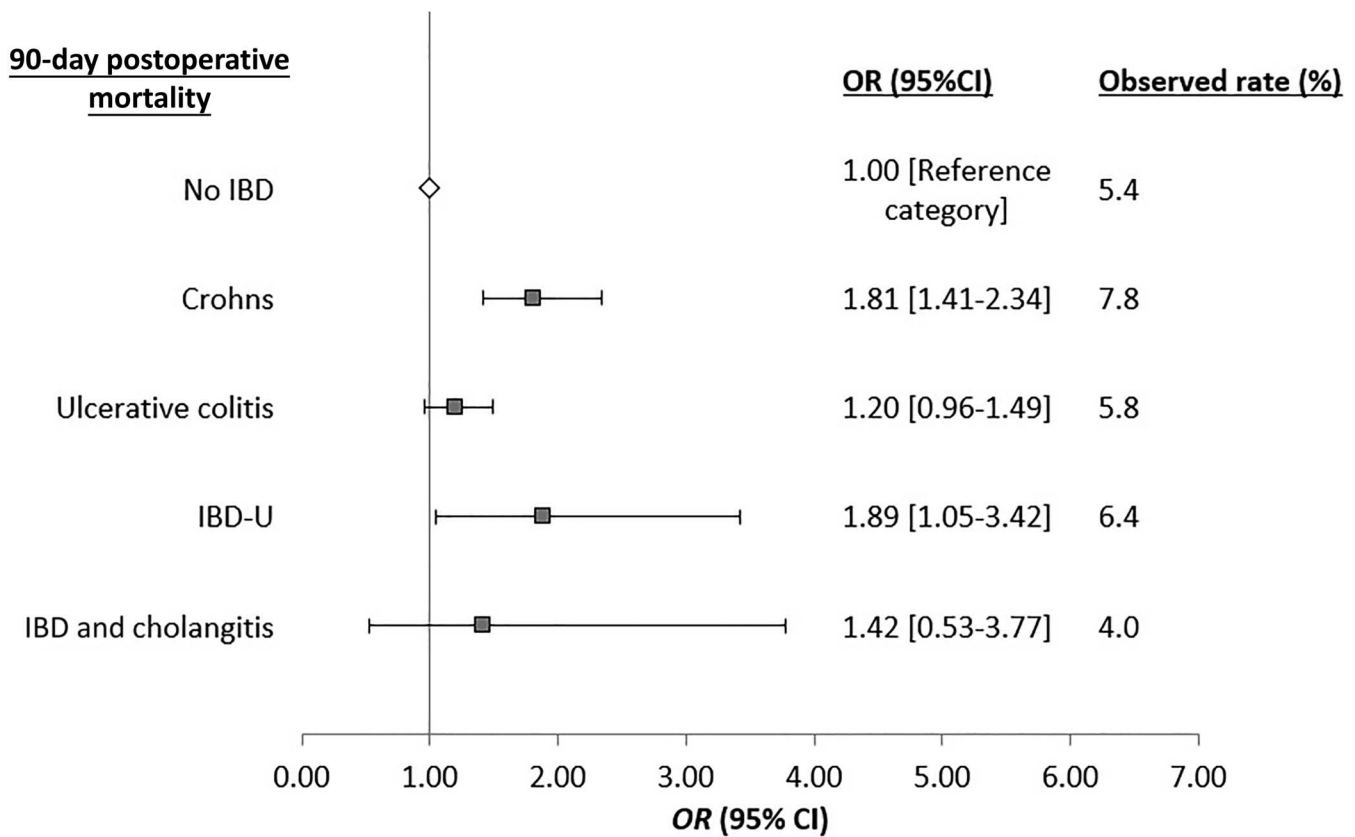
**Figure 2.** Kaplan-Meier estimate of the survival function and number of patients at risk for time from initial major surgical resection of CRC to diagnosis of a metachronous tumor, by IBD status and type of major surgical resection. CRC, colorectal cancer; IBD, inflammatory bowel diseases.

more early-stage cancers, which may be a result of increased surveillance, but the risk of death within 2 years of cancer diagnosis is higher for each stage of disease. Another finding is that those with IBD-C had the worst prognosis and were 68% more likely to die within 2 years of diagnosis than those without IBD. Furthermore, the rate of synchronous CRC was 9% in this group.

Diagnosis of IBD was associated with an increased incidence of both right-sided colonic and rectal tumors. A higher number of rectal tumors have been observed in those with UC (incidence rate ratio 1.90, 95% CI 1.05–3.43), but not Crohn's, in a matched cohort study from America (24). Longstanding colonic inflammation is one of the strongest risk factors for the development of IBD-CRC (6), and dysplasia tends to arise in a preneoplastic field of chronic inflammation (25). Therefore, the higher incidence of rectal tumors could be explained by distal colitis in those with UC.

The reduced survival in IBD-CRC reported here is in line with previous population-based studies, which report higher adjusted risk of early death of up to twice that of sporadic cancer (3,26–28).

One of the larger, earlier studies was from the surveillance, epidemiology, and end results-Medicare-linked database in the United States. Here, IBD-CRCs diagnosed up to 2006 were in younger patients, were in more early stage and had worse cancer-specific survival (mean, 32.9 vs 42.4 months) (5). Single-center studies from IBD specialist centers in America (29) and recently England (30) have shown reduced or equivalent early death, respectively, for IBD-CRC compared with controls without IBD (31), but pooled results from a recent meta-analysis report worse overall survival (32). Our contemporary English results show that little progress has been made to reduce these differences with worse stage-specific survival after 2 years, which is of concern. Postoperative mortality in the IBD-CRC group was high and rose further in CD at 7.4% within 90 days of surgery. These rates are higher than those reported elsewhere, with studies from the United States reporting rates between 2% and 6% (33–35). There are many reasons why postoperative mortality should be high in this group including comorbidity, challenging surgery, and medication use such as corticosteroids. Crohn's disease may also be associated with perforating disease and sepsis. Highlighting the



**Figure 3.** Adjusted logistic regression results for 90-day postoperative mortality. Adjusted for age, sex, Index of Multiple Deprivation, stage of disease, tumor site, year of diagnosis, Charlson score, operation type (OPCS code), and route to diagnosis. IBD, inflammatory bowel diseases; IBD-U, IBD unclassified.

postoperative risk is important when considering an operation and planning postoperative care.

Considering the risk of further CRC is important when deciding on whether to perform a segmental resection or total colectomy because the latter would potentially cure IBD in the case of UC and almost entirely mitigate further CRC risk. Segmental resections may be requested by patients to avoid having to live with an ileoanal pouch or stoma but expose the patient to risk of multiple CRCs. The proportion of those with UC undergoing segmental resections was 68%. This is higher than reported elsewhere; in a cohort study from Ontario in 2021, 46% (273/599) of those with UC underwent a segmental resection (36). The reasons for the high segmental rates are unclear and should be explored further. Many factors need to be considered including predicted survival after initial cancer, degree of colitis activity, quality of life, and challenges in colonoscopy surveillance such as postinflammatory polyps and scarring. The overall rate of synchronous and metachronous cancer was 3.2% and 1.7%, respectively, after a period of roughly 4 years, which was higher than that for those without IBD. When stratified by time period after segmental resection, the risk of metachronous CRC was 2%, 3%, and 6% after 3, 5, and 15 years, respectively, for those with IBD.

Those with a retained rectum or ileoanal pouch after a subtotal colectomy are advised to undergo endoscopic surveillance for metachronous CRC on an annual basis in some jurisdictions,

including the United Kingdom (37). The overall risk of such cancer was 2.4% in our population after ~4 years of follow-up for those with IBD. The risk for those with an ileal pouch-anal anastomosis was lower at <2%, although we are unable to give reliable estimates because of low numbers. When stratified by time period after surgery, the risk of metachronous CRC was 1%, 2%, and 5% after 3, 5, and 15 years, respectively. These findings should help inform patient-centered clinical decisions about the type of operation to perform. Further detailed work on the precise risk factors of further cancer is needed, but longer surveillance intervals or symptom-driven surveillance might be more appropriate.

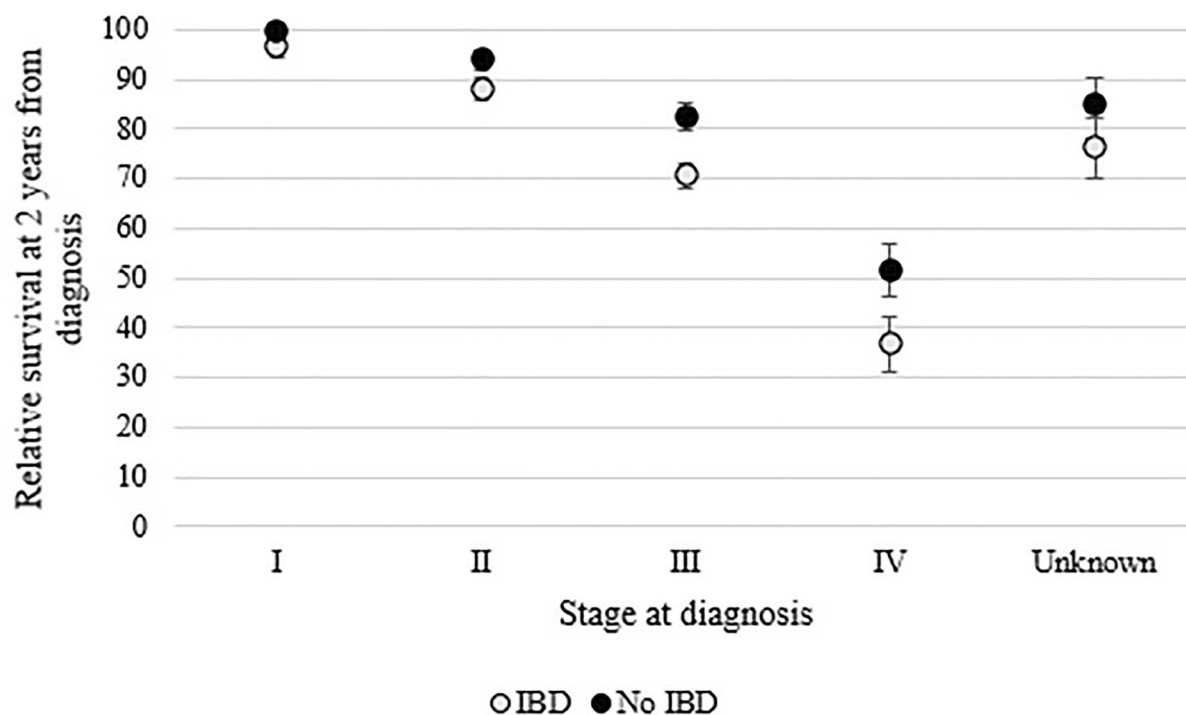
Overall, there were no differences in the CRC stage at diagnosis for those with and without a record of IBD. However, those with IBD undergoing more frequent endoscopies were more likely to be diagnosed with an early-stage CRC. National and international guidelines recommend colonoscopic surveillance after 8 to 10 years of disease and then to continue at regular intervals depending on individual risk factors (37). For those with the highest risk of CRC, annual colonoscopy is recommended, which is from diagnosis for those with IBD and PSC. Our results suggest that colonoscopy may be underutilized, especially in the cholangitis group where only 44% were undergoing annual colonoscopy. A recent single-center study from England has also suggested that surveillance is underutilized, with 27 of 42 cases of IBD-CRC not undergoing colonoscopic surveillance in line with BSG guidelines (38).



**Table 3.** Results of a Cox regression analysis for death within 2 year from CRC diagnosis

	HR	P value	Lower 95% CI	Upper 95% CI
No IBD	1.00	Reference category		
Type of IBD				
Crohn's	1.47	<0.01	1.38	1.57
UC	1.25	<0.01	1.19	1.31
IBD-U	1.73	<0.01	1.51	1.98
IBD and cholangitis	1.79	<0.01	1.45	2.22
Age at CRC diagnosis				
1.04	<0.01	1.04	1.04	
Sex				
Male	1.00	Reference category		
Female	0.90	<0.01	0.90	0.91
Comorbidity score				
0	1.00	Reference category		
1	1.26	<0.01	1.25	1.28
2	1.42	<0.01	1.40	1.44
≥3	1.68	<0.01	1.65	1.71
Socioeconomic status				
1—most affluent	1.00	Reference category		
2	1.09	<0.01	1.07	1.10
3	1.14	<0.01	1.13	1.16
4	1.22	<0.01	1.21	1.24
5—most deprived	1.32	<0.01	1.31	1.34
Year of diagnosis				
0.97	<0.01	0.97	0.97	
Stage of disease				
I	1.00	Reference category		
II	1.33	<0.01	1.31	1.36
III	2.09	<0.01	2.05	2.12
IV	5.93	<0.01	5.82	6.04
Unknown	2.30	<0.01	2.26	2.34
Tumor site				
Right colon	1.00	Reference category		
Left colon	0.87	<0.01	0.86	0.87
Colon, unspecified	1.07	<0.01	1.04	1.09
Rectum	0.87	<0.01	0.86	0.88
Primary procedure				
Major resection	1.00	Reference category		
Minor surgical procedure	1.31	<0.01	1.29	1.34
Bypass, stoma, or stent	3.38	<0.01	3.32	3.44
No NHS surgery	2.74	<0.01	2.71	2.77
Route to CRC diagnosis				
Nonemergency	1.00	Reference category		
Emergency	1.74	<0.01	1.72	1.76

CRC, colorectal cancer; IBD, inflammatory bowel diseases; IBD-U, IBD unclassified; NHS, National Health Service; UC, ulcerative colitis.



		Relative survival	Lower 95%CI	Upper 95%CI
I	IBD	97.0	94.6	98.8
	No IBD	99.5	99.3	99.8
II	IBD	88.1	85.8	90.2
	No IBD	94.0	93.8	94.3
III	IBD	70.7	68.1	73.3
	No IBD	82.6	82.4	82.9
IV	IBD	36.6	31.3	42.0
	No IBD	51.6	51.0	52.3
Unknown	IBD	76.6	70.0	82.1
	No IBD	85.0	84.3	85.6

**Figure 4.** Unadjusted relative survival estimates at 2 years from diagnosis. IBD, inflammatory bowel diseases.

At the population level, the evidence for the efficacy of surveillance is quite sparse, but suggests a modest reduction in odds of death due to CRC, a higher detection of early-stage disease, and a lower overall rate of CRC (39,40). The investigation and treatment paradigm is changing for IBD-associated dysplasia and early CRC. The traditional algorithm was to try to diagnose cancer at an early stage or detect premalignant dysplasia that could be treated with prophylactic total colectomy. With enhanced detection and endoscopic resection techniques, precancerous lesions or even noninvasive cancers themselves can be managed endoscopically. Unfortunately, only 15% of IBD-CRC was diagnosed at stage I, so more work is needed in both detection and prevention.

This study demonstrated a significantly higher proportion of IBD-CRC cases diagnosed by the emergency route, which is associated with poorer outcomes. In the United Kingdom, there is an urgent 2-week fast-track pathway whereby primary care clinicians can refer those with red-flag symptoms of CRC for investigation. The decision about whether to refer somebody with IBD poses a clinical challenge because the symptoms of an IBD flare (change in bowel habit, bloody diarrhea, abdominal pain, and weight loss) are also the red-flag symptoms of CRC. This is further complicated because the fecal calprotectin level, which is used as a screening test for inflammation and IBD activity, is also raised in CRC and was initially developed as a potential tumor marker for CRC (41). There was also a significant reduction in the proportion of IBD-CRC diagnosed by the English NHS Bowel Cancer Screening Programme. There is no dedicated national CRC screening and surveillance programme for those with IBD and people may be deterred from participating as the symptoms of IBD are similar to CRC, and active inflammation may cause a falsely elevated stool screening test (42). This is in this study with only 1.6% being diagnosed by this route vs 7.9% for those without IBD. The reduction in diagnosis by screening or urgent routes can be explained by a younger age at diagnosis overall in the IBD group, but ~85% of the IBD cases were older than 50 years, so it is unlikely that this explains all the differences seen. Those with IBD are more likely to be engaged with hospital IBD services and more likely to contact secondary care directly with symptoms, and similarly general practitioners would contact secondary care directly rather than initiating a new urgent referral. This could explain the higher rates of other routes to diagnosis among those with IBD. This group consists of outpatient and inpatient diagnoses and is, therefore, likely to represent the secondary care engagement previously described.

This study is potentially limited because the data are from routinely collected clinical codes and as such are subject to data quality and ascertainment bias. This risk should be small because previous validation studies have shown 96% accuracy for routine data collected in HES (43). While the method used to identify IBD in this study (diagnostic codes recorded during inpatient admission to hospital) could lead to an underestimation of cases, most IBD services in England are now coordinated through secondary care. Cholangitis is an established risk factor of IBD-CRC. In this study, the group with IBD-C had the worst prognosis overall. There is no specific code for PSC in *ICD-10*, and our group includes both acute (bacterial) and chronic bile duct inflammation (K83.0). It cannot be certain that these cases do have PSC, and

this is a limitation. However, this group had the worst overall prognosis, and because acute cholangitis has no reported association with adverse events in CRC, this may underestimate the magnitude of the adverse association with PSC. Immortal time bias is an important consideration for our analyses on metachronous CRC because we have shown that survival is shorter for these cancers with less time to develop further CRC.

There is a need to perform detailed case reviews of these cancers to find the reasons for the poorer outcomes. It is possible that surveillance colonoscopy, which is effective in reducing death from sporadic CRC, is not as effective for IBD-CRC. Consistent evidence now shows that the risk of post-colonoscopy CRC, one that occurs after a reportedly normal test, is higher in those with IBD (44–46). These cancers have shorter survival than those detected by colonoscopy (47,48), and further work is needed to determine whether improvements in the quality of colonoscopy can reduce the number of missed cancers. There may be additional methods of IBD-CRC screening and surveillance that will improve early detection and prevention. For example, a 2019 study showed that multitarget fecal DNA samples have 92% sensitivity and 90% specificity for detecting IBD-CRC or high-grade dysplasia. This sensitivity drops to 64% for advanced adenomas, which included lesions of >1 cm with any degree of dysplasia or CRC (49), but specificity is maintained at 90%. Tests such as these may have a role as an adjunct to colonoscopy in groups at high risk of IBD-CRC or those with difficult-to-survey colons who are not surgical candidates.

CRC remains an important complication of IBD, and unfortunately, outcomes are worse than for those without IBD. There is an urgent need to try to improve early detection and define those at greatest risk of adverse outcomes to provide more risk-based and personalized care.

## ACKNOWLEDGEMENT

This work uses data that have been provided by patients and collected by NHS as part of their care and support. The data are collated, maintained, and quality-assured by the National Cancer Registration and Analysis Service, which is part of NHS Digital. Access to the data was facilitated by the Office for Data Release and the Cancer Research UK-funded UK Colorectal Cancer Intelligence Hub (C23424/A23706).

## CONFLICTS OF INTEREST

**Guarantors of the article:** Nicholas Burr, BSc, MBBS, MRCP, MD.

**Specific author contributions:** R.J.B. and N.B.: conceptualization, methodology, validation, formal analysis, writing—original draft, and writing—review and editing. V.S., J.T., M.H., P.F., A.R., M.R., and R.V.: writing—original draft and writing—review and editing. A.D.: validation, writing—original draft, and writing—review & editing. E.M.: validation, writing—original draft, writing—review and editing, and funding acquisition.

**Financial support:** Cancer Research UK (grant C23434/A23706) supported this work. The study funder was not involved in the design of the study; the collection, analysis, and interpretation of data; and writing the report and did not impose any restrictions regarding the publication of the report.

**Potential competing interests:** None to report.

## Study Highlights

### WHAT IS KNOWN

- ✓ Colonic inflammatory bowel diseases (IBDs) are associated with an increased risk of colorectal cancer (CRC).
- ✓ There is a lack of contemporary population-based data, which has prevented the exploration of the epidemiology of this association.

### WHAT IS NEW HERE

- ✓ Using English population-level data, when compared with cases of CRC without a record of IBD:
- ✓ IBD-CRCs are more likely to be in the right colon and occur in younger people
- ✓ IBD-CRC has worse outcomes, with; increased risk of death within 2 years of CRC diagnosis, increased risk of death at 90 days (5.4% for IBD-CRC) after surgical treatment, double the overall risk of synchronous CRC, increased risk of metachronous CRC after a segmental resection or colectomy with potential residual colonic or rectal mucosa.

## REFERENCES

1. Munkholm P. Review article: The incidence and prevalence of colorectal cancer in inflammatory bowel disease. *Aliment Pharmacol Ther* 2003;18:1–5.
2. Sebastian S, Hernández V, Myrelid P, et al. Colorectal cancer in inflammatory bowel disease: Results of the 3rd ECCO pathogenesis scientific workshop (I). *J Crohns Colitis*. 2014;8:5–18.
3. Ording AG, Horváth-Puhó E, Erichsen R, et al. Five-year mortality in colorectal cancer patients with ulcerative colitis or Crohn's disease: A nationwide population-based cohort study. *Inflamm Bowel Dis* 2013;19:800–5.
4. Rhodes JM, Campbell BJ. Inflammation and colorectal cancer: IBD-associated and sporadic cancer compared. *Trends Molecular Medicine* 2002;8:10–6.
5. Gearhart SL, Nathan H, Pawlik TM, et al. Outcomes from IBD-associated and non-IBD-associated colorectal cancer: A surveillance epidemiology and end results medicare study. *Dis Colon Rectum* 2012;55:270–7.
6. Rutter M, Saunders B, Wilkinson K, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. *Gastroenterology* 2004;126:451–9.
7. Arif AA, Chahal D, Ladua GK, et al. Hereditary and inflammatory bowel disease-related early onset colorectal cancer have unique characteristics and clinical course compared with sporadic disease. *Cancer Epidemiol Biomarkers Prev* 2021;30:1785–91.
8. Askari A, Nachiappan S, Murphy J, et al. PWE-259 Colorectal cancer (CRC) patients with inflammatory bowel disease (IBD) are at increased risk of poor outcomes post surgery in England. *Gut* 2015;64:A326–A327.
9. World Health Organization. ICD 10: International Statistical Classification of Diseases and Related Health Problems. 10 edn. Amer Psychiatric Pub, 1992. Geneva, Switzerland.
10. University of Oxford. UK colorectal cancer intelligence Hub (<https://www.ndph.ox.ac.uk/corectr/about>) (2020). Accessed April 11, 2022.
11. Noble M, McLennan D, Wilkinson K. The English Indices of Deprivation. ODPM Publications: London, UK, 2007.
12. Public Health England. Routes to diagnosis: Exploring emergency presentation ([http://www.ncin.org.uk/publications/data\\_briefings/routes\\_to\\_diagnosis\\_exploring\\_emergency\\_presentations](http://www.ncin.org.uk/publications/data_briefings/routes_to_diagnosis_exploring_emergency_presentations)). Accessed March 16, 2022.
13. Ellis-Brookes L, McPhail S, Ives A, et al. Routes to diagnosis for cancer: Determining the patient journey using multiple routine data sets. *Br J Cancer* 2012;107:1220–6.
14. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis* 1987;40:373–83.
15. Soetikno RM, Lin OS, Heidenreich PA, et al. Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis: A meta-analysis. *Gastrointest Endosc* 2002;56:48–54.
16. National Cancer Intelligence Network. Major Surgical Resections England, 2004–2006, 2011 (<http://www.ncin.org.uk/view?rid=540>). Accessed December 7, 2021.
17. Morris EJA, Taylor EF, Thomas JD, et al. Thirty-day postoperative mortality after colorectal cancer surgery in England. *Gut* 2011;60:806–13.
18. UK Colorectal Cancer Intelligence Hub. CORECT-R Data Catalogue V1.0, 2020 ([https://www.ndph.ox.ac.uk/corectr/files/corect-r-data-catalogue\\_oct20.pdf](https://www.ndph.ox.ac.uk/corectr/files/corect-r-data-catalogue_oct20.pdf)). Accessed March 8, 2022.
19. NHS Classifications Service NCFH. OPCS Classification of Interventions and Procedures Version 4.5. TSO: London, UK, 2009.
20. Munie S, Hyman N, Osler T. Fate of the rectal stump after subtotal colectomy for ulcerative colitis in the era of ileal pouch–anal anastomosis. *JAMA Surg* 2013;148:408–11.
21. Derikx LAAP, de Jong ME, Hoentjen F, et al. Short article: Recommendations on rectal surveillance for colorectal cancer after subtotal colectomy in patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2018;30:843–6.
22. Dickman PWE. Estimating and modelling relative survival. *Stata J* 2015;15:186–215.
23. Mark's Hospital Foundation St. Statistics–Inflammatory Bowel Disease (<https://www.stmarkshospitalfoundation.org.uk/how-we-are-saving-lives/statistics/#:~:text=In%20the%20UK%20it%20is,increased%20chance%20of%20requiring%20surgery>) (2022). Accessed March 8, 2022.
24. Bernstein CN, Blanchard JF, Kliever E, et al. Cancer risk in patients with inflammatory bowel disease: A population-based study. *Cancer* 2001;91:854–62.
25. Risques RA, Lai LA, Himmetoglu C, et al. Ulcerative colitis-associated colorectal cancer arises in a field of short telomeres, senescence, and inflammation. *Cancer Res* 2011;71:1669–79.
26. Söderlund S, Brandt L, Lapidus A, et al. Decreasing time-trends of colorectal cancer in a large cohort of patients with inflammatory bowel disease. *Gastroenterology* 2009;136:1561–7; quiz 1818–9.
27. Watanabe T, Konishi T, Kishimoto J, et al. Japanese Society for Cancer of the Colon and Rectum. Ulcerative colitis-associated colorectal cancer shows a poorer survival than sporadic colorectal cancer: A nationwide Japanese study. *Inflamm Bowel Dis* 2011;17:802–8.
28. Herrinton LJ, Liu L, Levin TR, et al. Incidence and mortality of colorectal adenocarcinoma in persons with inflammatory bowel disease from 1998 to 2010. *Gastroenterology* 2012;143:382–9.
29. Delaunoy T, Limburg PJ, Goldberg RM, et al. Colorectal cancer prognosis among patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2006;4:335–42.
30. Askari A, Guillén LS, Millan M, et al. Colorectal tumour characteristics and oncological outcome in patients with inflammatory bowel disease. *Surg Pract* 2020;24:60–8.
31. Vitali F, Wein A, Rath T, et al. The outcome of patients with inflammatory bowel disease-associated colorectal cancer is not worse than that of patients with sporadic colorectal cancer—a matched-pair analysis of survival. *Int J Colorectal Dis* 2022;37:381–91.
32. Lu C, Schardey J, Zhang T, et al. Survival outcomes and clinicopathological features in inflammatory bowel disease-associated colorectal cancer: A systematic review and meta-analysis. *Ann Surg* 2021.
33. de Vries S, Jeffe DB, Davidson NO, et al. Postoperative 30-day mortality in patients undergoing surgery for colorectal cancer: Development of a prognostic model using administrative claims data. *Cancer Causes Control* 2014;25:1503–12.
34. Schootman M, Lian M, Pruitt SL, et al. Hospital and geographic variability in thirty-day all-cause mortality following colorectal cancer surgery. *Health Serv Res* 2014;49:1145–64.
35. Fazio VW, Tekkis PP, Remzi F, et al. Assessment of operative risk in colorectal cancer surgery: The Cleveland Clinic Foundation colorectal cancer model. *Dis Colon Rectum* 2004;47:2015–24.
36. Bogach J, Pond G, Eskicioglu C, et al. Extent of surgical resection in inflammatory bowel disease associated colorectal cancer: A population-based study. *J Gastrointest Surg* 2021;25:2610–8.
37. Cairns SR, Scholefield JH, Steele RJ, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). *Gut* 2010;59:666–89.
38. Gordon C, Chee D, Hamilton B, et al. Root-cause analyses of missed opportunities for the diagnosis of colorectal cancer in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2021;53:291–301.

39. Lutgens MWMD, Oldenburg B, Siersema PD, et al. Colonoscopic surveillance improves survival after colorectal cancer diagnosis in inflammatory bowel disease. *Br J Cancer* 2009;101:1671–5.
40. Ananthakrishnan AN, Cagan A, Cai T, et al. Colonoscopy is associated with a reduced risk for colon cancer and mortality in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2015;13:322–9.e1.
41. Roseth AG, Kristinsson J, Fagerhol MK, et al. Faecal calprotectin: A novel test for the diagnosis of colorectal cancer? *Scand J Gastroenterol* 1993;28:1073–6.
42. Bye WANT, Parker CE, Jairath V, et al. Strategies for detecting colon cancer in patients with inflammatory bowel disease. *Cochrane Database Syst Rev* 2017;9:CD000279.
43. Burns EM, Rigby E, Mamidanna R, et al. Systematic review of discharge coding accuracy. *J Public Health (Oxf)* 2012;34:138–48.
44. Mooiweer E, van der Meulen-de Jong AE, Ponsioen CY, et al. Dutch Initiative on Crohn's and Colitis. Incidence of interval colorectal cancer among inflammatory bowel disease patients undergoing regular colonoscopic surveillance. *Clin Gastroenterol Hepatol* 2015;13:1656–61.
45. Burr NE, Derbyshire E, Taylor J, et al. Variation in post-colonoscopy colorectal cancer across colonoscopy providers in English National Health service: Population based cohort study. *BMJ* 2019;367:l6090.
46. Schönfeldt Troelsen F, Sørensen HT, Pedersen L, et al. Risk of a post-colonoscopy colorectal cancer diagnosis in patients with inflammatory bowel disease: A population-based cohort study. *Endoscopy* 2021;53:1023–33.
47. Macken E, Van Dongen S, De Brabander I, et al. Post-colonoscopy colorectal cancer in Belgium: Characteristics and influencing factors. *Endosc Int open* 2019;7:E717–E727.
48. Troelsen FS, Sørensen HT, Crockett SD, et al. Characteristics and survival of patients with inflammatory bowel disease and postcolonoscopy colorectal cancers. *Clin Gastroenterol Hepatol* 2022;20:e984–e1005.
49. Kisiel JB, Klepp P, Allawi HT, et al. Analysis of DNA methylation at specific loci in stool samples detects colorectal cancer and high-grade dysplasia in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2019;17:914–21.e5.

---

This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.