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Review

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Malignant Transformation of Long-Standing Ileal Crohn's Disease Likely Favors Signet Ring Cell Adenocarcinoma Histology

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Abstract

Signet ring cell adenocarcinomas (SRCCs) are a rare and aggressive histological subtype of adenocarcinomas typically with poor prognosis usually secondary to late stage at detection. In the small bowel, they constitute only 1% of all malignancies. In the last decade, there have been multiple case reports and small case series that have identified SRCCs, typically in the ileum, in patients with Crohn's disease. Crohn's disease is a transmural inflammatory condition that normally manifests in the distal ileum and colon, and is known to temporally increase the risk of malignancy. Given the profound rarity of SRCCs, establishing an association between Crohn's disease and SRCC is challenging. In this study, we performed a systematic review of case reports and small case series describing small bowel SRCCs in Crohn's disease patients. Most cases were found in the distal/terminal ileum, at a mean age of 59 years old. Virtually all tumors were locally advanced (pathological T stage 3 and 4), typically with at least N1 nodal disease. Two case studies (one is a case-control study and the other a cohort design) demonstrated that small bowel SRCC, as opposed to conventional adenocarcinoma, was significantly correlated to a history of Crohn's disease (35% vs. 0%, 73.5% vs. 28.5%), with a propensity to arise in the ileum (95% vs. 30%, 66.7% vs. 42.1%), and at earlier mean age (43 vs. 68 years, 53.7 vs. 61.7 years). We additionally used the Surveillance, Epidemiology, and End Results (SEER) database for insights into the clinicoepidemiological characteristics of ileum SRCCs. SRCCs composed 28.1% of all ileal SRCCs, compared to 11.0% for the adenocarcinomas, with a younger age at diagnosis (60.7 vs. 64.6 years), more distant disease at presentation (41.3% vs. 26.4%), and shorter overall median survival time (20 vs. 39 months). In summary, while there is limited direct evidence to support an association between small bowel SRCC and Crohn's disease, the phenomenon has been increasingly documented in the literature in the last decade. Clinicians treating Crohn's disease patients should consider this in their differential diagnosis, particularly when managing disease complications, as early detection and surgical intervention offer the best prognosis.

Keywords: Colitis; poorly cohesive carcinomas; Mucinous carcinomas; Signet ring cell carcinomas; Transmural inflammation

Introduction

It is well established that patients with inflammatory bowel disease (IBD), such as ulcerative colitis and Crohn's disease, are at least a three-fold increased risk of colorectal cancer (CRC) compared to the average population via carcinogenic processes secondary to chronic inflammation, and this risk increases with time of disease duration [1]. Multiple algorithms exist, but generally speaking, colonoscopy screening for dysplasia begins 8 - 10 years after diagnosis and continues at subsequent 1- to 5-year intervals depending on the overall risk assessment [2]. Unlike ulcerative colitis, which is a disease process limited to the mucosa of the colon, Crohn's disease is a transmural inflammatory process that can occur anywhere within the gastrointestinal tract, though the distal ileum and colon are typically the most affected. While population registry data do support an increased extracolonic risk of malignancy in Crohn's disease, mechanisms of pathogenesis are poorly understood [3].

Signet ring cell adenocarcinomas (SRCCs) are a particularly rare (under 1% of all adenocarcinomas) and aggressive histological subtype, defined as such if greater than 50% of tumor cells have abundant intracytoplasmic mucin that displaces the nuclei to the periphery [4]. Prognosis is typically poor, often owing to advanced disease at the time of diagnosis [4]. Nearly 80% of all SRCCs occur in the stomach and colon, and another 5% in the esophagus, while only 1% arise in the small bowel [4]. We have previously shown that across almost all cancer sites, SRCC histology is an independent predictor of increased mortality risk when compared to conventional histologies, even after controlling for age, sex, race, detection stage, grade differentiation, and multimodal treatment [4, 5]. In recent years, multiple case reports have documented cases of small bowel SRCC in patients with Crohn's disease. Given the rarity of such a diagnosis, there is no systematic description of the characteristics of this disease entity.

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In this review, we systematically summarize the demographic features and clinical presentation of Crohn's disease patients with small bowel SRCCs and compare these features to small bowel SRCCs from a population level analysis of the Surveillance, Epidemiology, and End Results (SEER) database [6]. The intention of this work is to increase awareness of the probable association between these two conditions, for which early suspicion and subsequent diagnosis are essential to improve the chances of survival.

Materials and Methods

MEDLINE, Embase, and Web of Science were searched from inception to May 31, 2023, without language restrictions using a prospectively registered PROSPERO protocol (CRD42022370768). The search terms used were ("signet ring" OR "mucinous") and ("small" or "small intestine") and ("Crohn" OR "colitis" or "inflammatory"). Two reviewers independently assessed all citations for eligibility (Crohn's disease diagnosis, duration of disease, small bowel location of SRCC, pathology, patient outcomes), and disagreements were resolved by discussion. If patients were presented in multiple publications, the most recent publication was selected for analysis. Google Translate was used to translate non-English articles. For bias assessment, case reports were assessed using the CARE (CAse REports) guidelines [7] (Supplementary Material 1, www.wjon.org), or the Institute of Health Economics Quality Appraisal for Case Series Studies for case series (three more patients) [8] (Supplementary Material 2, www.wjon.org). Studies were considered to have a low risk of bias if at least 80% of criteria were met, moderate risk if at least 60% of criteria were met, and high risk if less than 60% of criteria were met. Given the low number of articles in the literature, all articles were included in the review.

The National Cancer Institute's SEER database using 18 SEER cancer registries was interrogated using data from 1992 to 2016, via a complete case analysis, as previously described [4]. Small bowel cases were selected with the site International Classification of Diseases for Oncology (ICD-O)-3 recode 21030, and cases were further site localized to the duodenum with ICD-O-3 code C17.0, jejunum C17.1, and ileum C17.2. Conventional adenocarcinomas were selected with the histology ICD-O-3 code 814x/x, and SRCCs with 849x/x. Baseline patient characteristics were compared with the *t* and χ^2 tests for continuous and categorical variables, respectively. Univariate and multivariable Cox proportional hazard regressions were used to determine the association of mortality with cancer histology type. All hazard ratios (HRs) were calculated with 95% confidence intervals. All P values were two-sided, with a threshold of 0.05 to determine statistical significance. Using SEER 18 (2000 - 2018) data with SEER*Stat 8.4.2 (Surveillance Research Program, National Cancer Institute, Calverton, MD, USA), incidences rates were calculated to the 2000 United Sates standard population with the age variable recode < 1 year old, and cause-specific survival was age-standardized to the International Cancer Survival Standard 1-Age 15+ variable via the actuarial method. Data release from the SEER database does not require informed patient consent or approval by the Institutional Review Board. The SEER database was accessed in compliance with signed user agreements.

Results

Systematic review of Crohn's disease patients with SRCC

Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of our literature search. In total, we identified 454 articles, and after removing duplicates, 245 records were screened by titles and abstracts, with 28 articles selected for a full review. Eight articles were excluded as indicated (Fig. 1). Twenty articles (15 case reports and five case series) were included for subsequent bias assessment (Supplementary Material 1, 2, www.wjon.org) [9-28]. Two case reports were deemed high risk for bias, while the remaining articles were all rated as moderate risk for bias (Supplementary Material 1, 2, www.wjon.org).

In summary, the 20 articles included 40 patients with both Crohn's disease and a diagnosis of small bowel SRCC, with nearly all cases arising in the distal/terminal ileum (Table 1) [9-28]. Patients presented at an approximate mean age of 59 years old, with a range from 31 to 76. When provided, the range of Crohn's disease duration prior to SRCC diagnosis spanned from 0 to 44 years. Patients that were diagnosed with SRCC at the same time as Crohn's disease ranged in age from 47 to 68 years. The most common patient presentations were obstruction, perforation, flares refractory to treatment, or SRCC found on colonoscopy biopsy. Virtually all tumors were locally advanced (pathological T stage 3 and 4), typically with at least N1 (one to two positive regional lymph nodes) nodal disease. Limited follow-up/survival time data was only on the order of a few months. All but four of the studies were published in 2012 and later (Table 1) [9-28].

Two of these case studies examined associations between small bowel adenocarcinomas and Crohn's disease. The first is a case-control study from France published in 2005 that specifically studied characteristics of small bowel adenocarcinomas in patients with Crohn's disease (20 patients) compared to *de novo* cases (40 patients) [10]. In patients with Crohn's disease, the median age of cancer diagnosis was 43 years old compared to 68 years old in *de novo* cases [10]. In Crohn's disease patients, 19/20 cases arose in the ileum, and 7/20 had SRCC histology, while in the *de novo* group, only 12/40 case arose in the ileum (16/40 in jejunum, 12/40 mid bowel), and no cases had SRCC histology [10]. The second series is a cohort study from the United States published in 2022, which compared small bowel poorly cohesive carcinomas (PCCs) (which is an umbrella group including SRCCs) (15 patients) to conventional adenocarcinomas (95 patients) [26]. Like the French study, PCC patients had an earlier mean age of diagnosis at 53.7 years compared to 61.1 years, and a higher propensity in the ileum (66.7% vs. 42.1%) [26]. Etiology (Crohn's disease, celiac disease, Lynch syndrome, and sporadic) was compared between the two groups, and only Crohn's disease was significant enriched in the PCC group (P

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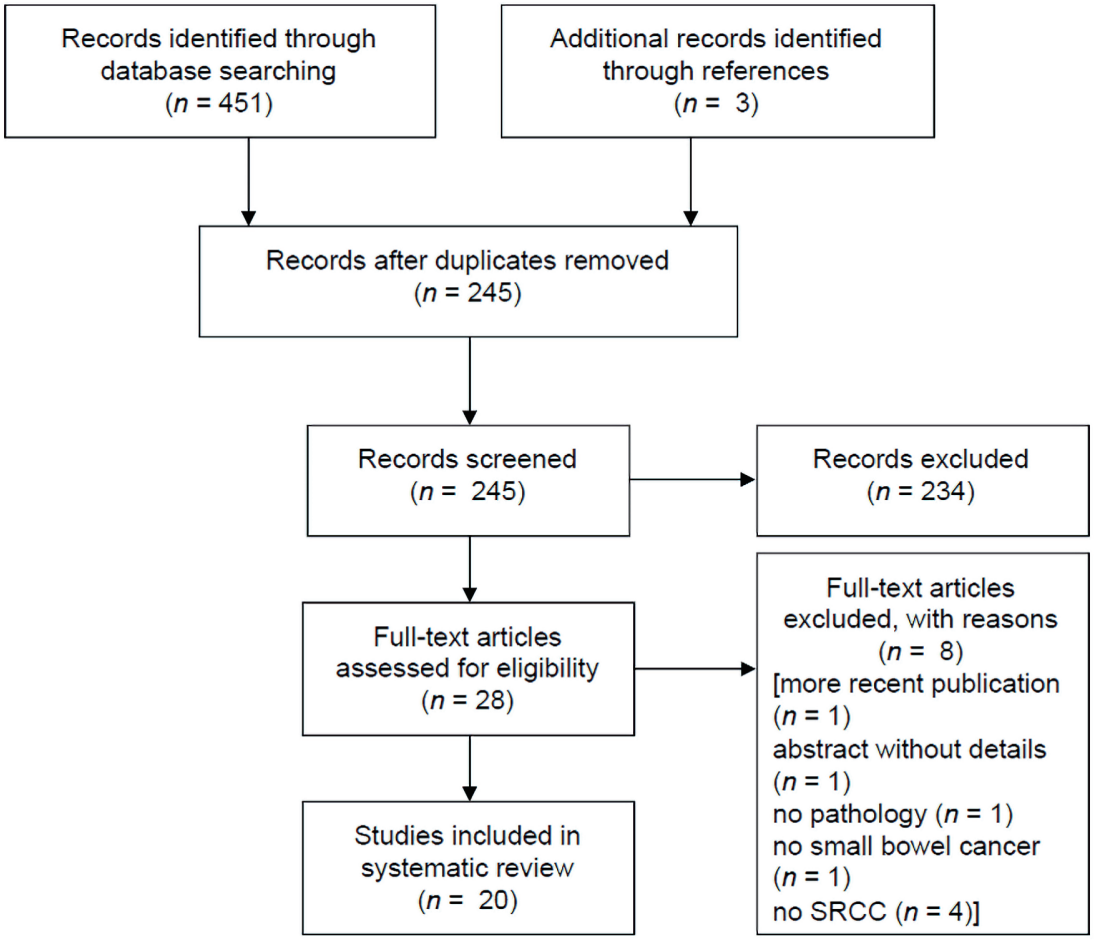

Figure 1. PRISMA study selection flow chart. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

= 0.002), present in 73.4% cases of PCC but only 28.5% of conventional adenocarcinomas [26].

Insights into the clinicopathological characteristics of small bowel SRCCs

A total of 6,111 patients with nonvariant small bowel adenocarcinoma and 327 with small bowel SRCC were eligible for analysis (Table 2). Of these, about 87% of adenocarcinomas and 83% of SRCC tumors were localizable to the duodenum, jejunum, or ileum. For comparison purposes, Table 2 includes clinicoepidemiological data for all small bowel cases, with further breakdown by small bowel location (duodenum, jejunum, ileum).

SRCCs were enriched in the ileum at 28.1% of all small bowel SRCCs, compared to 11.0% for the adenocarcinomas. Ileum SRCC patients were significantly younger at mean age of diagnosis at 60.7 years compared to 64.6 years for ileum adenocarcinomas (Table 2). The likelihood of distant disease at presentation was nearly double for ileum SRCCs compared to adenocarcinomas (41.3% vs. 26.4%), and by similar margins, 72% of ileum SRCC cases were poorly differentiated vs. 34.0% of adenocarcinomas. In both groups, about 94% of patients received surgery, while 59.8% of SRCC patients also had chemotherapy, compared to 37.9% for adenocarcinomas. Overall median survival was 20 months for ileal SRCC and 39.3 months for ileal conventional adenocarcinomas (Table 2). For the small bowel overall, the univariate mortality HR for SRCCs over adenocarcinomas was 1.35 (95% confidence interval 1.18 - 1.54), and multivariable 1.23 (1.06 - 1.41) controlling for age, sex, race, detection stage, grade differentiation, and use of surgery, radiotherapy, and chemotherapy (Table 3). For the ileum specifically, the univariate mortality HR increased to 2.23 (1.71 - 2.90), but statistical significance was lost after multivariable adjustment (1.25 (0.93 - 1.69)) (Table 3).

Discussion

Small bowel SRCC is an exceedingly rare diagnosis, accounting for 0.1-0.3% of all malignancies, and about 1% of all small bowel malignancies [4, 19], making it an extremely difficult disease pathology to study. Through the sequalae of chronic inflammation, Crohn's disease patients are at known increased risk of both small bowel (and large intestine) malignancies, though the exact risk magnitude is difficult to calculate with

Table 1. Data Extraction From Included Studies in the Systematic Review

Age, sex	Crohn's duration (years)	Surgical indication	Histology (location)
36, M	7	Obstruction	SRCC, adjacent high-grade dysplasia (ileum)
SBA in CD median 43 (range 33 - 72)	-		CD: SRCC 7/20 (19/20 ileum, 1/20 jejunum)
SBA *de novo* median 68 (range 41 - 95)			*De novo*: SRCC 0/40 (12/40 ileum, 16/40 jejunum, 12/40 mid bowel)
31, F	15	Complex fistulae and large abscess unresponsive to conservative treatment	SRCC (distal ileum)
55, M	31	TI obstruction	SRCC, villous adenoma (ileum)
64, M	15	Symptomatic CD	SRCC (ileum)
40, F	19	Crohn's flare with medically refractory symptoms	SRCC (TI)
59, M	28	No surgery due to widespread metastasis on diagnosis; diagnosed due to symptoms of Crohn's flare	SRCC (11 cm proximal to ileocecal valve)
Three cases, mean age 50.6 (range 31 - 76)	Mean 23.4 (range 1 - 47)	-	Two cases: SRCC (small bowel)
			One case: SRCC (at site of prior anastomosis)
64, M	8	Ileal obstruction	SRCC (ileum)
47, F	0, diagnosed at presentation	2 weeks: abdominal pain, watery diarrhea, SRCC found on colonoscopy	SRCC (distal ileum)
51, M	0, diagnosed at presentation	6 months: bloody diarrhea, pain, tenesmus, weight loss; started on systemic therapy for Crohn's and perforated	SRCC (ileum)
58, F	0, diagnosed at presentation	TI stenosis without complete obstruction, SRCC found on colonoscopy biopsies	SRCC (TI, invading adjacent sigmoid)
46, M	15	Obstruction	SRCC, villous dysplasia (distal ileum)
64, M	32	Obstructive symptoms and low-grade dysplasia on preoperative colonoscopy biopsy	SRCC, adenomatous dysplasia (distal ileum)
63, M	32	Symptomatic CD refractory to steroids and TNF blockade	SRCC (ileum), with carcinomatosis
68, M	0, diagnosed at presentation	Perforation	SRCC (40 cm from ileocecal valve)
44, F	-	Hematochezia, SRCC diagnosed on endoscopy	SRCC (TI)
67, M	44	SRCC on colonoscopy biopsy after medically managed flare	SRCC, tubulovillous adenoma (distal ileum)
64, M	3	Acute abdomen, TI perforation	SRCC (distal ileum)
53.73 ± 14.52 (mean ± SD); 4/15, F	-	11/15 cases CD	SRCC, 66.7% ileum, 20% duodenum, 13.3% jejunum
68, F	0, diagnosed at presentation	Newly diagnosed Crohn's, colonoscopy biopsy positive for cancer	SRCC (arising from tubulovillous adenoma of TI)
41, M	Suspected new diagnosis of Crohn's	Anemia, weight loss, fistula to buttock	SRCC (TI)

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Table 1. Data Extraction From Included Studies in the Systematic Review - *(continued)*

Age, sex	Pathological features	Postoperative treatment	Follow-up (f/u) or survival time	Country, year	Reference
36, M	pT4N0M0	-	42 mo f/u (alive, with recurrence)	USA, 1987	[9]
SBA in CD median 43 (range 33 - 72)	-	-		France, 2005	[10]
SBA *de novo* median 68 (range 41 - 95)					
31, F	2/7 positive lymph nodes	FOLFOX	13 mo f/u (alive)	South Korea, 2007	[11]
55, M	16/16 positive lymph nodes, proficient MMR	Chemotherapy	-	Israel, 2011	[12]
64, M	pT4N1M0	-	-	France, 2012	[13]
40, F	pT4N0M1G3; proficient MMR; *KRAS* mutant	Chemotherapy	-	Germany, 2013	[14]
59, M	-	Cisplatin monotherapy	6 mo (died from disease)	Italy, 2013	[15]
Three cases, mean age 50.6 (range 31 - 76)	pT4bN2aMx; + LVI	-	Recurred and died	Italy, 2014	[16]
	pT3NxMx; + LVI		Alive		
	pT4b.NxM1 + LVI		Recurred and died (f/u unknown)		
64, M	Multiple mitoses, PNI, pseudopyloric metaplasia	-	-	Spain, 2014	[17]
47, F	pT3N1M0R0	FOLFOX	1 mo f/u (alive)	Portugal, 2016	[18]
51, M	pT4N1M0R0	FOLFOX	1 mo f/u (alive)	Portugal, 2016	[18]
58, F	PNI, pseudopyloric metaplasia, pT4N2M0	FOLFOX	5 mo f/u (alive)	Portugal, 2018	[19]
46, M	G3, T4N1M1; proficient MMR, *BRAF*/*KRAS* WT	-	11 mo (died from disease)	France, 2017	[20]
64, M	G3, T4N0M0; germline mutation of *HLML1* and *PMS2*, *BRAF*/*KRAS* WT	-	66 mo f/u (alive)	France, 2017	[20]
63, M	pT4aN2M1; 12/15 positive nodes; proficient MMR; + LVI, + *PNI*	-	-	USA, 2018	[21]
68, M	pT4N0M0	Referred to medical oncology	9 mo f/u (alive, NED)	Algeria, 2019	[22]
44, F	pT4aN1M0; *RAS*/*RAF* WT	FOLFOX	-	USA, 2019	[23]
67, M	G3, pT2N1M0	FOLFOX	-	USA, 2020	[24]
64, M	G2, pT4N1Mx. 9/25 positive lymph nodes	Chemotherapy	-	Romania, 2021	[25]
53.73 ± 14.52 (mean ± SD); 4/15, F	pT3 in 46.7% and pT4 in 53.3%; positive nodes; 93.3% proficient MMR; 53.3%; + LVI 93.3%; + PNI 93.3%	-	-	Italy, 2022	[26]
68, F	pT4 (no other information)	FOLFOX	3 mo f/u (alive)	USA, 2022	[27]
41, M	pT4bN2b, MMR proficient; + LVI; + PNI; *KRAS* WT, negative for NTRK, BRAF, TNB, HER-2, PIK3 and PDL1	FOLFOX	3 mo f/u (alive)	USA, 2022	[28]

M: male; F: female; FOLFOX: folinic acid, fluorouracil, and oxaliplatin; MMR: mismatch repair; LVI: lymphovascular invasion; PNI: perineural invasion; WT: wild type; SBA: small bowel adenocarcinoma; CD: Crohn's disease; SRCC: signet ring cell adenocarcinoma; TI: terminal ileum; SD: standard deviation; TNF: tumor necrosis factor; mo: month; NED: no evidence of disease.

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Table 2. Baseline Demographics and Clinical Characteristics of Small Bowel Cancers From SEER

Location	Small bowel			Duodenum		
	Adenocarcinoma	Signet ring	P value	Adenocarcinoma	Signet ring	P value
N (%)	6,111 (100)	327 (100)	-	3,702 (60.6)	151 (46.2)	-
Age (years) (%)						
0 - 14	0 (0)	0 (0)	< 0.001	0 (0)	0 (0)	0.02
15 - 29	42 (0.7)	5 (1.5)		17 (0.5)	2 (1.3)	
30 - 49	794 (13.0)	55 (16.8)		344 (9.3)	19 (12.6)	
50 - 69	2,533 (41.4)	157 (48.0)		1,416 (38.2)	71 (47.0)	
70 - 85	2,129 (34.8)	90 (27.5)		1,465 (39.6)	47 (31.1)	
> 85	613 (10.0)	20 (6.1)		460 (12.4)	12 (7.9)	
Mean (SD)	66.4 (14.5)	62.7 (14.3)	< 0.001	68.9 (13.8)	64.7 (14.2)	< 0.001
Sex (%)						
Male	3,244 (53.1)	185 (56.6)	0.22	1,941 (52.4)	88 (58.3)	0.16
Female	2,867 (46.9)	142 (43.4)		1,761 (47.6)	63 (41.7)	
Race (%)						
White	4,521 (74.0)	263 (80.4)	0.01	2,733 (73.8)	112 (74.2)	0.31
Black	1,136 (18.6)	39 (11.6)		637 (17.2)	21 (13.9)	
Other	454 (7.4)	25 (7.6)		332 (9.0)	18 (11.9)	
Detection stage (%)						
In situ	32 (0.5)	0 (0)	< 0.001	25 (0.7)	0 (0)	0.21
Localized	1,237 (20.2)	33 (10.1)		617 (16.7)	19 (12.6)	
Regional	2,100 (34.4)	142 (43.4)		1,223 (33.0)	61 (40.4)	
Distant	2,227 (36.4)	132 (40.4)		1,383 (37.4)	57 (37.7)	
Unstaged	515 (8.4)	20 (6.1)		454 (12.3)	14 (9.3)	
Grade differentiation (%)						
Well	453 (7.4)	0 (0)	< 0.001	266 (7.2)	0 (0)	< 0.001
Moderate	2,559 (41.9)	16 (4.9)		1,427 (38.5)	7 (4.6)	
Poor	1,880 (30.8)	229 (70.0)		1,124 (30.4)	103 (68.2)	
Undifferentiated	62 (1.0)	9 (2.8)		28 (0.8)	5 (3.3)	
Unknown	1,157 (18.9)	73 (22.3)		857 (23.1)	36 (23.8)	
Surgery (%)						
Yes	3,671 (60.1)	219 (67.0)	0.01	1,579 (42.7)	67 (44.4)	0.68
No	2,440 (39.9)	109 (33.0)		2,123 (57.3)	84 (55.6)	
Radiotherapy (%)						
Yes	604 (9.9)	34 (10.4)	0.76	510 (13.8)	28 (18.5)	0.1
No	5,507 (90.1)	293 (89.6)		3,192 (86.2)	123 (81.5)	
Chemotherapy (%)						
Yes	2,452 (40.1)	160 (48.9)	0.002	1,380 (37.3)	63 (41.7)	0.27
No	3,659 (59.9)	167 (51.1)		2,322 (62.7)	88 (58.3)	
Incidence rate (95% CI)	5.29 (5.18 - 5.41)	0.27 (0.24 - 0.29)	-	3.15 (3.07 - 3.24)	0.14 (0.12 - 0.15)	-
CSS (%) (95% CI)						
1-year	56.2 (54.9 - 57.5)	53.7 (48.0 - 59.1)	-	47.5 (45.8 - 49.1)	42.0 (33.9 - 49.8)	-
2-year	42.3 (41.0 - 43.7)	30.1 (24.7 - 35.6)		33.6 (31.9 - 35.3)	22.5 (15.7 - 30.0)	
5-year	28.2 (26.7 - 29.3)	16.4 (12.0 - 21.3)		22.7 (19.5 - 22.6)	17.8 (11.6 - 25.1)	
10-year	23.8 (22.5 - 25.1)	13.8 (9.7 - 18.8)		18.8 (16.0 - 19.1)	16.2 (10.0 - 23.6)	
Median (Months)	16.5	14.2		10.9	5.7	

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Table 2. Baseline Demographics and Clinical Characteristics of Small Bowel Cancers From SEER - *(continued)*

Location	Jejunum			Ileum		
	Adenocarcinoma	Signet ring	P value	Adenocarcinoma	Signet ring	P value
N (%)	959 (15.7)	29 (8.9)	-	670 (11.0)	92 (28.1)	-
Age (years) (%)						
0 - 14	0 (0)	0 (0)	0.35	0 (0)	0 (0)	0.13
15 - 29	13 (1.4)	1 (3.4)		8 (1.2)	2 (2.2)	
30 - 49	206 (21.5)	8 (27.6)		106 (15.8)	17 (18.5)	
50 - 69	476 (49.6)	9 (31.0)		295 (44.0)	50 (54.3)	
70 - 85	221 (23.0)	9 (31.0)		197 (29.4)	18 (19.6)	
> 85	43 (4.5)	2 (6.9)		64 (9.6)	5 (5.4)	
Mean (SD)	60.2 (14.5)	60.7 (16.8)	0.81	64.6 (14.9)	60.7 (14.0)	0.02
Sex (%)						
Male	538 (56.1)	13 (44.8)	0.23	345 (51.5)	55 (59.8)	0.14
Female	421 (43.9)	16 (55.2)		325 (48.5)	37 (40.2)	
Race (%)						
White	686 (71.5)	24 (82.8)	0.25	540 (80.6)	84 (91.3)	0.04
Black	225 (23.5)	3 (10.3)		93 (13.9)	6 (6.5)	
Other	48 (5.0)	2 (6.9)		37 (5.5)	2 (2.2)	
Detection stage (%)						
In situ	0 (0)	0 (0)	0.04	5 (0.7)	0 (0)	< 0.001
Localized	247 (25.8)	4 (13.8)		211 (31.5)	5 (5.4)	
Regional	382 (39.8)	16 (55.2)		268 (40.0)	49 (53.3)	
Distant	314 (32.7)	7 (24.1)		177 (26.4)	38 (41.3)	
Unstaged	16 (1.7)	2 (6.9)		9 (1.3)	0 (0)	
Grade differentiation (%)						
Well	58 (6.0)	0 (0)	< 0.001	78 (11.6)	0 (0)	< 0.001
Moderate	519 (54.1)	3 (10.3)		296 (44.2)	6 (6.5)	
Poor	294 (30.7)	10 (62.1)		228 (34.0)	71 (77.2)	
Undifferentiated	10 (1.0)	1 (3.4)		14 (2.1)	3 (3.3)	
Unknown	78 (8.1)	7 (24.1)		54 (8.1)	12 (13.0)	
Surgery (%)						
Yes	865 (90.2)	23 (79.3)	0.06	632 (94.3)	87 (94.6)	0.93
No	94 (9.8)	6 (20.7)		38 (5.7)	5 (5.4)	
Radiotherapy (%)						
Yes	37 (3.9)	1 (3.4)	0.91	27 (4.0)	1 (1.1)	0.16
No	922 (96.1)	28 (96.6)		643 (96.0)	91 (98.9)	
Chemotherapy (%)						
Yes	483 (50.4)	15 (51.7)	0.89	254 (37.9)	55 (59.8)	< 0.001
No	476 (49.6)	14 (48.3)		416 (62.1)	37 (40.2)	
Incidence rate (95% CI)	0.77 (0.73 - 0.82)	0.02 (0.01 - 0.03)	-	0.59 (0.55 - 0.63)	0.07 (0.06 - 0.08)	-
CSS (%) (95% CI)						
1-year	76.9 (74.0 - 79.6)	58.7 (35.5 - 76.1)	-	72.7 (69.0 - 76.0)	72.3 (61.8 - 80.4)	-
2-year	62.8 (59.5 - 66.0)	24.5 (9.0 - 44.0)		59.9 (55.8 - 63.8)	38.6 (27.9 - 49.2)	
5-year	41.5 (37.9 - 45.1)	24.5 (9.0 - 44.0)		46.3 (42.0 - 50.5)	7.9 (3.0 - 15.8)	
10-year	40.9 (32.6 - 40.0)	16.3 (3.6 - 37.2)		41.7 (37.1 - 46.2)	5.9 (1.8 - 13.6)	
Median (Months)	40.9	13.3		39.3	20.0	

Incidence rates per 1 million. CSS: cause-specific survival; CI: confidence interval.

Table 3. Derived Univariate and Multivariable Cox-Proportional Hazard Ratios of Mortality Comparing Signet Ring Cell Adenocarcinomas to Conventional Adenocarcinomas

Location	Univariate (95% CI)	Multivariable (95% CI)
Small bowel	1.35 (1.18 - 1.54)	1.23 (1.06 - 1.41)
Duodenum	1.25 (1.02 - 1.52)	1.19 (0.97 - 1.46)
Jejunum	1.94 (1.24 - 3.04)	1.87 (1.19 - 2.95)
Ileum	2.23 (1.71 - 2.90)	1.25 (0.93 - 1.69)

Multivariable hazard ratios were corrected for age, sex, race, detection stage, grade differentiation, surgery, radiotherapy, and chemotherapy. CI: confidence interval.

ranges from 3- to 60-fold [12]. As is typical for most small bowel cancer research management algorithms, our knowledge is largely derived from studies of much more prevalent CRC. Consequently, a similar linkage between increased colorectal SRCC and IBD, which includes Crohn's disease, has also been proposed [29]. One recent large case-control study showed that SRCC or mucinous adenocarcinomas comprised 66% of all rectal adenocarcinomas in IBD patients, as opposed to 16.6% of the control group with no previous IBD history [30]. The sequence of chronic inflammation-dysplasia-cancer described in IBD-related CRC, tends to produce more serrated rather than polypoid precursor lesions, where *APC* gene loss of function is a late event rather than early, and *P53* mutation burden is higher compared to sporadic CRC [30]. However, whether these mutations are drivers or passengers of SRCC/mucin-overproduction pathology is not known.

Over the past decade, the number of case reports and small case series correlating small bowel SRCCs to a previous history of Crohn's disease has become sizeable, suggesting more than a mere correlative link between the two disease processes. This is further supported by at least two case-control/cohort studies which demonstrate a significant enrichment of small bowel SRCC events in patients with an underlying diagnosis of Crohn's disease [10, 26]. Unfortunately, any molecular study to substantiate a causal relationship between Crohn's disease and SRCC development would require input from international-level consortiums. To put into perspective the rarity of small bowel SRCCs, particularly in the ileum, a query of nearly 30 years of data from the SEER database, which tracks every cancer diagnosis from over one-third of the entire United States population [6], produced only 92 eligible cases, which resulted in a calculated age-adjusted incident rate of 0.7 cases per 10 million population. For comparison, cases of colorectal SRCC are on the order of 45 cases per 10 million population, or nearly 60-fold more, and yet these cancers comprise only about 1% of all CRC cases [4].

In summary, we wish to impart on clinicians who manage patients with IBD including Crohn's disease, to have an extremely low threshold to fully investigate changes in patient symptomatology. This would particularly apply to cases of poorly responding or long-standing disease, because these patients are at significant risk of malignant transformation. From this work, we postulate that an ileal malignancy secondary to Crohn's disease might have a uniquely increased probability of being a SRCC over a conventional adenocarcinoma. SRCCs tend to have an overall worse prognosis compared to conventional adenocarcinomas, secondary to increased rates of poor tumor differentiation, nodal involvement, and metastatic potential, and decreased response rates to systemic therapy [4]. Therefore, for these patients, endoscopic surveillance, particularly with ileocecal valve intubation and biopsy of any suspicious lesions, is critical for early cancer diagnosis and subsequent surgical treatment, which offers the best chance of survival. Finally, to better understand tumor biology for cancers with rare histologies, we would additionally encourage biobanking of surgical specimens, along with archiving of patient clinicodemographic data, for future analyses.

Supplementary Material

Suppl 1. Risk of bias assessment for all included case studies (CARE (CAse REports) guidelines). Red indicates high risk of bias, yellow indicates moderate risk of bias.

Suppl 2. Risk of bias assessment for all included case series (Institute of Health Economics Quality Appraisal for Case Series Studies). Yellow indicates moderate risk of bias.

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Conflict of Interest

None to declare.

Author Contributions

MGKB designed the study and conducted the search and SEER analysis. EDN and MGKB independently reviewed the selected case studies. MGKB wrote the original draft, and EDN and SBLO reviewed and edited the draft. SBLO supervised the project. All authors have read and agreed to the published version of the manuscript.

Data Availability

All data supporting the findings of this study are available within the article.

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Abbreviations

CRC: colorectal cancer; HR: hazard ratio; IBD: inflammatory bowel disease; PCC: poorly cohesive carcinoma; SRCC: signet ring cell adenocarcinoma

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