Colorectal Cancer in Inflammatory Bowel Disease: Epidemiology, Pathogenesis and Surveillance

Zhen-Hua Wang    Jing-Yuan Fang

Division of Gastroenterology and Hepatology, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai Institute of Digestive Disease; Key Laboratory of Gastroenterology & Hepatology, Ministry of Health; State Key Laboratory of Oncogene and Related Genes, Shanghai, China

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Abstract
Background: Inflammatory bowel disease (IBD; including ulcerative colitis and Crohn’s disease) is associated with an increased risk for colorectal cancer (CRC). Chronic mucosal inflammation is a key factor in the onset of carcinogenesis in IBD patients. Although most gene alterations that cause sporadic CRCs also occur in patients with IBD-associated CRC, some gene sequences and mutation frequencies differ between sporadic CRCs and IBD-associated CRCs.

Summary: This review explores the incidence of CRC in IBD patients, with the goal of identifying the risk and protective factors for CRC in order to facilitate dysplasia management via individualized surveillance strategies. Key Message: The incidence of CRC is higher among IBD patients. Identifying the risk and protective factors for CRC will facilitate dysplasia management via individualized surveillance strategies. Practical Implications: Several risk factors, including active inflammation, the coexistence of primary sclerosing cholangitis, a family history of sporadic CRC and the extent and duration of colonic disease, can lead to the development of CRC in patients with IBD. These risk factors should be utilized in individualized surveillance strategies to lower CRC incidence among IBD patients. Use of 5-aminosalicylic acid may play an important role in CRC prevention. Until newer, more reliable markers of IBD-associated CRC risk are found, dysplasia will continue to be the best marker of CRC risk in IBD. Dysplasia management continues to play a key role in preventing the progression of carcinogenesis.
Introduction

Patients with inflammatory bowel disease (IBD), i.e. ulcerative colitis (UC) or Crohn's disease (CD), have an increased risk of developing colorectal cancer (CRC). Although most gene alterations that cause sporadic CRCs also occur in patients with IBD-associated CRC, the involved gene sequences and mutation frequencies differ between sporadic CRCs and IBD-associated CRCs. Chronic mucosal inflammation is a key factor in the CRC carcinogenesis in IBD patients, and hence 5-aminosalicylic acid (5-ASA), which is anti-inflammatory, acts as a chemopreventive agent for CRC in patients with IBD. Colonoscopy surveillance to detect dysplasia has been shown to decrease the incidence of CRC. This paper aims to explore the risk and protective factors for CRC development in IBD patients in order to facilitate the formulation of individualized CRC surveillance strategies and the proper management of dysplasia in this patient population.

Epidemiology of IBD-Associated CRC

CRC Risk in UC

The most recent meta-analysis of CRC, which was published in 2014, found that the overall risk of CRC in 181,923 UC patients was 1.69/1,000/year; this risk was 0.91/1,000/year in the first decade after the diagnosis of UC, 4.07/1,000/year in the second decade and 4.55/1,000/year in the third decade [1]. These rates are lower than those reported by a meta-analysis published in 2001 [2]: 3/1,000/year overall and 2, 8 and 18% in the first, second and third decades after diagnosis, respectively. This decrease in risk may be attributable to the widespread use of aminosalicylates, which are believed to have a chemoprotective effect in IBD, to the more liberal and early use of colectomy for medically refractory UC and, possibly, to surveillance colonoscopy. However, the current CRC incidence rates among IBD patients remain considerably higher than those in the general population. The CRC incidence among the general population has been reported to range from 0.4/1,000/year in Australia, New Zealand, the USA and Western Europe to 0.1/1,000/year in Africa [3].

CRC Risk in CD

The global incidence rate of CRC among patients with CD is 2.5%, which increases to 5.6% among patients with CD of the colon; the relative risk for CRC is 3.2 among patients with ileocolitis, and there is no increase in CRC risk (relative risk = 1) in CD patients with small bowel involvement only [4]. This increased risk of CRC among CD patients has been confirmed by a meta-analysis of 12 hospital- and population-based studies [5]. This meta-analysis found a relative risk of 4.5 (1.3–14.9) among CD patients with colonic disease, whereas the risk in CD patients with ileal disease only did not differ from the risk in the general population, with a relative risk of 1.1 (0.8–1.5) [5]. Regardless of CD distribution, the cumulative risk of CRC among CD patients was 2.9% 10 years after the diagnosis of CD, 5.6% after 20 years and 8.3% after 30 years [5].

Risk Factors for IBD-Associated CRC

The factors that have been found to increase the risk of CRC incidence among IBD patients are listed in table 1.
Active Inflammation

Active inflammation was recently confirmed in clinical studies to play a key role in CRC carcinogenesis among IBD patients. A history of severe inflammatory conditions, such as pseudopolyps, a shortened or tubular colon and stricture formation, significantly increase the risk of CRC among IBD patients [6].

Primary Sclerosing Cholangitis

Many clinical studies have demonstrated that primary sclerosing cholangitis (PSC) is associated with an increased risk of CRC in IBD [7]. For example, a case-control study performed by Broomé et al. [8] found a cumulative CRC risk of 9% after 10 years of disease progression, 21% after 20 years and 50% after 25 years among patients presenting with IBD complicated by PSC. The corresponding CRC risk among patients with UC only was 2, 5 and 10%, respectively [8]. Moreover, this increased risk persisted even after liver transplantation [9].

Family History of CRC

A family history of sporadic CRC is also a risk factor for cancer. IBD patients with a first-degree relative with CRC have twice the risk of developing CRC than IBD patients without a family history of CRC [10, 11]. Moreover, among IBD patients who have a first-degree relative in whom CRC was diagnosed before the age of 50 years, the risk of IBD progression to CRC increases ninefold [11]. However, the presence of a first-degree relative with IBD does not increase the risk of CRC among healthy family members [11].

Extent and Duration of IBD

The extent of colonic inflammation is a risk factor for CRC. UC patients with extensive disease (pancolitis and left-sided colitis) have a greater risk of developing CRC than do UC patients with only proctitis or proctosigmoiditis [12]. IBD duration is one of the most important risk factors for CRC among IBD patients. CRC risk is significantly increased after 8 years of IBD and continues to increase in subsequent years [13].

Factors Protecting against IBD-Associated CRC

5-ASA

5-ASA is the most commonly used drug for CRC prophylaxis among IBD patients. In 2005, Velayos et al. [14] performed a meta-analysis involving a total of 1,932 subjects, including 334 patients with CRC and 140 patients with dysplasia. Their study confirmed that the use of 5-ASA showed a protective association with CRC (odds ratio: 0.51; 95% confidence interval: 0.37–0.69) or a combined endpoint of CRC/dysplasia (odds ratio: 0.51; 95% confidence
interval: 0.38–0.69). Recently, two large population-based studies [15, 16] showed the following: (i) regular 5-ASA users had a lower risk for CRC than non-regular users, (ii) no significant prophylactic effect was found among sulfasalazine users, and (iii) among 5-ASA users, the protective effect was only significant among subjects who had been taking 5-ASA for more than 13 years.

**Folic Acid**

Although epidemiologic studies have demonstrated that folate deficiency may be a risk factor for CRC [17], the protective effect of folate supplementation against CRC among IBD patients remains controversial. Thus far, only one small-scale case-control study has found a significant protective effect of folate supplementation [18]. No statistically significant effect of folate supplementation was observed in other case-control studies [19–21]. Therefore, folate supplementation, though essential to correct folate deficiency, cannot be considered to be an effective prophylactic therapy for decreasing CRC risk among IBD patients.

**Ursodeoxycholic Acid**

Ursodeoxycholic acid (UDCA) has been suggested to play a protective role in UC complicated by PSC. Among PSC patients, those taking high doses of UDCA (13–15 mg/kg/day) had a more than 4-year increase in survival [22]. Despite the significant decrease in mortality among UDCA-treated PSC patients, UDCA did not decrease the risk of CRC or dysplasia in these patients [23]. Therefore, whether UDCA protects IBD patients with or without concomitant PSC from progression to CRC remains unknown.

**Total Colectomy**

As mentioned above, two meta-analyses [1, 2] from different time periods suggest that the incidence of IBD-associated CRC is in decline. A cohort study conducted in Denmark between 1962 and 1987 reported only 13 cases of CRC among 1,160 UC patients [24]. The annual risk was 0.06%. The 30-year cumulative CRC risk was 2.1%. The rate of surgery for UC in Denmark is among the highest reported worldwide, and this is a plausible explanation for the very low risk of CRC in this population.

**Pathophysiology**

Sporadic CRC and IBD-associated CRC develop through different molecular carcinogenesis pathways. Sporadic CRC is the result of two important types of genomic instability: chromosomal instability (85%) and microsatellite instability (15%) [25]. Both these mechanisms operate in IBD-associated CRC, but at different times and with different frequencies [25]. APC gene function loss is typically an early event in sporadic CRCs; however, in IBD-associated CRCs, APC dysfunction is seldom seen, and if present, usually occurs very late [26–28]. In contrast, the loss or mutation of p53 chromosomes often occurs in the early stages of IBD-associated CRC, but is believed to be a late event in the carcinogenesis of sporadic CRC. In IBD-associated CRCs, microsatellite instability affects carcinogenesis. In contrast, in sporadic CRCs, methylation of the hMLH1 promoter leading to transcriptional silencing of hMLH1 is the most frequent event; hMLH1 promoter methylation is unusual in IBD-associated CRCs [29].

Recently, an increasing body of evidence has shown that chronic inflammation plays an important role in CRC carcinogenesis by producing a suitable microenvironment for CRC formation and progression. Proinflammatory cytokines secreted by infiltrating inflammatory and immune cells, prostaglandins induced by cyclooxygenase in epithelial cells and enhanced
reactive oxygen and nitrogen species alter many molecules, including DNA, RNA, proteins and lipids. Moreover, the formation of DNA adducts is induced, which causes point mutations in genes and in CpG islands involved in DNA methylation. Finally, local cytokines and prosta-
glandins inhibit apoptosis and promote cell proliferation [30].

**Surveillance Colonoscopy**

To determine whether surveillance colonoscopy is effective in IBD patients, we must verify whether this strategy reduces CRC-related mortality. As yet, no randomized controlled trial has investigated the effectiveness of surveillance colonoscopy. Numerous case series [31–35] and three case-control studies [36–38] have demonstrated a benefit of surveillance colonoscopy in IBD patients. However, the Cochrane Group conducted a pooled analysis of the published studies on UC patients and concluded that there was no clear evidence that surveillance colonoscopy decreases mortality in patients with extensive UC [39]. They did find, however, that CRC tended to be detected at an earlier stage and had a better prognosis in patients who underwent surveillance than in those who did not [39]. Thus, there is indirect evidence that colonoscopy surveillance is effective at reducing the mortality of IBD-associated CRC. Therefore, patients should be advised to undergo surveillance colonoscopy, which enables the detection of dysplasia or early-stage CRC.

Our current knowledge of the efficacy of colonoscopy surveillance is based on random biopsies of colorectal mucosa. Careful inspection of the mucosa along with a sufficient number of biopsy specimens from all anatomic segments of the colon is required. To detect dysplasia and/or cancer, rigorous colonoscopy surveillance, including the acquisition of at least 33 random biopsy specimens from all portions of the colon in patients with pancolitis, must be performed [40]. Since dysplasia and cancer are more common in the left colon, it is recommended that more extensive sampling be performed in the left colon, particularly in the rectum. Biopsy specimens should be obtained separately from areas of flat mucosa surrounding the bases of adenoma-like and non-adenoma-like dysplasia-associated lesions or masses (DALMs). Chromoendoscopy or other image-enhancing techniques are recommended for physicians with experience with these techniques. With the use of enhanced endoscopic techniques, targeted biopsies may be performed as an alternative to obtaining random biopsy specimens. Poor patient compliance with surveillance programs reduces the effectiveness of surveillance.

The 2004 American College of Gastroenterology guidelines [41] recommend that after 8–10 years of colitis, surveillance colonoscopy should be performed once every year or every 2 years with multiple biopsies taken at regular intervals in patients with left-sided colitis or pancolitis. Patients with proctitis and proctosigmoiditis are not considered to be at an increased risk for cancer, and thus are recommended to undergo average-risk surveillance [41].

**Dysplasia Management**

Despite having some limitations as a prognostic marker, dysplasia is still considered the best marker of CRC risk in IBD. CRC carcinogenesis in IBD follows a sequential progression from inflammation to low-grade dysplasia (LGD) and then high-grade dysplasia (HGD). Although this model is conceptually useful and serves as a reasonable paradigm, it is by no means absolute. CRC can occur in patients without a history of dysplasia [42]. In addition, not all patients with LGD will progress to CRC by way of HGD [43]. Nevertheless, until newer,
more reliable markers of IBD-associated CRC risk are confirmed, clinical practice relies mainly on the endoscopic and pathologic identification of dysplasia.

**Raised Dysplastic Lesions**

Raised, endoscopically visible, dysplastic lesions in IBD have been referred to by the acronym 'DALM'. Recent studies suggest that IBD-related DALMs may be broadly separated into those that appear similar to sporadic adenomas in non-IBD patients, referred to as adenoma-like DALMs, and those that do not resemble adenoma-like DALMs, referred to as non-adenoma-like DALMs [44–46].

Adenoma-like DALMs are well-circumscribed, smooth, papillary, non-necrotic, sessile or pedunculated polyps that are similar to sporadic adenomas; they are usually readily accessible and can be removed via routine endoscopic methods [44]. Other synonyms used to describe these lesions include adenoma-like polyps, adenoma-like dysplastic polyps, polypoid dysplasia and adenoma-like masses. Non-adenoma-like DALMs contain velvety patches, plaques, irregular bumps and nodules, wart-like thickenings, stricturing lesions and broad-based masses [47, 48]. Non-adenoma-like DALMs represent a heterogeneous group of dysplastic lesions that have a strong positive association with CRC. There is a high possibility of CRC in patients with endoscopically unresectable non-adenoma-like DALMs, ranging from 38 to 83% [33, 49, 50]. Therefore, it is recommended that IBD patients with an endoscopically unresectable, non-adenoma-like DALM, regardless of the dysplasia grade, undergo colectomy [51]. In contrast, adenoma-like DALMs located outside or proximal to areas of known colitis may be considered to be sporadic in origin and thus treated conservatively with polypectomy and continued active surveillance [52]. Similarly, adenoma-like DALMs located within areas of known colitis may also be treated conservatively with polypectomy and continued surveil-
lance if the lesion has been excised completely, there is no dysplasia at the margins of the specimen and there is no evidence of flat dysplasia elsewhere in the colon, either adjacent to or distant from the polypoid lesion [45, 51]. These recommendations apply to patients with UC, regardless of age and duration/extent of colitis [45, 51, 52]. A treatment algorithm for UC patients with adenoma-like or a non-adenoma-like DALMs is proposed in figure 1 [52].

Flat Dysplasia

Flat dysplasia refers to lesions that are not raised, minimally raised or occasionally invisible. Concomitant CRC may be present in 42–67% of patients with flat HGD. If immediate colectomy is not conducted when HGD is first detected, CRC will develop in 25–32% of patients on long-term follow-up [53]. Therefore, although the evidence is considered to be of fair quality due to its retrospective character, colectomy is recommended for all patients with flat HGD. The management of patients with LGD is more controversial. Like patients with flat HGD, patients with flat LGD may have concomitant CRC; however, the rate is lower, though in general still considerable. The prevalence rate of concomitant CRC is 19–27% among patients who have undergone colectomy within a few months of a colonoscopy that showed LGD as the most advanced histologic abnormality [53]. One recent meta-analysis revealed that the positive predictive value of LGD for progression to HGD and/or CRC is approximately 18% [54]. Thus, the decision to undergo colectomy versus continued surveillance in the setting of flat LGD should be individualized and discussed at length among the patient, gastroenterologist and colorectal surgeon.

Conclusions

UC and CD are associated with an increased risk of CRC. The risk factors for CRC among IBD patients include severe inflammation, coexisting PSC, family history of sporadic CRC, large extent of colonic involvement and long duration of disease. Tumorigenesis within the colon depends on unique environmental, genetic and immunologic factors in IBD patients. The chemoprevention of CRC remains an important goal, and retrospective data suggest that 5-ASA plays an important role in this context. Colonoscopy surveillance programs, with multiple biopsies performed every 1–2 years, are key components in the early detection of CRC in IBD patients. Newer methods such as chromoendoscopy are currently being investigated as complementary techniques to enhance the early detection of dysplasia and cancer in this high-risk population.

References


43 Ullman T: Hold the bone: good news for young women with IBD. Inflamm Bowel Dis 2003;9:396–397.


