World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v20.i33.11486

World J Gastroenterol 2014 September 7; 20(33): 11486-11495
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (3): Inflammatory bowel disease

Small bowel adenocarcinoma and Crohn's disease: Any further ahead than 50 years ago?

Caitlin Cahill, Philip H Gordon, Andrea Petrucci, Marylise Boutros

Caitlin Cahill, Philip H Gordon, Andrea Petrucci, Marylise Boutros, McGill University Department of Surgery; Sir Mortimer B. Davis Jewish General Hospital Colorectal Surgery, Montreal PQ H3T 1E2, Canada

Author contributions: Cahill C, Gordon PH and Boutros M contributed equally to this work; Cahill C, Gordon PH and Boutros M designed the research; Cahill C, Petrucci A and Gordon PH performed the research, Petrucci A performed the data collection for our institutional series; Cahill C, Gordon PH and Boutros M analyzed the data; Cahill C, Gordon PH, Petrucci A and Boutros M wrote the manuscript; Gordon PH and Boutros M revised the manuscript.

Correspondence to: Marylise Boutros, MD, FRCS(C), McGill University Department of Surgery; Sir Mortimer B. Davis Jewish General Hospital Colorectal Surgery, 3755 Cote Ste Catherine G-314, Montreal PQ H3T 1E2, Canada. mboutros@jgh.mcgill.ca
Telephone: +1-514-340-8222-3256 Fax: +1-514-340-7560
Received: March 4, 2014 Revised: May 8, 2014
Accepted: May 26, 2014
Published online: September 7, 2014

Abstract

This review of the literature on small bowel carcinoma associated with Crohn's disease specifically addresses the incidence, risk factors, and protective factors which have been identified. It also reviews the clinical presentation, the current modalities of diagnosis, the pathology, treatment, and surveillance. Finally, the prognosis and future direction are addressed. Our experience with small bowel adenocarcinoma in Crohn's disease is reported. Readers will be provided with a better understanding of this rare and often poorly recognized complication of Crohn's disease.

Key words: Crohn's disease; Small bowel adenocarcinoma; Cancer risk; Cancer malignancy; Incidental carcinoma; Late complications of Crohn's disease; Inflammatory bowel disease

Core tip: This review of the literature on small bowel carcinoma associated with Crohn's disease specifically addresses the incidence, risk factors, and protective factors which have been identified. It also reviews the clinical presentation, the current modalities of diagnosis, the pathology, treatment, and surveillance. Finally, the prognosis and future direction are addressed. Our experience with small bowel adenocarcinoma in Crohn's disease is reported. Readers will be provided with a better understanding of this rare and often poorly recognized complication of Crohn's disease.

Cahill C, Gordon PH, Petrucci A, Boutros M. Small bowel adenocarcinoma and Crohn's disease: Any further ahead than 50 years ago? *World J Gastroenterol* 2014; 20(33): 11486-11495 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i33/11486.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i33.11486

INTRODUCTION

Over the past several decades it has become increasingly recognized that small bowel adenocarcinoma is an undeniable complication of Crohn's disease of the small intestine. The exact magnitude of this risk is virtually impossible to determine. The first case of small bowel carcinoma in Crohn's disease was reported by Ginzburg in 1956. Since then, there have been countless published case reports as well as numerous retrospective reviews and cohort studies which have attempted to define the occurrence of small bowel carcinoma in Crohn's disease.

This review of the literature on small bowel carcinoma associated with Crohn's disease specifically addresses the incidence, risk factors, and protective factors which have been identified. It will also review the clinical pre-

sentation, the current modalities of diagnosis, the pathology, treatment, and surveillance. Finally, the prognosis and future direction will be addressed. Our experience with small bowel adenocarcinoma in Crohn's disease is reported. Readers will be provided with a better understanding of this rare and often poorly recognized complication of Crohn's disease.

INCIDENCE

The relative risk of developing carcinoma of the small bowel in patients with Crohn's disease has been estimated to range from 6 to 320[1]. Jess *et al*[2] studied a population-based cohort of 374 patients with Crohn's disease in order to determine the long term risk of intestinal and extra-intestinal malignancies. The risk of small bowel adenocarcinoma was increased by more than 60 fold as compared to the general population. On the basis of 5000 cases of Crohn's disease reported in the world literature, Amman[3] calculated an association with carcinoma of 0.08%, which, he emphasized, was lower than the incidence of carcinoma of the small bowel in the absence of Crohn's disease, which he estimated at 0.098% in 137124 autopsies. However, the incidence in Crohn's disease may be higher than reported as the associated carcinoma may have been missed due to inadequate histopathologic study. These observational series serve to underline the possible fallacies of mass statistics collected from the literature.

Our review of the literature revealed 220 reported cases of adenocarcinoma associated with small bowel Crohn's disease. Since we do not have the number of patients who suffered from Crohn's disease of the small bowel from which those patients were extracted, the actual incidence of carcinoma associated with Crohn's cannot be calculated. These numbers were obtained through a Medline search from the years 1975 to 2013. Some of the reports were reviews and hence there may be some duplication of cases in the series reported.

There is nevertheless a general consensus that the risk of developing small bowel adenocarcinoma is greater in patients with Crohn's disease than in the general population. The exact magnitude of the increased risk is difficult to determine because information derived from population-based studies, case-controlled studies, physician surveys, and case reports have been combined.

Many reports have documented that adenocarcinoma of the small bowel is a complication of Crohn's disease and this has been well reviewed by Kerber[4] and Frank[5]. Sometimes the patients who develop an adenocarcinoma are those with small bowel-limited Crohn's disease but most often there is a combination of those with both small and large bowel Crohn's disease. Patients with longstanding small bowel Crohn's disease are thought to have an increased risk of small bowel carcinoma[6-9].

In a meta-analysis by von Roon *et al*[10], the relative risk of developing small bowel carcinoma in the 9642 patients was 28.37. The incidence rate of small bowel carcinoma in 12740 patients was 1.55 per 100000 patient years. In the review by Von Roon, the mean duration of Crohn's disease before the onset of carcinoma was 9 years (range 0.8-41). The relative risk of developing small bowel carcinoma compared to the background population was higher in North America (RR = 41.23), the United Kingdom (RR = 40) and Scandinavia (RR = 21.3).

Shaukat *et al*[11] studied all cases of small bowel carcinoma in persons 67 years and older in the Surveillance Epidemiology and End Results catchment area. They identified 923 cases of small bowel carcinoma and 142273 controls and found a strong association between Crohn's disease and small bowel carcinoma [odds ratio (OR) = 12.02]. The prevalence of Crohn's disease in patients with small bowel carcinoma was low (1.6%) so the absolute risk remains low.

RISK AND PROTECTIVE FACTORS

Numerous risk factors for developing small bowel carcinoma in Crohn's disease have been postulated in the literature. Many purported risk factors surfaced as a result of observed trends across case reports such as previous strictureplasty[12-15] and excluded/bypassed bowel segments[16-18]. Approximately 30% of reported small bowel carcinomas in Crohn's disease occurred in patients who had bypassed loops[19]. This complication stresses the need to encourage resection rather than bypass. Lashner[20] reported a case control study of carcinoma of the small bowel in Crohn's disease in which each case was matched to 4 randomly selected controls from an inflammatory bowel disease registry. The following factors were significantly associated with small bowel carcinoma in Crohn's disease: (1) occupation, with three cases having had exposure to halogenated aromatic compounds and aliphatic amines, asbestos, and cutting oil solvents and abrasives; and (2) 6-mercaptopurine use (OR = 10.8).

Several studies reported that the risk of developing small bowel carcinoma was according to the anatomic location of the Crohn's disease (Table 1). For example, the odds ratio of developing small bowel carcinoma was found to be much higher in 363 patients whose disease was confined to the small bowel (RR = 158.5) than in the 507 patients with ileocolic Crohn's disease (RR = 83.8)[10].

Table 1 displays a review of the studied risk factors for small bowel carcinoma in Crohn's disease in the literature, highlighting which authors agree and disagree with a purported risk factor. Clinicians should perhaps be more vigilant for small bowel carcinoma in patients with inflammation restricted to the small bowel versus ileocolic inflammation.

Protective factors against development of small bowel carcinoma in Crohn's disease have been less frequently studied, but available information is cited in Table 2. In a study of 29 patients with Crohn's disease and small bowel carcinoma Piton *et al*[21] found that small bowel resection and prolonged use of salicylates may protect against small bowel carcinoma in Crohn's disease patients.

Table 1 Risk factors for small bowel cancer in Crohn's disease

		Risk factors for small bowel cancer?	
		Yes	No
Crohn's related risk factors			
1	"Long" duration of CD	Greenstein *et al*[68] (mean 33.5 yrs) Greenstein *et al*[24] (mean 22 yrs) Jess *et al*[2] (median 16 yrs) Kamiya *et al*[69] (one case 18 yrs) Kersting *et al*[65] (one case 16 yrs) Kvist *et al*[70] (mean 29 yrs) Mellemkjaer *et al*[71] (mean 22 yrs) Michelassi *et al*[55] (mean 19.6 yrs) Mizushima *et al*[72] (mean 14 yrs) Munkholm *et al*[8] (mean 13.5 yrs) Palascak-Juif *et al*[27] (median 15 yrs) Petras *et al*[46] (mean 20 yrs) Ribeiro *et al*[1] (mean 26.5 yrs) Savoca *et al*[62] (one case 20 yrs) Sigel *et al*[48] (median 12 yrs) Solem *et al*[26] (median 21 yrs) Widmar *et al*[23] (mean 25.3 yrs)	Jess *et al*[73] Laukoetter *et al*[63]
2	Area of CD inflammation	Jess *et al*[2] Michelassi *et al*[55] Mizushima *et al*[72] Munkholm *et al*[8] Palascak-Juif *et al*[27] Ribeiro *et al*[1] Savoca *et al*[62] Solem *et al*[26] von Roon *et al*[10]	Laukoetter *et al*[63]
3	Jejunal CD	Lashner[20]	Palascak-Juif *et al*[27] Solem *et al*[26]
4	Strictures	Jaskowiak *et al*[15] Kersting *et al*[65] Lakatos *et al*[74] Petras *et al*[46] Ribeiro *et al*[1]	Solem *et al*[26]
5	Fistula	Kersting *et al*[65] Laukoetter *et al*[63] Ribeiro *et al*[1]	Lashner *et al*[20] Solem *et al*[26]
6	Bypassed segment	Greenstein *et al*[75]	Lashner[20] Palascak-Juif *et al*[27] Ribeiro *et al*[1] Solem *et al*[26]
7	CD Medications	[1]Lashner[20]	Canavan *et al*[76] Solem *et al*[26]
8	"Young" age	Freeman *et al*[60] (mean 45.7 yrs) Hoffman *et al*[7] (mean 46 yrs) Kersting *et al*[65] (one case 34 yrs) Laukoetter *et al*[63] (20 yrs earlier) Michelassi *et al*[55] (mean 47.7 yrs) Palascak-Juif *et al*[27] (median 47 yrs) Petras *et al*[46] (mean 46 yrs) Savoca *et al*[62] (mean 38 yrs) Sigel *et al*[48] (median 42 yrs) Widmar *et al*[23] (mean 55.4 yrs)	Jess *et al*[73] (median 66 yrs) Munkholm *et al*[8] (mean 70.5 yrs)
General risk factors			
9	Gender		Jess *et al*[2] Petras *et al*[46]
10	Male	Lakatos *et al*[74] Michelassi *et al*[55] Shaukat *et al*[11] Sigel *et al*[48] Ribeiro *et al*[1] Widmar *et al*[23]	Lashner[20] Palascak-Juif *et al*[27]
11	Female	Freeman *et al*[60]	
12	Black race	Shaukat *et al*[11]	
13	Past corticosteroid use		Kaerlev *et al*[67]
14	Past use of radioactive medication		Kaerlev *et al*[67]
15	Liver disease (cirrhosis/ hepatitis)		Kaerlev *et al*[67]
16	Gallstones		Kaerlev *et al*[67]
17	Previous cholecystectomy	Chen *et al*[64]	Kaerlev *et al*[67]
18	Prior history of peptic ulcer disease	Chen *et al*[64]	Kaerlev *et al*[67]
19	Celiac disease	Kaerlev *et al*[67]	
20	Prior malignancy		Solem *et al*[26]
21	Blood type B		Chen *et al*[64]
22	Rh type		Chen *et al*[64]
23	Tobacco	Chen *et al*[64] Lakatos *et al*[74]	Chow *et al*[77] Negri *et al*[25]
24	Alcohol	Chen *et al*[64]	Chow *et al*[77] Negri *et al*[25]
25	Diet	[2]Negri *et al*[25] [3]Chow *et al*[77]	
26	Lower education level	Kaerlev *et al*[67]	
27	Geographic location	[4]von Roon *et al*[10]	
28	Hazardous occupation	[5]Lashner[20]	
29	Marital status		Chen *et al*[64]
30	Religion		Chen *et al*[64]
31	Room type		Chen *et al*[64]

[1]6-MP; [2]Bread, pasta, rice, sugar, red meat; [3]Red meat, salt-cured foods, smoked foods; [4]North America higher risk; [5]Exposure to halogenated aromatic compounds and aliphatic amines, asbestos, solvents, oils, abrasives. CD: Crohn's disease.

CLINICAL PRESENTATION

Obstruction is the most common presenting manifestation in small bowel carcinoma in Crohn's disease with symptoms of nausea, vomiting and abdominal pain. Other possible presentations are hemorrhage, fistula, or perforation[22-24]. Unfortunately, all of these symptoms are hard to differentiate from those of a Crohn's exacerbation, which partly explains the challenge of detecting small bowel carcinoma in this patient population and results in the majority of diagnoses being made at the time of operation or postoperatively. In fact, only a small minority (< 5%) is diagnosed preoperatively[22]. Furthermore, Collier *et al*[19] described that over 50% of small bowel carcinomas in resected Crohn's disease segments were unsuspected or incidentally found by the pathologist.

Table 2 Protective factors for small bowel cancer in Crohn's disease

		Protective factor against small bowel cancer?	
		Yes	No
1	Diet	[1]Negri *et al*[25]	[2]Chow *et al*[77]
2	5-ASA	Piton *et al*[21] Solem *et al*[26]	
3	CD medications		Canavan *et al*[76] Solem *et al*[26] (other than 5-ASA)

[1]Coffee, fish, vegetables, fruit; [2]Fruits and vegetables. 5-ASA: 5-aminosalicylic acid.

Two important clinical indicators of malignancy are recrudescent symptoms after long periods of relative quiescence and small bowel obstruction that is refractory to medical therapy[23]. Therefore, it is prudent to consider a surgical assessment of patients with longstanding symptomatic Crohn's disease who fail to respond to conservative management.

The usual age of diagnosis of small bowel carcinoma in Crohn's disease patients is 45 to 55 years[4,6,7,22,23]. This is in contrast to small bowel carcinoma *de novo* which is usually diagnosed between 60 and 69 years of age[25]. Crohn's disease will often predate the carcinoma diagnosis by 20 to 25 years[4,22-24,26].

Palascak-Juif *et al*[27] studied 20 patients with Crohn's disease-associated small bowel carcinoma recruited from French university hospitals and compared them to 40 patients with small bowel carcinoma *de novo* recruited from a population-based registry. Small bowel carcinoma occurred after a median time of 15 years of Crohn's disease and was located within the inflamed areas of the ileum (19) or jejunum (1), whereas in patients with small bowel carcinoma *de novo* it was distributed all along the small intestine. The median age of diagnosis of small bowel carcinoma was 47 years (range 33-72 years) in patients with Crohn's disease and 68 years (range 41-95 years) in those with small bowel carcinoma *de novo*. The cumulative risk of small bowel carcinoma was 0.2% and 2.2% after 10 and 25 years of small bowel Crohn's disease, respectively. The diagnosis was made preoperatively in 1 of 20 patients with Crohn's disease and 22 of 40 patients with small bowel carcinoma *de novo*. Signet ring cells were found in 35% of Crohn's disease cancers but not in patients with small bowel carcinoma *de novo*. Relative survival at 2 and 5 years was not significantly different between these two categories of patients (54% *vs* 37% and 35% *vs* 30%; with and without Crohn's disease, respectively).

In a retrospective review from 1993 to 2009, Widmar *et al*[23] identified 29 patients with small bowel carcinoma (22 ileal and 5 jejunal) in Crohn's disease. There were no carcinomas in excluded intestinal loops. The median age of onset of Crohn's disease symptoms was 25 years and the median age at cancer diagnosis was 55.4 years, for a mean interval of 25.3 years. Widmar found that 75% of carcinomas arose in the terminal ileum, a location that only accounts for 13% of sporadic small bowel adenocarcinomas[28]. Patients with Crohn's disease developed adenocarcinoma at an average age of 48 years versus 65 in the general population, with a male to female ratio of 3 to 1.

Solem *et al*[26] described the clinical features, outcomes, and risk factors of small bowel carcinoma in Crohn's disease. Nine cases (4 males) were identified. The patients presented with abdominal pain (89%), obstruction (89%), and weight loss (78%). The carcinoma was located in the ileum in 8 patients (89%) and in the jejunum in 1 patient (11%). All cases but one had advanced disease with either lymph node involvement or metastases. The mortality rates at 1 and 2 years were 42% and 61%, respectively.

Floch *et al*[29] reviewed 47 previously reported small bowel carcinomas in Crohn's disease. The average age of the Crohn's carcinomas was 46.5 years while that for the *de novo* group was 55 years. The sexual ratios were 2.46:1 and 2:1 males to females for the respective groups. The *de novo* carcinomas had a slight predilection for the duodenum (4.7%) while the latter group had a heavy predilection for the ileum (70.8%) and contained no duodenal carcinomas. The prognosis of the Crohn's group appeared to be much worse than that of the *de novo* group with five year survivals of 3.7 and 20%-22%, respectively. Late diagnosis in the enteritis group was felt to be the major reason for this.

Hoffman *et al*[7] also reviewed the literature and found 49 cases and added two of their own. The Crohn's associated carcinomas differed from carcinoma not associated with Crohn's in that (1) mean age of carcinoma discovery was less (46 years *vs* 64 years); (2) more carcinomas arose in the ileum (76% *vs* 27%); (3) diagnosis and cure were less successful; and (4) they occurred more frequently.

The review by Fresko *et al*[30] of 59 reported cases of carcinoma of the small bowel in Crohn's disease, to which they added three of their own cases, revealed that (1) carcinoma develops at a younger age than in carcinoma *de novo*; (2) there is no difference in incidence of carcinoma in the first, second and third decades after onset of symptoms of Crohn's disease; (3) 73% of neoplasms arose in the ileum; (4) in all but one case it developed in inflamed segments of bowel; and (5) in 31% of cases carcinoma developed in a bypassed segment of bowel. They concluded that Crohn's carcinoma is a complication of Crohn's disease and not a chance co-existence of the two diseases in the patient.

DIAGNOSIS

The clinical diagnosis of small bowel carcinoma in Crohn's disease patients based on symptoms and physical examination is quite difficult, if not impossible. Indeed, many patients with carcinoma of the small bowel are not suspected of having a malignancy even at time of operation[5,6,31-33]. Most cases of small bowel carcinoma have been in segments involved with Crohn's disease. These malignancies were indistinguishable radiologically from

longstanding Crohn's disease. In two of the patients described by Kerber[4] and Frank[5], there was "shouldering", destruction, and a mass.

In general, imaging techniques may miss small lesions and may not be able to differentiate areas of small bowel carcinomas from those of severe Crohn's disease. Routine computed tomography (CT) exposes patients to radiation, and although magnetic resonance (MR) imaging does not, it is time consuming and costly[34]. Buckley *et al*[35] found CT staging of small bowel carcinoma to be 47% accurate but errors occurred in patients with Crohn's disease. Enteroclysis is invasive and requires special training[36]. The usefulness of FDG-PET is limited by the background chronic inflammation of Crohn's[37].

Video capsule endoscopy is challenged by issues of visualization (*i.e.*, limited field of vision, non-continuous image capture, lesions hidden in folds), inadequate preparation, and the stenosing nature of Crohn's disease[36] that may prohibit a capsule from passing. Furthermore, lesion localization can be difficult and it does not allow for tissue sampling[38].

Enteroscopic techniques do allow direct visualization and tissue sampling but are invasive, labor intensive, and may be limited by the length and tortuosity of the small bowel. Intraoperative endoscopy is now reserved for lesions which are not accessible by balloon enteroscopy[39].

Despite their disadvantages, there are published cases demonstrating the utility of some of the techniques listed above. Placé and colleagues[40] observed two different patterns using MR-enterography: the first was a long, circumferential, asymmetric, and heterogeneous thickening of the ileum with a visible nodule on free induction echo stimulated acquisition images, and the other was a mass of the terminal ileum showing restricted diffusion on diffusion weighted MR imaging. Soyer *et al*[41] evaluated 7 patients with small bowel carcinoma, and on CT enterography the carcinoma was visible in five patients. Four different patterns were individualized including small bowel mass (2 patients), long stenosis with heterogeneous submucosal layer (2 patients), short and severe stenosis with proximal small bowel dilatation (2 patients), and sacculated small bowel loop with irregular and asymmetric circumferential thickening (1 patient). Stratification, fat stranding, and comb signs were present in 2, 2, and 1 patient(s), respectively. Nevertheless, adenocarcinoma may be completely indistinguishable from benign fibrotic or acute inflammatory strictures.

A case reported by Kodaira *et al*[42] highlighted the unique successful combination of PET/CT and double balloon enteroscopy for the diagnosis of small bowel carcinoma in a Crohn's disease patient. Van Weyenberg *et al*[43] found both MR enterclysis and video capsule endoscopy useful but they believe that MR enterclysis is the better option. Ultimately, a combination of methods is likely the present day solution.

On the basis of their study of patients in whom adenocarcinoma of the small bowel developed as a complication of Crohn's disease, Kerber[4] and Frank[5] concluded: (1) the development of adenocarcinoma is more likely to be seen in patients with longstanding disease; (2) classical radiographic appearance of carcinoma may not be seen; (3) a progressive change in radiographic appearance over time with the development of masses, fistulas, strictures and obstruction should raise the suspicion of coexisting carcinoma; (4) malignancy should be considered when there is a longstanding quiescent disease activity followed by a recrudesces of symptoms with concurrent radiographic changes; and (5) fistulas may be associated with carcinoma in two ways: a mass produced by carcinoma or carcinoma arising in chronic fistulas from Crohn's disease. Contrary to prior recommendations, they suggest that obtaining radiographic examinations to document changing patterns of disease displays an important role in the management of patients with Crohn's disease and may lead to earlier detection of complicating carcinoma thus improving prognosis in such patients.

PATHOLOGY

In contrast to *de novo* small bowel carcinomas which are most often in the duodenum (55%)[28], 75% of Crohn's related small bowel carcinomas are ileal[22,28]. Miller *et al*[44] noted that all small bowel carcinomas associated with Crohn's disease were ileal in location. Watanabe *et al*[45] published a summary of small bowel carcinoma within Crohn's disease up until 1991 documenting only adenocarcinomas and signet ring cell carcinomas (Table 3). Petras *et al*[46] reported four patients with small intestinal carcinoma: three with poorly differentiated or signet ring cell type carcinomas and one with mucinous type. All four patients had high grade dysplasia in the mucosa immediately adjacent to the carcinoma, supporting the dysplasia-carcinoma sequence believed to occur in Crohn's disease as with ulcerative colitis[47,48]. A wider variety of malignancies have been reported and are noted in Table 3, including sarcomas, lymphomas, and carcinoids.

TREATMENT

The treatment of choice is wide resection of the small bowel segment harboring the carcinoma as well as resection of the corresponding mesentery and lymph nodes[22]. Pancreaticoduodenectomy for lesions of the second or third portion of the duodenum and right colectomy for carcinoma of the distal ileum would be required[49].

Evidence regarding the value of adjuvant chemotherapy for small bowel carcinoma is sparse and consists mostly of small retrospective reviews. Most available data is from experience in managing ampullary adenocarcinoma. Fishman *et al*[50] reported response rates upwards of 30% in the palliative setting: 33% with Gemcitabine, 50% with 5-FU or Capcitabine, and 42% with Platinum- or Irinotecan-based therapy.

PROGNOSIS

The prognosis of Crohn's associated small bowel carcinoma varies among reported studies but has been noted

Table 3 Histopathology of small bowel cancers in Crohn's disease

Histology	Watanabe *et al*[45]	Update since 1991
Adenocarcinoma	61 cases reported up until 1991 as quoted by Watanabe	Barwood *et al*[14] Chan *et al*[78] Chen *et al*[64] Christodoulou *et al*[79] Dossett *et al*[22] Feldstein *et al*[49] Fell *et al*[80] Fielding *et al*[9] Gillen *et al*[81] Gusakova *et al*[82] Jaskowiak *et al*[15] Jess *et al*[73] Kamiya *et al*[69] Katsanos *et al*[83] Kersting *et al*[65] Koga *et al*[84] Kronberger *et al*[85] Lindgren *et al*[86] Mellemjaker *et al*[71] Menon *et al*[12] Michelassi *et al*[55] Palascak-Juif *et al*[27] Partridge *et al*[13] Ribeiro *et al*[1] Richards *et al*[54] Rubio *et al*[87] Sammartino *et al*[88] Sigel *et al*[48] Solem *et al*[26]
Sarcoma		Gollop *et al*[89] (leiomyosarcoma) Jess *et al*[73] (leiomyosarcoma) Fielding *et al*[9] (reticulum-cell sarcoma)
Local lymphoma		Jess *et al*[73]
Carcinoid		Chen *et al*[64] Kvist *et al*[70] Mellemkjaer *et al*[71] Savoca *et al*[62]
Poorly differentiated		Petras *et al*[46] Savoca *et al*[62] Simpson *et al*[47]
Signet ring	8 cases reported up until 1991 as quoted by Watanabe	

to be poorer than the *de novo* small bowel carcinomas[24]. Most small bowel carcinomas in Crohn's disease present at a younger age and are more diffusely and distally located than *de novo* carcinomas, usually making them undiagnosable at a curable stage. Indeed, two-thirds of cases present with intestinal obstruction. Greenstein[51] reported two year disease survival for small bowel carcinoma in Crohn's disease as 9% compared with 15%-25% for *de novo* carcinomas. Mortality for carcinoma in excluded bowel has been reported to be as high as 100%[51]. One report of carcinomas developing in small bowel Crohn's strictures found only 9 such cases[52]. All patients had Crohn's disease for more than ten years. The average age of patients was 48 years compared to 65 years for *de novo* carcinomas. In patients with Crohn's disease, carcinoma affects the ileum twice as commonly as the jejunum and four times as commonly as the duodenum. Fifty-nine percent of all carcinomas complicating Crohn's disease were discovered incidentally during pathologic examination of resected specimens. If small bowel alone is considered this figure rises to 70%.

Small bowel carcinomas associated with Crohn's disease tends to be poorly differentiated and are associated with a poor prognosis[4,5,19,33,53]. Two year survival rates have been found to be as low as 27%[22]. In a report by Richards[54] with three ileal carcinomas, survival ranged from 8 to 44 mo.

Michelassi *et al*[55] reported 14 cases of intestinal carcinoma complicating Crohn's disease, 7 occurring in the small intestine and 7 in the large bowel. Two thirds of patients were male. The average age at time of diagnosis of Crohn's disease and carcinoma was 28 and 48 years respectively. In five patients with small bowel carcinoma the diagnosis was made at laparotomy. In the remaining cases only careful histologic examination revealed the carcinoma. Six small bowel carcinomas were located in the ileum. Two small bowel carcinomas were multi-focal and had surrounding mucosal dysplasia. No patient with regional or distal metastases survived five years in comparison with an 83% five year actuarial survival rate in patients with carcinoma confined to the intestinal wall. Mean survival was 6 mo for patients with small bowel carcinoma.

Hawker *et al*[53] reported the clinical and pathological details of three cases diagnosed between 1968-1980 with a review of 58 patients from the literature. Of the 61 cases, 41 carcinomas occurred in the ileum, 18 in the jejunum, 1 in the duodenum and ileum, and 1 in the ileum and colon. Eighteen occurred in bypassed intestinal loops. The prognosis was poor: 44 patients (72%) died with a mean interval of only 7.9 mo from the diagnosis of their malignancy.

Widmar *et al*[23] reported significant differences in the two year survival for node negative versus node positive carcinomas (79.3% *vs* 49%) and for localized versus metastatic disease (92.3% *vs* 33.3%). Overall, 36 mo survival was 69.3% compared to 40% among those without excluded loops. Sixteen patients had long periods of quiescent disease before the diagnosis (7-45 years) and 16 required operation for bowel obstruction that was refractory to medical management.

OUR EXPERIENCE

From 1990 to 2013, 10 patients with underlying Crohn's disease and small bowel adenocarcinoma were treated at our institution. In our series, there were twice as many males as females. The median age of Crohn's diagnosis was 28 years and the median age of small bowel adenocarcinoma diagnosis was 57 years; this interval is consistent with the literature. In none of the 10 patients was the diagnosis known preoperatively. Nine patients presented with a clinical picture of obstruction that did not respond to steroid treatment and required operation. Of the nine, two were found to have metastatic disease secondary to small bowel adenocarcinoma

at the time of operation, while the diagnosis for the remaining seven was made on final pathology examination. The tenth patient in our series had refractory Crohn's disease and was incidentally found to have terminal ileal adenocarcinoma on final pathology.

An equal number of patients had Crohn's disease isolated to their small bowel as concomitant small and large bowel disease. None of our patients had bypassed loops of small bowel. In fact, only three patients had had previous operations for Crohn's disease. All but one of our patients had terminal ileal adenocarcinomas; the exception was one jejunal carcinoma. Moreover, all patients had either stricturing and/or fistulizing Crohn's disease. Four of our 10 patients had been treated with 5-ASA, a reported protective factor. All patients had a history of remote immunomodulator use but none were on maintenance immunomodulators at the time of presentation; if they were receiving medical therapy, it was solely high dose steroids. This is consistent with the conclusions made by Kerber[4] and Frank[5] concerning the development of a small bowel adenocarcinoma after a period of quiescent Crohn's disease. As reported by others, the prognosis for small bowel adenocarcinoma in our series was also quite poor: the carcinoma-related mortality in our series is 70%.

SURVEILLANCE

It has become increasingly recognized that the risk of developing carcinoma of the colon in patients with colonic Crohn's disease is comparable to those with chronic ulcerative colitis. Hence, regular colonoscopic surveillance in search of dysplastic changes is in order. However, no similar surveillance for patients with small bowel Crohn's disease is possible.

Greenstein[24] suggests that surveillance should consist of regular abdominal examinations and that the recurrence of obstructive symptoms as well as the development of new symptoms should not be ignored especially after long quiescent periods.

CEA levels, found to be elevated in up to 38% of patients with active Crohn's disease[56,57], have not been found to be useful in monitoring for small bowel carcinoma[19,58].

LIMITATIONS

Each of the studies included in this descriptive view has its own limitations. A descriptive review such as ours could not possibly be exhaustive if it had strict inclusion/exclusion criteria. Thus we chose to include data and observations from all available studies despite their limitations.

It is difficult to draw conclusions regarding the cumulative incidence of small bowel carcinoma in Crohn's disease from studies with such a low frequency of event as small bowel carcinoma. Compared to current data, incidence values from older studies may actually be overestimated, as 5-ASA formulations (possibly protective against small bowel carcinoma) were released in the late 70's and 80's, late in the observation period of most cohorts[59]. Furthermore, the majority of reports did not have small bowel carcinoma as a primary outcome. Analysis did not routinely address incidence and discussions were sometimes not exclusive to the small bowel (*e.g.*, "intestinal"[60], "upper digestive tract"[61], or discussing risk factors for small bowel and colorectal carcinomas together[62]). Studies rarely controlled for immunosuppressive agents, tobacco or alcohol[63], and those that did examine such exposures did not provide quantitative data[64]. Finally, multiple biases inherent of retrospective and single-centre studies exist in the available literature. For example, a high incidence of small bowel carcinoma in Crohn's disease may reflect a bias in tertiary hospitals[65] or a surveillance bias due to close monitoring of Crohn's disease patients[66], and reported risk factors may be a result of recall bias[67]. These limitations are inherent to the challenging problem of a rare disease that is difficult to diagnose.

CONCLUSION

In this review, we highlighted the available current evidence and the gaps of knowledge, technology, and clinical guidelines required for improving care of Crohn's disease patients at risk of this devastating problem. Although the association of carcinoma in Crohn's disease and the need to screen Crohn's disease of the colon is well established, carcinoma associated with Crohn's disease of the small bowel is difficult to diagnose and indeed is often not identified until operation for what is believed to be an exacerbation or non-response to medical therapy. Sadly, the diagnosis is often made after careful examination of the resection specimen by the pathologist. Over the decades there has been a lack of significant improvement in prognosis. There is a need to elucidate screening modalities to facilitate earlier diagnosis and treatment.

REFERENCES

1 **Ribeiro MB**, Greenstein AJ, Heimann TM, Yamazaki Y, Aufses AH. Adenocarcinoma of the small intestine in Crohn's disease. *Surg Gynecol Obstet* 1991; **173**: 343-349 [PMID: 1948581]

2 **Jess T**, Winther KV, Munkholm P, Langholz E, Binder V. Intestinal and extra-intestinal cancer in Crohn's disease: follow-up of a population-based cohort in Copenhagen County, Denmark. *Aliment Pharmacol Ther* 2004; **19**: 287-293 [PMID: 14984375 DOI: 10.1111/j.1365-2036.2004.01858.x]

3 **Ammann R**, Bivetti J, Kobler E, Peter P. [Gastroenterologic roentgen quiz]. *Leber Magen Darm* 1977; **7**: 91-130 [PMID: 323609]

4 **Kerber GW**, Frank PH. Carcinoma of the small intestine and colon as a complication of Crohn disease: radiologic manifestations. *Radiology* 1984; **150**: 639-645 [PMID: 6695061]

5 **Frank JD**, Shorey BA. Adenocarcinoma of the small bowel as a complication of Crohn's disease. *Gut* 1973; **14**: 120-124 [PMID: 4696534 DOI: 10.1136/gut.14.2.120]

6 **Darke SG**, Parks AG, Grogono JL, Pollock DJ. Adenocarcinoma and Crohn's disease. A report of 2 cases and analysis of the literature. *Br J Surg* 1973; **60**: 169-175 [PMID: 4693566 DOI: 10.1002/bjs.1800600302]

7 **Hoffman JP**, Taft DA, Wheelis RF, Walker JH. Adenocarcinoma in regional enteritis of the small intestine. *Arch*

Surg 1977; **112**: 606-611 [PMID: 856102 DOI: 10.1001/archsurg.1977.01370050066011]
8 **Munkholm P**, Langholz E, Davidsen M, Binder V. Intestinal cancer risk and mortality in patients with Crohn's disease. *Gastroenterology* 1993; **105**: 1716-1723 [PMID: 8253348]
9 **Fielding JF**, Prior P, Waterhouse JA, Cooke WT. Malignancy in Crohn's disease. *Scand J Gastroenterol* 1972; **7**: 3-7 [PMID: 5010506 DOI: 10.3109/00365527209180730]
10 **von Roon AC**, Reese G, Teare J, Constantinides V, Darzi AW, Tekkis PP. The risk of cancer in patients with Crohn's disease. *Dis Colon Rectum* 2007; **50**: 839-855 [PMID: 17308939 DOI: 10.1007/s10350-006-0848-z]
11 **Shaukat A**, Virnig DJ, Howard D, Sitaraman SV, Liff JM, Lederle FA. Crohn's disease and small bowel adenocarcinoma: a population-based case-control study. *Cancer Epidemiol Biomarkers Prev* 2011; **20**: 1120-1123 [PMID: 21467236 DOI: 10.1158/1055-9965.EPI-10-1281]
12 **Menon AM**, Mirza AH, Moolla S, Morton DG. Adenocarcinoma of the small bowel arising from a previous strictureplasty for Crohn's disease: report of a case. *Dis Colon Rectum* 2007; **50**: 257-259 [PMID: 17180254 DOI: 10.1007/s10350-006-0771-3]
13 **Partridge SK**, Hodin RA. Small bowel adenocarcinoma at a strictureplasty site in a patient with Crohn's disease: report of a case. *Dis Colon Rectum* 2004; **47**: 778-781 [PMID: 15037927 DOI: 10.1007/s10350-003-0101-y]
14 **Barwood N**, Platell C. Case report: adenocarcinoma arising in a Crohn's stricture of the jejunum. *J Gastroenterol Hepatol* 1999; **14**: 1132-1134 [PMID: 10574144]
15 **Jaskowiak NT**, Michelassi F. Adenocarcinoma at a strictureplasty site in Crohn's disease: report of a case. *Dis Colon Rectum* 2001; **44**: 284-287 [PMID: 11227948 DOI: 10.1007/BF02234306]
16 **Greenstein AJ**, Janowitz HD. Cancer in Crohn's disease. The danger of a by-passed loop. *Am J Gastroenterol* 1975; **64**: 122-124 [PMID: 1181914]
17 **Senay E**, Sachar DB, Keohane M, Greenstein AJ. Small bowel carcinoma in Crohn's disease. Distinguishing features and risk factors. *Cancer* 1989; **63**: 360-363 [PMID: 2910443]
18 **Schuman BM**. Adenocarcinoma arising in an excluded loop of ileum. *N Engl J Med* 1970; **283**: 136-137 [PMID: 5423151 DOI: 10.1056/NEJM197007162830308]
19 **Collier PE**, Turowski P, Diamond DL. Small intestinal adenocarcinoma complicating regional enteritis. *Cancer* 1985; **55**: 516-521 [PMID: 3965106]
20 **Lashner BA**. Risk factors for small bowel cancer in Crohn's disease. *Dig Dis Sci* 1992; **37**: 1179-1184 [PMID: 1499440 DOI: 10.1007/BF01296557]
21 **Piton G**, Cosnes J, Monnet E, Beaugerie L, Seksik P, Savoye G, Cadiot G, Flourie B, Capelle P, Marteau P, Lemann M, Colombel JF, Khouri E, Bonaz B, Carbonnel F. Risk factors associated with small bowel adenocarcinoma in Crohn's disease: a case-control study. *Am J Gastroenterol* 2008; **103**: 1730-1736 [PMID: 18564124 DOI: 10.1111/j.1572-0241.2008.01847.x]
22 **Dossett LA**, White LM, Welch DC, Herline AJ, Muldoon RL, Schwartz DA, Wise PE. Small bowel adenocarcinoma complicating Crohn's disease: case series and review of the literature. *Am Surg* 2007; **73**: 1181-1187 [PMID: 18092659]
23 **Widmar M**, Greenstein AJ, Sachar DB, Harpaz N, Bauer JJ, Greenstein AJ. Small bowel adenocarcinoma in Crohn's disease. *J Gastrointest Surg* 2011; **15**: 797-802 [PMID: 21336499 DOI: 10.1007/s11605-011-1441-x]
24 **Greenstein AJ**. Cancer in inflammatory bowel disease. *Mt Sinai J Med* 2000; **67**: 227-240 [PMID: 10828908]
25 **Negri E**, Bosetti C, La Vecchia C, Fioretti F, Conti E, Franceschi S. Risk factors for adenocarcinoma of the small intestine. *Int J Cancer* 1999; **82**: 171-174 [PMID: 10389747]
26 **Solem CA**, Harmsen WS, Zinsmeister AR, Loftus EV. Small intestinal adenocarcinoma in Crohn's disease: a case-control study. *Inflamm Bowel Dis* 2004; **10**: 32-35 [PMID: 15058524 DOI: 10.1097/00054725-200401000-00005]
27 **Palascak-Juif V**, Bouvier AM, Cosnes J, Flourié B, Bouché O, Cadiot G, Lémann M, Bonaz B, Denet C, Marteau P, Gambiez L, Beaugerie L, Faivre J, Carbonnel F. Small bowel adenocarcinoma in patients with Crohn's disease compared with small bowel adenocarcinoma de novo. *Inflamm Bowel Dis* 2005; **11**: 828-832 [PMID: 16116317 DOI: 10.1097/01.mib.0000179211.03650.b6]
28 **Howe JR**, Karnell LH, Menck HR, Scott-Conner C. The American College of Surgeons Commission on Cancer and the American Cancer Society. Adenocarcinoma of the small bowel: review of the National Cancer Data Base, 1985-1995. *Cancer* 1999; **86**: 2693-2706 [PMID: 10594865]
29 **Floch HF**, Slattery LR, Hazzi CG. Carcinoma of the small intestine in regional enteritis: presentation of a case and review of the literature. *Am J Gastroenterol* 1978; **70**: 520-527 [PMID: 369360]
30 **Fresko D**, Lazarus SS, Dotan J, Reingold M. Early presentation of carcinoma of the small bowel in Crohn's disease ("Crohn's carcinoma"). Case reports and review of the literature. *Gastroenterology* 1982; **82**: 783-789 [PMID: 7060898]
31 **Lightdale CJ**, Sternberg SS, Posner G, Sherlock P. Carcinoma complicating Crohn's disease. Report of seven cases and review of the literature. *Am J Med* 1975; **59**: 262-268 [PMID: 1155482 DOI: 10.1016/0002-9343(75)90361-7]
32 **Smith TR**, Conradi H, Bernstein R, Greweldinger J. Adenocarcinoma arising in Crohn's disease: report of two cases. *Dis Colon Rectum* 1980; **23**: 498-503 [PMID: 7438952 DOI: 10.1007/BF02987086]
33 **Traube J**, Simpson S, Riddell RH, Levin B, Kirsner JB. Crohn's disease and adenocarcinoma of the bowel. *Dig Dis Sci* 1980; **25**: 939-944 [PMID: 7449590 DOI: 10.1007/BF01308045]
34 **Elsayes KM**, Al-Hawary MM, Jagdish J, Ganesh HS, Platt JF. CT enterography: principles, trends, and interpretation of findings. *Radiographics* 2010; **30**: 1955-1970 [PMID: 21057129 DOI: 10.1148/rg.307105052]
35 **Buckley JA**, Siegelman SS, Jones B, Fishman EK. The accuracy of CT staging of small bowel adenocarcinoma: CT/pathologic correlation. *J Comput Assist Tomogr* 1997; **21**: 986-991 [PMID: 9386295 DOI: 10.1097/00004728-199711000-00025]
36 **Engin G**. Computed tomography enteroclysis in the diagnosis of intestinal diseases. *J Comput Assist Tomogr* 2008; **32**: 9-16 [PMID: 18303282 DOI: 10.1097/rct.0b013e318059bed7]
37 **Ikeuchi H**, Nakano H, Uchino M, Nakamura M, Matsuoka H, Fukuda Y, Matsumoto T, Takesue Y, Tomita N. Intestinal cancer in Crohn's disease. *Hepatogastroenterology* 2008; **55**: 2121-2124 [PMID: 19260489]
38 **Vere CC**, Foarfă C, Streba CT, Cazacu S, Pârvu D, Ciurea T. Videocapsule endoscopy and single balloon enteroscopy: novel diagnostic techniques in small bowel pathology. *Rom J Morphol Embryol* 2009; **50**: 467-474 [PMID: 19690776]
39 **Schulz HJ**, Schmidt H. Intraoperative enteroscopy. *Gastrointest Endosc Clin N Am* 2009; **19**: 371-379 [PMID: 19647646 DOI: 10.1016/j.giec.2009.04.011]
40 **Placé V**, Hristova L, Dray X, Lavergne-Slove A, Boudiaf M, Soyer P. Ileal adenocarcinoma in Crohn's disease: magnetic resonance enterography features. *Clin Imaging* 2012; **36**: 24-28 [PMID: 22226439 DOI: 10.1016/j.clinimag.2011.03.006]
41 **Soyer P**, Hristova L, Boudghène F, Hoeffel C, Dray X, Laurent V, Fishman EK, Boudiaf M. Small bowel adenocarcinoma in Crohn disease: CT-enterography features with pathological correlation. *Abdom Imaging* 2012; **37**: 338-349 [PMID: 21671043 DOI: 10.1007/s00261-011-9772-3]
42 **Kodaira C**, Osawa S, Mochizuki C, Sato Y, Nishino M, Yamada T, Takayanagi Y, Takagaki K, Sugimoto K, Kanaoka S, Furuta T, Ikuma M. A case of small bowel adenocarcinoma in a patient with Crohn's disease detected by PET/CT and double-balloon enteroscopy. *World J Gastroenterol* 2009; **15**: 1774-1778 [PMID: 19360924 DOI: 10.3748/wjg.15.1774]
43 **Van Weyenberg SJ**, Bouman K, Jacobs MA, Halloran BP,

Van der Peet DL, Mulder CJ, Van Kuijk C, Van Waesberghe JH. Comparison of MR enteroclysis with video capsule endoscopy in the investigation of small-intestinal disease. *Abdom Imaging* 2013; **38**: 42-51 [PMID: 22527155 DOI: 10.1007/s00261-012-9892-4]
44 **Miller TL**, Skucas J, Gudex D, Listinsky C. Bowel cancer characteristics in patients with regional enteritis. *Gastrointest Radiol* 1987; **12**: 45-52 [PMID: 3792758 DOI: 10.1007/BF01885102]
45 **Watanabe M**, Nakano H, Takano E, Miyachi I, Ito M, Kawase K. A case of small bowel carcinoma in Crohn's disease. *Gastroenterol Jpn* 1991; **26**: 514-522 [PMID: 1916160]
46 **Petras RE**, Mir-Madjlessi SH, Farmer RG. Crohn's disease and intestinal carcinoma. A report of 11 cases with emphasis on associated epithelial dysplasia. *Gastroenterology* 1987; **93**: 1307-1314 [PMID: 2824276]
47 **Simpson S**, Traube J, Riddell RH. The histologic appearance of dysplasia (precarcinomatous change) in Crohn's disease of the small and large intestine. *Gastroenterology* 1981; **81**: 492-501 [PMID: 7250636]
48 **Sigel JE**, Petras RE, Lashner BA, Fazio VW, Goldblum JR. Intestinal adenocarcinoma in Crohn's disease: a report of 30 cases with a focus on coexisting dysplasia. *Am J Surg Pathol* 1999; **23**: 651-655 [PMID: 10366146 DOI: 10.1097/00000478-199906000-00003]
49 **Feldstein RC**, Sood S, Katz S. Small bowel adenocarcinoma in Crohn's disease. *Inflamm Bowel Dis* 2008; **14**: 1154-1157 [PMID: 18275076 DOI: 10.1002/ibd.20393]
50 **Fishman PN**, Pond GR, Moore MJ, Oza A, Burkes RL, Siu LL, Feld R, Gallinger S, Greig P, Knox JJ. Natural history and chemotherapy effectiveness for advanced adenocarcinoma of the small bowel: a retrospective review of 113 cases. *Am J Clin Oncol* 2006; **29**: 225-231 [PMID: 16755174]
51 **Greenstein A**. Malignancy in Crohn's disease. *Perspect Colon Rectal Surg* 1995; **8**: 137-159
52 **Balaji V**, Thompson MR, Marley NJ, Golding PL. Occult small bowel adenocarcinoma in a Crohn's stricture. *J R Soc Med* 1997; **90**: 45 [PMID: 9059383]
53 **Hawker PC**, Gyde SN, Thompson H, Allan RN. Adenocarcinoma of the small intestine complicating Crohn's disease. *Gut* 1982; **23**: 188-193 [PMID: 7040175 DOI: 10.1136/gut.23.3.188]
54 **Richards ME**, Rickert RR, Nance FC. Crohn's disease-associated carcinoma. A poorly recognized complication of inflammatory bowel disease. *Ann Surg* 1989; **209**: 764-773 [PMID: 2543338 DOI: 10.1097/00000658-198906000-00014]
55 **Michelassi F**, Testa G, Pomidor WJ, Lashner BA, Block GE. Adenocarcinoma complicating Crohn's disease. *Dis Colon Rectum* 1993; **36**: 654-661 [PMID: 8348849 DOI: 10.1007/BF02238592]
56 **Thompson WG**, Gillies RR, Silver HK, Shuster J, Freedman SO, Gold P. Carcinoembryonic antigen and alpha 1-fetoprotein in ulcerative colitis and regional enteritis. *Can Med Assoc J* 1974; **110**: 775-777 [PMID: 4825147]
57 **Rule AH**, Goleski-Reilly C, Sachar DB, Vandevoorde J, Janowitz HD. Circulating carcinoembryonic antigen (CEA): relationship to clinical status of patients with inflammatory bowel disease. *Gut* 1973; **14**: 880-884 [PMID: 4761608 DOI: 10.1136/gut.14.11.880]
58 **Meryn S**, Lochs H. Diagnostic usefulness of plasma carcinoembryonic antigen (CEA) levels in Crohn's disease. *Dig Dis Sci* 1983; **28**: 478-479 [PMID: 6839911 DOI: 10.1007/BF02430539]
59 **Jess T**, Gamborg M, Matzen P, Munkholm P, Sørensen TI. Increased risk of intestinal cancer in Crohn's disease: a meta-analysis of population-based cohort studies. *Am J Gastroenterol* 2005; **100**: 2724-2729 [PMID: 16393226 DOI: 10.1111/j.1572-0241.2005.00287.x]
60 **Freeman HJ**. Tabulation of myeloid, lymphoid and intestinal malignancies in Crohn's disease. *Can J Gastroenterol* 2002; **16**: 779-784 [PMID: 12464971]
61 **Gyde SN**, Prior P, Macartney JC, Thompson H, Waterhouse JA, Allan RN. Malignancy in Crohn's disease. *Gut* 1980; **21**: 1024-1029 [PMID: 7461462 DOI: 10.1136/gut.21.12.1024]
62 **Savoca PE**, Ballantyne GH, Cahow CE. Gastrointestinal malignancies in Crohn's disease. A 20-year experience. *Dis Colon Rectum* 1990; **33**: 7-11 [PMID: 2295280 DOI: 10.1007/BF02053192]
63 **Laukoetter MG**, Mennigen R, Hannig CM, Osada N, Rijcken E, Vowinkel T, Krieglstein CF, Senninger N, Anthoni C, Bruewer M. Intestinal cancer risk in Crohn's disease: a meta-analysis. *J Gastrointest Surg* 2011; **15**: 576-583 [PMID: 21152994 DOI: 10.1007/s11605-010-1402-9]
64 **Chen CC**, Neugut AI, Rotterdam H. Risk factors for adenocarcinomas and malignant carcinoids of the small intestine: preliminary findings. *Cancer Epidemiol Biomarkers Prev* 1994; **3**: 205-207 [PMID: 8019367]
65 **Kersting S**, Bruewer M, Laukoetter MG, Rijcken EM, Mennigen R, Buerger H, Senninger N, Krieglstein CF. Intestinal cancer in patients with Crohn's disease. *Int J Colorectal Dis* 2007; **22**: 411-417 [PMID: 16847674 DOI: 10.1007/s00384-006-0164-z]
66 **Ekbom A**, Helmick C, Zack M, Adami HO. Extracolonic malignancies in inflammatory bowel disease. *Cancer* 1991; **67**: 2015-2019 [PMID: 2004319]
67 **Kaerlev L**, Teglbjaerg PS, Sabroe S, Kolstad HA, Ahrens W, Eriksson M, Guénel P, Hardell L, Launoy G, Merler E, Merletti F, Stang A. Medical risk factors for small-bowel adenocarcinoma with focus on Crohn disease: a European population-based case-control study. *Scand J Gastroenterol* 2001; **36**: 641-646 [PMID: 11424324 DOI: 10.1080/003655201750163150]
68 **Greenstein AJ**, Sachar D, Pucillo A, Kreel I, Geller S, Janowitz HD, Aufses A. Cancer in Crohn's disease after diversionary surgery. A report of seven carcinomas occurring in excluded bowel. *Am J Surg* 1978; **135**: 86-90 [PMID: 623378 DOI: 10.1016/0002-9610(78)90015-6]
69 **Kamiya T**, Ando T, Ishiguro K, Maeda O, Watanabe O, Hibi S, Mimura S, Ujihara M, Hirayama Y, Nakamura M, Miyahara R, Ohmiya N, Goto H. Intestinal cancers occurring in patients with Crohn's disease. *J Gastroenterol Hepatol* 2012; **27** Suppl 3: 103-107 [PMID: 22486881 DOI: 10.1111/j.1440-1746.2012.07082.x]
70 **Kvist N**, Jacobsen O, Nørgaard P, Ockelmann HH, Kvist HK, Schou G, Jarnum S. Malignancy in Crohn's disease. *Scand J Gastroenterol* 1986; **21**: 82-86 [PMID: 3952455 DOI: 10.3109/00365528609034627]
71 **Mellemkjaer L**, Johansen C, Gridley G, Linet MS, Kjaer SK, Olsen JH. Crohn's disease and cancer risk (Denmark). *Cancer Causes Control* 2000; **11**: 145-150 [PMID: 10710198 DOI: 10.1023/A:1008988215904]
72 **Mizushima T**, Ohno Y, Nakajima K, Kai Y, Iijima H, Sekimoto M, Nishida T, Nezu R, Ito T, Doki Y, Mori M. Malignancy in Crohn's disease: incidence and clinical characteristics in Japan. *Digestion* 2010; **81**: 265-270 [PMID: 20134166 DOI: 10.1159/000273784]
73 **Jess T**, Loftus EV, Velayos FS, Harmsen WS, Zinsmeister AR, Smyrk TC, Schleck CD, Tremaine WJ, Melton LJ, Munkholm P, Sandborn WJ. Risk of intestinal cancer in inflammatory bowel disease: a population-based study from Olmsted county, Minnesota. *Gastroenterology* 2006; **130**: 1039-1046 [PMID: 16618397 DOI: 10.1053/j.gastro.2005.12.037]
74 **Lakatos PL**, David G, Pandur T, Erdelyi Z, Mester G, Balogh M, Szipocs I, Molnar C, Komaromi E, Kiss LS, Lakatos L. Risk of colorectal cancer and small bowel adenocarcinoma in Crohn's disease: a population-based study from western Hungary 1977-2008. *J Crohns Colitis* 2011; **5**: 122-128 [PMID: 21453881 DOI: 10.1016/j.crohns.2010.11.005]
75 **Greenstein AJ**, Sachar DB, Smith H, Janowitz HD, Aufses AH. Patterns of neoplasia in Crohn's disease and ulcerative colitis. *Cancer* 1980; **46**: 403-407 [PMID: 7388778]

76 **Canavan C**, Abrams KR, Mayberry J. Meta-analysis: colorectal and small bowel cancer risk in patients with Crohn's disease. *Aliment Pharmacol Ther* 2006; **23**: 1097-1104 [PMID: 16611269 DOI: 10.1111/j.1365-2036.2006.02854.x]

77 **Chow WH**, Linet MS, McLaughlin JK, Hsing AW, Chien HT, Blot WJ. Risk factors for small intestine cancer. *Cancer Causes Control* 1993; **4**: 163-169 [PMID: 8481495 DOI: 10.1007/BF00053158]

78 **Chan RC**, Katelaris PH, Stewart P, Lin BP. Small bowel adenocarcinoma with high levels of microsatellite instability in Crohn's disease. *Hum Pathol* 2006; **37**: 631-634 [PMID: 16647963 DOI: 10.1016/j.humpath.2005.12.013]

79 **Christodoulou D**, Skopelitou AS, Katsanos KH, Katsios C, Agnantis N, Price A, Kappas A, Tsianos EV. Small bowel adenocarcinoma presenting as a first manifestation of Crohn's disease: report of a case, and a literature review. *Eur J Gastroenterol Hepatol* 2002; **14**: 805-810 [PMID: 12169995 DOI: 10.1097/00042737-200207000-00018]

80 **Fell J**, Snooks S. Small bowel adenocarcinoma complicating Crohn's disease. *J R Soc Med* 1987; **80**: 51-52 [PMID: 3560126]

81 **Gillen CD**, Wilson CA, Walmsley RS, Sanders DS, O'Dwyer ST, Allan RN. Occult small bowel adenocarcinoma complicating Crohn's disease: a report of three cases. *Postgrad Med J* 1995; **71**: 172-174 [PMID: 7746780 DOI: 10.1136/pgmj.71.833.172]

82 **Gusakova I**, Mermershtain W, Cohen Y, Ariad S. Small bowel adenocarcinoma in crohn disease patient complicated by microangiopathic hemolytic anemia. *Am J Clin Oncol* 2003; **26**: 483-485 [PMID: 14528075 DOI: 10.1097/01.coc.0000037111.19239.FE]

83 **Katsanos KH**, Christodoulou DK, Michael M, Ioachim E, Tsianos GV, Agnantis N, Tsianos EV. Inflammatory bowel disease-related dysplasia and cancer: A referral center study in northwestern Greece. *Eur J Intern Med* 2005; **16**: 170-175 [PMID: 15967331 DOI: 10.1016/j.ejim.2004.09.016]

84 **Koga H**, Aoyagi K, Hizawa K, Iida M, Jo Y, Yao T, Oohata Y, Mibu R, Fujishima M. Rapidly and infiltratively growing Crohn's carcinoma of the small bowel: serial radiologic findings and a review of the literature. *Clin Imaging* 1999; **23**: 298-301 [PMID: 10665347 DOI: 10.1016/S0899-7071(99)00149-7]

85 **Kronberger IE**, Graziadei IW, Vogel W. Small bowel adenocarcinoma in Crohn's disease: a case report and review of literature. *World J Gastroenterol* 2006; **12**: 1317-1320 [PMID: 16534894]

86 **Lindgren A**, Wallerstedt S, Olsson R. Prevalence of Crohn's disease and simultaneous occurrence of extraintestinal complications and cancer. An epidemiologic study in adults. *Scand J Gastroenterol* 1996; **31**: 74-78 [PMID: 8927944 DOI: 10.3109/00365529609031630]

87 **Rubio CA**, Befritz R, Poppen B, Svenberg T, Slezak P. Crohn's disease and adenocarcinoma of the intestinal tract. Report of four cases. *Dis Colon Rectum* 1991; **34**: 174-180 [PMID: 1993415 DOI: 10.1007/BF02049994]

88 **Sammartino P**, Sibio S, Di Giorgio A, Caronna R, Viscido A, Zippi M, Biacchi D, Accarpio F, Mingazzini P, Caprilli R. Two synchronous adenocarcinomas of the small bowel in a patient with undiagnosed Crohn's disease of the terminal ileum. *Int J Colorectal Dis* 2006; **21**: 388-391 [PMID: 16059693 DOI: 10.1007/s00384-005-0005-5]

89 **Gollop JH**, Phillips SF, Melton LJ, Zinsmeister AR. Epidemiologic aspects of Crohn's disease: a population based study in Olmsted County, Minnesota, 1943-1982. *Gut* 1988; **29**: 49-56 [PMID: 3343012 DOI: 10.1136/gut.29.1.49]

P- Reviewer: Maharshak N **S- Editor**: Ding Y **L- Editor**: A
E- Editor: Wang CH

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327