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Contents

Monthly Volume 15 Number 8 August 15, 2023

REVIEW

- 1317 Update and latest advances in mechanisms and management of colitis-associated colorectal cancer
Dan WY, Zhou GZ, Peng LH, Pan F

MINIREVIEWS

- 1332 Breast cancer metastasizing to the upper gastrointestinal tract (the esophagus and the stomach): A comprehensive review of the literature
Da Cunha T, Restrepo D, Abi-Saleh S, Dharan M
- 1342 Research progress on drug delivery systems for curcumin in the treatment of gastrointestinal tumors
Wu X, Yang Y

ORIGINAL ARTICLE

Basic Study

- 1349 Potential of damage associated molecular patterns in synergising radiation and the immune response in oesophageal cancer
Donlon NE, Davern M, Sheppard A, O'Connell F, Moran B, Nugent TS, Heeran A, Phelan JJ, Bhardwaj A, Butler C, Ravi N, Donohoe CL, Lynam-Lennon N, Maher S, Reynolds JV, Lysaght J
- 1366 LINC01268 promotes epithelial-mesenchymal transition, invasion and metastasis of gastric cancer *via* the PI3K/Akt signaling pathway and targeting MARCKS
Tang LH, Ye PC, Yao L, Luo YJ, Tan W, Xiang WP, Liu ZL, Tan L, Xiao JW
- 1384 Antitumor activity of miR-188-3p in gastric cancer is achieved by targeting CBL expression and inactivating the AKT/mTOR signaling
Lin JJ, Luo BH, Su T, Yang Q, Zhang QF, Dai WY, Liu Y, Xiang L
- 1400 Physcion increases the sensitivity of hepatocellular carcinoma to sorafenib through miRNA-370/PIM1 axis-regulated glycolysis
Pan XP, Jiya BR, Wang F, Lan Z

Clinical and Translational Research

- 1412 Expression patterns of cluster of differentiation 147 impact the prognosis of hepatocellular carcinoma
Xu YJ, He HJ, Wu P, Li WB

Case Control Study

- 1424 Fecal microbial biomarkers combined with multi-target stool DNA test improve diagnostic accuracy for colorectal cancer
Fan JQ, Zhao WF, Lu QW, Zha FR, Lv LB, Ye GL, Gao HL

Retrospective Cohort Study

- 1436** Comparison of clinicopathological characteristics and survival outcomes between gallbladder mucinous adenocarcinoma and gallbladder adenocarcinoma: A propensity score-matched study

Yang WW, Fang YT, Niu YR, Sun YK

- 1451** Incidence and prevalence of gastric neuroendocrine tumors in patients with chronic atrophic autoimmune gastritis

Massironi S, Gallo C, Elvevi A, Stegagnini M, Coltro LA, Invernizzi P

Retrospective Study

- 1461** Epidemiologic characteristics and risk factors associated with overall survival for patients with mucinous colorectal cancer: A population-based study

Jiang J, Tang XW, Huang S, Hu N, Chen Y, Luo B, Ren WS, Peng Y, Yang WX, Lü MH

- 1475** Carcinoembryonic antigen, carbohydrate antigen 199 and carbohydrate antigen 724 in gastric cancer and their relationship with clinical prognosis

Wang R, Zuo CL, Zhang R, Zhu LM

Observational Study

- 1486** Development and application of hepatocellular carcinoma risk prediction model based on clinical characteristics and liver related indexes

Liu ZJ, Xu Y, Wang WX, Guo B, Zhang GY, Luo GC, Wang Q

CASE REPORT

- 1497** Gastric neuroendocrine tumors in a BRCA2 germline mutation carrier: A case report

Zhang HF, Zheng Y, Wen X, Zhao J, Li J

Contents

World Journal of Gastrointestinal Oncology
Monthly Volume 15 Number 8 August 15, 2023

ABOUT COVER

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Update and latest advances in mechanisms and management of colitis-associated colorectal cancer

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Abstract

Colitis-associated colorectal cancer (CAC) is defined as a specific cluster of colorectal cancers that develop as a result of prolonged colitis in patients with inflammatory bowel disease (IBD). Patients with IBD, including ulcerative colitis and Crohn's disease, are known to have an increased risk of developing CAC. Although the incidence of CAC has significantly decreased over the past few decades, individuals with CAC have increased mortality compared to individuals with sporadic colorectal cancer, and the incidence of CAC increases with duration. Chronic inflammation is generally recognized as a major contributor to the pathogenesis of CAC. CAC has been shown to progress from colitis to dysplasia and finally to carcinoma. Accumulating evidence suggests that multiple immune-mediated pathways, DNA damage pathways, and pathogens are involved in the pathogenesis of CAC. Over the past decade, there has been an increasing effort to develop clinical approaches that could help improve outcomes for CAC patients. Colonoscopic surveillance plays an important role in reducing the risk of advanced and interval cancers. It is generally recommended that CAC patients undergo endoscopic removal or colectomy. This review summarizes the current understanding of CAC, particularly its epidemiology, mechanisms, and management. It focuses on the mechanisms that contribute to the development of CAC, covering advances in genomics, immunology, and the microbiome; presents evidence for management strategies, including endoscopy and colectomy; and discusses new strategies to interfere with the process and development of CAC. These scientific findings will pave the way for the management of CAC in the near future.

Key Words: Colitis-associated colorectal cancer; Inflammatory bowel disease; Colonoscopic surveillance; Epidemiology; Mechanisms; Management

Core Tip: Colitis-associated colorectal cancer (CAC) is defined as a specific cluster of colorectal cancers that develop as a result of prolonged colitis in patients with inflammatory bowel disease (IBD). Patients with IBD are known to have an increased risk of developing CAC. Accumulating evidence suggests that multiple immune-mediated pathways, DNA damage pathways, and pathogens are involved in the pathogenesis of CAC. This review summarizes the current understanding of CAC, particularly its epidemiology, mechanisms, and management. These scientific findings will pave the way for the management of CAC in the near future.

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INTRODUCTION

Colitis-associated colorectal cancer (CAC) is defined as a specific type of colorectal cancer (CRC) that develops in patients with inflammatory bowel disease (IBD) as a result of prolonged colitis, especially in ulcerative colitis (UC). The unadjusted overall incidence of CAC was 95/100000 person-years (py), which is twice the overall risk compared to the general population[1]. Patients with IBD have an increased risk of both CAC diagnosis and CAC death compared with the general population[2] but a significantly worse overall survival than those with non-IBD[3]. Although the incidence and mortality of CAC have been in decline over the past few decades, they remain elevated, and every 3041 UC patients correspond to one additional CRC death[2].

The mechanisms underpinning CAC pathogenesis remain elusive, but accumulated evidence suggests that genetics and epigenetics, immunity and inflammation, and microbiota are all involved in CAC pathogenesis. Given this evidence, new strategies are being applied to the treatment of CAC. Therefore, we provide a comprehensive and critical review of recent advances in CAC, focusing on its epidemiology, pathogenesis, and management, including surveillance, surgery, chemoprevention, and new strategies for CAC treatment.

EPIDEMIOLOGY AND RISK FACTORS

It is widely recognized that long-standing colitis increases the risk of CAC, but estimates of the risk vary widely in the available studies. An approximately 2-fold increase in the risk of developing CAC[1,4-7] and a 1.7-fold increase in the risk of death have been reported[8]. Based on a population-based cohort study, there is 1 additional CRC diagnosis per 1058 UC patients and 1 additional CRC death per 3041 UC patients per 5 years[2]. The prevalence of CAC fluctuates with multiple factors, such as time, region, disease classification, extent, and duration. A previous meta-analysis reported that the prevalence of UC-associated CRC was 3.7%[9], while recent meta-analyses indicated a lower prevalence of UC-associated CRC in Asia at 0.85%[10], which could be explained by optimized surveillance and better chemoprevention.

Disease classification, extent, and duration

The cumulative incidence of CAC varies across studies. A large Swedish population-based cohort study reported an overall cumulative incidence of CAC of 1.0%, 1.5%, and 2.7% after 10, 20, and 30 years of disease, respectively[1]. The cumulative risk of UC-associated CRC appeared to be higher in Asia and was reported to be 0.02%, 4.81%, and 13.91% in Asian patients[10] as well as 1.15%, 3.56%, and 14.36% in Chinese[11] patients at 10, 20, and 30 years of disease diagnosis. In addition, a meta-analysis of population-based cohort studies reported the cumulative risks of CAC as 1% after 10 years, 2% after 20 years, and 5% after over 20 years of disease duration[6].

In addition to disease duration, disease classification and extent are also considered to be important parameters influencing an individual's risk of CAC. Compared with the general population, patients with UC and CD are associated with 1.47- to 2.70-fold and 1.51- to 2.10-fold increased risks of CRC, respectively[1,4-7]. Compared to those with proctitis UC, patients with extensive UC and left-sided UC are at higher risk of CRC[12]. Specially, certain populations with autoimmune diseases are known to have a higher risk of developing anal cancer than average, such as UC patients with an incidence rate of 276167 py and CD patients with an incidence rate of 614830 py[13].

Temporal and regional trends

It is noteworthy that the incidence of UC-associated CRC has steadily declined over the last six decades. The cumulative incidence declined from 33.1 per 1000 patients in studies published in the 1950s to 9.1 per 1000 patients in studies published in the last decade, while the incidence rates declined from 4.29 per 1000 py to 1.21 per 1000 py, respectively[14]. The prognosis for CAC has dramatically improved. Compared to the general population, cancer risk in IBD patients

decreased from a 5-fold increase in the 1960s to a 2-fold increase in the 2000–2004 follow-up period[1].

The worldwide cancer incidence rates of UC-associated CRC show considerable geographical variation. The overall incidence rate varies from 5/1000 person-years duration (pyd) in the USA, 4/1000 pyd in the UK, and 2/1000 pyd in Scandinavia[9]. Geography also plays an underlying role in CAC prognosis. The time of malignant transformation started after 10–20 years of CAC duration in Asian patients, whereas it significantly increased to more than 30 years in North American patients[12].

Risk factors

Recent data have shown an association between family history and CAC. Patients with a family history of CRC in a first-degree relative have an almost 8-fold increase in the risk of CAC, while those without a family history have a 4-fold increase in risk[15]. Additional risk factors include hyperlipidemia, obesity, and alcohol consumption for early-onset colorectal cancer[16].

Wijnands *et al*[17] summarized the data that describe the prognostic factors for advanced colorectal neoplasia in IBD, identifying risk factors (including extensive disease, low-grade dysplasia, colonic strictures, post-inflammatory polyps, primary sclerosing cholangitis, and family history of CRC) and protective factors (including colonoscopic surveillance, 5-aminosalicylic acid, thiopurines, and smoking).

PATHOGENESIS OF CAC

The main classical pathways recognized for CRC carcinogenesis are the adenoma-carcinoma sequence, the serrated pathway, and the inflammatory pathway. The “adenoma-carcinoma sequence” hypothesis suggests that the accumulation of genetic and epigenetic abnormalities drives the transformation of normal cells into adenomas that progress to CRC, explaining the pathogenesis of most CRCs. However, as a specific subtype of CRC, CAC, which develops progressively in patients with IBD, has a unique pathogenesis. Here, the pathogenesis and recent advances underlying CAC are reviewed by three mechanisms: Genetics and epigenetics, immunity and inflammation, and microbiota, illustrated in [Figure 1](#).

Genetics and epigenetics

DNA is the basis of genetic information, and maintaining its integrity is essential for life and health. In the early 1900s, scientists developed the idea that “at the molecular level, tumors are the result of damage to cellular DNA”. DNA damage, such as genetic mutations, double-strand breaks (DSBs), and oxidative stress, can be caused by endogenous (*e.g.*, reactive oxygen species) and exogenous factors (*e.g.*, UV light). According to the widely accepted theory, DSBs and oxidative stress are closely related to cancers. DSB is one of the most critical and dangerous types of DNA damage that, if not repaired, can lead to cell death. Oxidative stress to DNA and DSBs might drive colitis-associated colorectal carcinogenesis in IBD patients[18]. In contrast to UC, CAC has a unique mutational profile. It is notable that mutations in *NFKB1* are of high frequency in UC but are rarely found in CAC, which suggests a discrete mechanism in colorectal carcinogenesis[19]. A study investigating somatic mutations in CAC found high frequencies of *RNF43* mutations in CAC somatic cells. RNA-Seq analysis revealed elevated *c-Myc* and target gene expression in *RNF43*-mutated tumors, suggesting that *RNF43* is a driver of colorectal tumorigenesis[20]. In addition, the proto-oncogene *BMI1* and its target anti-oncogene *Reg3b* were identified as being closely associated with the development of CAC. A separate series of *in vitro* and *in vivo* studies demonstrated that *BMI1* expression was elevated in CAC patients, that high *BMI1* expression was associated with a lower response rate to antitumor necrosis factor α (TNF- α) therapy[21] and that *BMI1* and its homologue *MEL18* promoted cancer by inhibiting *Reg3b* expression[22].

Epigenetics is important for tumor initiation. The hypothesis of “epigenetic triggers in cancer initiation” is that once endogenous or environmental stimuli trigger epigenetic initiation in cancer-initiating cells, this leads to the development and progression of tumors[23]. *ELF4*, a member of the E-Twenty-Six domain transcription factor family, is involved in the regulation of a variety of DNA damage repair mechanisms. *ELF4* suppression caused by methylation of the promoter region is prevalent in UC and CAC, supporting the “epigenetic triggers in cancer initiation” hypothesis[24]. One study by Emmett and colleagues evaluated DNA methylation patterns in CAC and sporadic CRC and found that several genes were highly methylated in CAC, such as *MINT1*, *MYOD*, and the promoter regions of *EYA4* and *ESR*[25]. In addition to DNA methylation, defects in DNA glycosylation have also been implicated in the pathogenesis of CAC. A breakdown of the colonic mucus barrier mediated by impaired O-glycosylation expression was identified to result in spontaneous CAC in mice[26]. Based on these findings, genetics and epigenetics are involved in the development of CAC.

Immunity and inflammation

The most comprehensively studied proinflammatory and protumor pathways in CAC are the nuclear factor κ -light-chain-enhancer of activated B cells (NF- κ B), β -catenin-mediated Wnt signaling, signal transducer and activator of transcription 3 (STAT3)/interleukin-6 (IL-6), and IL-23/T helper 17 cell (Th17) pathways. It has been well established that activation of intestinal NF- κ B signaling promotes colitis-associated carcinogenesis[27]. DHX9 was overexpressed in CRC tissue and CAC mouse models. DHX9 was found to promote NF- κ B-mediated transcriptional activity and enhance the expression of downstream targets of NF- κ B, thereby promoting colorectal carcinogenesis[28]. In the early stages of colitis-associated carcinogenesis, the Wnt pathway is activated in 50% of cases[29]. Recent studies support the involvement of the WNT signaling pathway in the pathogenesis of CAC. The Wnt/ β -catenin signaling pathway is activated through the deletion of NHE8, a multifunctional protein expressed in colon stem cells, leading to increased expression of *Lgr5* in colon tissue,

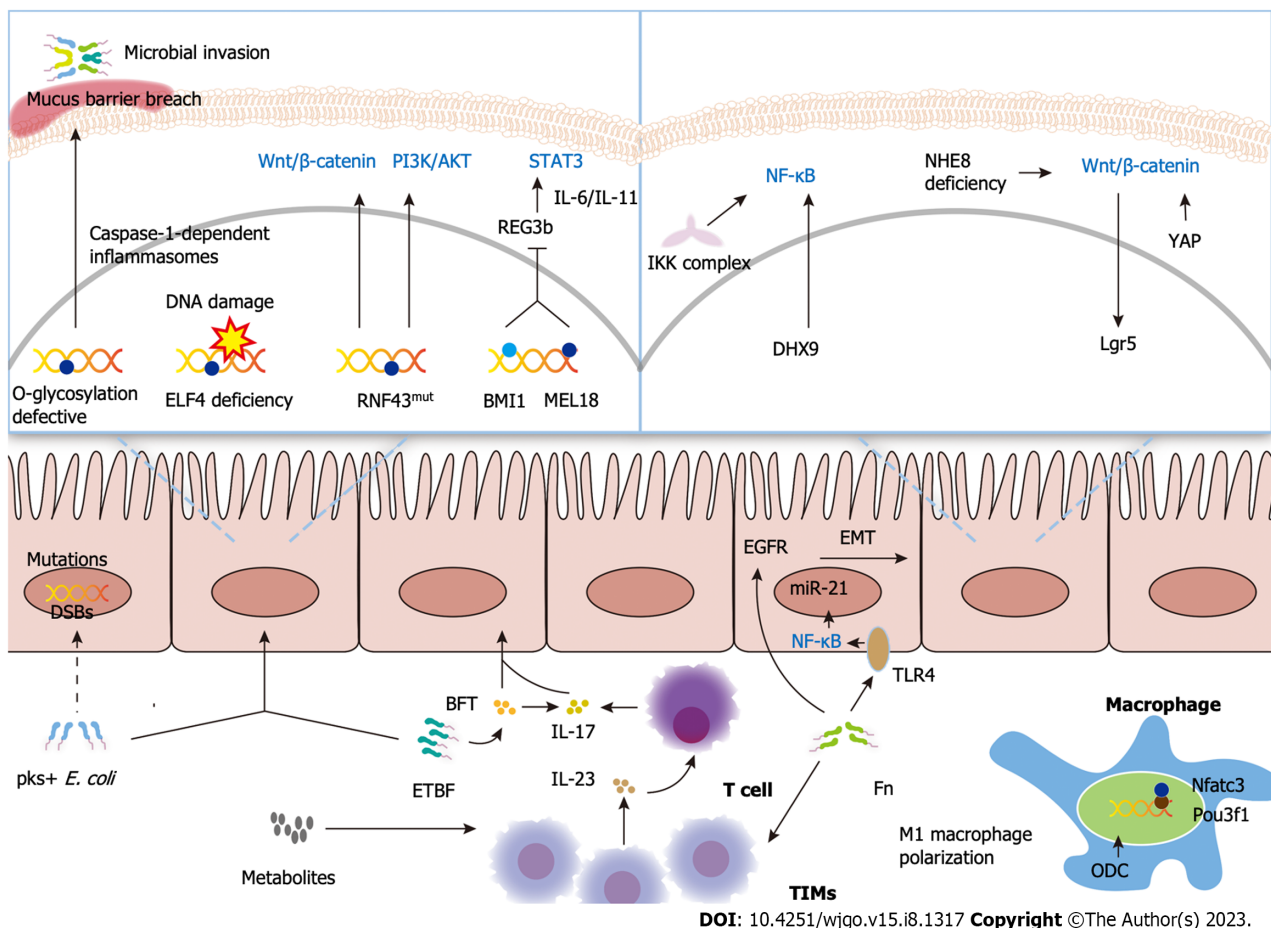


Figure 1 Different mechanisms of colitis-associated colorectal carcinogenesis. Recent advances underlying colitis-associated colorectal carcinogenesis include a variety of mechanisms, including genetics and epigenetics, immunity and inflammation, and microbiota. Their subtle and complex interactions contribute to the development of colorectal cancer (CAC): (1) DNA mutations, oxidative damage, DNA methylation and histone modifications promote colitis-associated colorectal carcinogenesis; (2) Classical signaling pathways such as NF- κ B, Wnt/ β -catenin, STAT3/IL-6 promote colitis-associated colorectal carcinogenesis. In addition, TIMs and macrophage polarization are also involved in carcinogenesis; and (3) Several bacteria (e.g., *E. coli*, ETBF, and Fn) and metabolites may cause DNA damage, inflammation, activation of several oncogenic signaling pathways and EMT, thereby promoting CAC. BFT: *Bacteroides fragilis* toxin; DSBs: Double-strand breaks; EMT: Epithelial-mesenchymal transition; *E. coli*: *Escherichia coli*; ETBF: Enterotoxigenic *Bacteroides fragilis*; Fn: *Fusobacterium nucleatum*; IKK: I κ B kinase; MEL18: Polycomb group ring finger 2; NFATc3: Nuclear factor of activated T cells 3; NF- κ B: Nuclear factor- κ B; ODC: Ornithine decarboxylase; PI3K: Phosphoinositide 3-kinase; Pou3f1: POU class 3 homeobox 1; STAT3: Signal transducer and activator of transcription 3; TIMs: Tumor-infiltrating myeloid cells; TLR4: Toll-like receptor 4.

which is a target gene for Wnt signaling and ultimately exhibits a favorable outcome of colitis-associated tumorigenesis [30]. Excess yes-associated protein 1 triggers the Wnt/ β -catenin signaling pathway and promotes colitis-associated tumorigenesis[31]. Furthermore, upregulation of IL-23 and IL-17 has been demonstrated in clinical CRC specimens and CRC mouse models. It has been shown that barrier disruption due to genetic damage leads to the invasion of microbial products, triggering IL-23- and IL-17-driven inflammatory infiltration of tumors, which in turn drives tumor growth[32].

Both the innate and adaptive immune systems play important roles in the development and progression of CAC. Macrophages are the most well-known member of the intrinsic immune system. Owing to the known potential of Pou3f1 in regulating immune responses and the immune system, investigators have investigated the role of Pou3f1 in colitis-associated colorectal tumorigenesis. Reduced secretion of inflammatory mediators in macrophages by knocking out Pou3f1 inhibited CAC development[33]. Ornithine decarboxylase in macrophages promotes colon carcinogenesis by impairing the M1 immune response[34]. Tumor-infiltrating T cells have been demonstrated to contribute to CAC immunosurveillance. Interestingly, the incidence of CAC was found to increase after an appendectomy, which may accelerate tumor development by inhibiting T-cell initiation and subsequently reducing cancer immune surveillance, as well as by dysbiosis of intestinal microbes and impairment of the intestinal barrier[35,36].

Microbiota

There are 3 main microbial hypotheses associated with the pathogenesis of CAC, including the “a-bug” hypothesis[37], the “driver-passenger” hypothesis[38], and the “common ground” hypothesis. According to the “common ground” hypothesis, exogenous and endogenous factors (unhealthy diet, exogenous contaminants, and chronic inflammation) create a “leaky gut” that allows pathogens to become highly permeable across cells and internalize bacteria, leading to chronic inflammation and morphological changes[39]. Accumulated evidence supports a significant role for the

microbiota in CRC development and progression, focusing on *Escherichia coli* (*E. coli*), *Bacteroides fragilis* (*B. fragilis*), and *Fusobacterium nucleatum* (*F. nucleatum*).

E. coli can produce colibactin, which is encoded by the pathogenicity island polyketide synthesis (pks) gene. *E. coli* carrying the pks island causes DSBs and activation of the DNA damage checkpoint pathway, which may be a predisposing factor for CRC development[40]. A novel area of research confirmed a distinct mutational signature with unique single-base substitution, insertion, and deletion mutations in CRC caused by colibactin from pks⁺ *E. coli*[41]. However, there appeared to be no significant differences between pks⁺ *E. coli* and the prevalence of CRC or colorectal adenoma lesion patients in a Japanese prospective cohort study[42] and a Canadian cohort study[43]. Adherent invasive *E. coli* (AIEC)-associated genes, including chitinase 3-like1, carcinoembryonic antigen-related cell adhesion molecule 6, and claudin-2, as well as the protein expression of these genes, were found to be upregulated in CAC samples, suggesting an underlying link between AIEC and CAC[44].

Unlike pks⁺ *E. coli*, no unique mutational signature was produced by enterotoxigenic *B. fragilis* (ETBF). Allen *et al*[45] performed whole-exome sequencing and whole-genome sequencing and found that errors in DNA mismatch repair and homologous recombination DNA damage repair were involved in the pathogenesis of ETBF-induced CRC. Notably, a unique ETBF-associated colonic immune infiltrate was observed in a CRC murine model. The combined effect of IL-17 and *B. fragilis* toxin, specifically secreted by ETBF on colon epithelial cells, ultimately led to the suppression of T-cell proliferation[46].

In addition, *F. nucleatum* may contribute to the development and progression of CRC in several ways. It promotes epithelial-mesenchymal transition through the epidermal growth factor receptor signaling pathway, thereby accelerating the progression of CAC[47]; it recruits tumor-infiltrating immune cells, leading to a proinflammatory microenvironment conducive to colorectal carcinogenesis[48]; and it activates the NF- κ B signaling pathway by activating Toll-like receptor 4 signaling, thereby upregulating microRNA-21 expression and leading to accelerated tumor progression[49]. Further efforts must be made to unravel the complexity between the microbiota and CAC.

SURVEILLANCE AND MANAGEMENT OF CAC AND COLORECTAL DYSPLASIA

Surveillance colonoscopy in patients with IBD may allow earlier detection of colorectal neoplasms and therefore improve prognosis. Research from the Cochrane Library has confirmed a significant reduction in mortality associated with CAC in the surveillance group compared to the non-surveillance group[50]. Given the evidence, surveillance colonoscopy is warranted in patients with IBD, especially those at high risk for CAC. To standardize the management of patients after the onset of IBD, many guidelines or expert consensus have been published to guide endoscopic surveillance in patients with IBD (Table 1)[51-64]. There is considerable variation in the recommendations of these guidelines, which detail the timing of surveillance colonoscopy, surveillance intervals, and new screening modalities.

The initiation of surveillance colonoscopy and endoscopic options for dysplasia is basically consistent across guidelines, and patients with IBD are recommended to initiate colonoscopy over 8 years or 8-10 years after the onset of symptoms in most guidelines. In patients with IBD and concomitant primary sclerosing cholangitis, it is recommended that colonoscopic surveillance be initiated at the time of diagnosis due to the increased risk of CRC developing in these patients[51]. Colonoscopy has always been the basic option for CAC surveillance. Guidelines for endoscopic surveillance are constantly being revised to consider the new endoscopic techniques and technologies that have emerged in recent years. High-definition white light endoscopy and chromoendoscopy to detect colorectal dysplasia have recently been recommended as endoscopic options in most guidelines. Compared with the white-light colonoscopy group, the neoplasia detection rate was 2-fold higher in the chromoendoscopy group. The incidence of UC-associated CRC in patients who had ever undergone chromoendoscopy was significantly lower than in those who had never undergone chromoendoscopy[65].

It is difficult to make a clear macroscopic distinction between CAC and sporadic CRC. In contrast to sporadic CRC, CAC appears to have distinguishing clinicopathologic features, evolving from a polymorphous dysplastic lesion rather than a polypoid adenoma[66]. It is characterized by the lack of tumor histologic heterogeneity, tumor necrosis, Crohn's-like reaction, the presence of mucin, and signet ring cell differentiation and tumor well differentiation[67].

Previous viewpoints supported IBD patients with non-adenoma-like dysplasia-related lesions or masses were recommended to undergo colectomy, whereas IBD patients with adenoma-like dysplasia-related lesions or masses could be safely managed with polypectomy and continued surveillance in the absence of flat dysplasia elsewhere in the colon [68]. The mainstream consensus is that endoscopic resection should be considered for all clearly delineated dysplastic-appearing lesions without evidence of invasive cancer or significant submucosal fibrosis. Endoscopic mucosal resection or endoscopic submucosal dissection may be considered for complex lesions not amenable to standard polypectomy, such as large and highly irregular lesions[52].

SURGICAL TREATMENT FOR CAC

After a long course of the disease, a large number of IBD patients opt for surgery. Based on a long-term follow-up study of Australian IBD patients, the cumulative incidence of colectomy was estimated to be 15%, 26%, and 31% at 10, 20, and 30 years in patients with UC, whereas the cumulative incidence of resection was 32%, 43%, and 53% at 5, 10, and 15 years in patients with CD[69]. Indications for surgery in patients with IBD vary among guidelines (Table 2)[70-72]. The Chinese consensus recommends surgery for UC combined with massive hemorrhage, intestinal perforation, malignancy or high

Table 1 Summary of guidelines and consensus statements reporting on colonoscopic surveillance in inflammatory bowel disease

Society	Disease type	Initiation	Risk categories	Surveillance intervals	Endoscopic selection of dysplasia detection
ACG, 2019; Guideline [51]	UC	8 yr; concomitant PSC: From diagnosis	No specific recommendation	UC: 1-3 yr; concomitant PSC: 1 yr	Dye spray chromoendoscopy with methylene blue or indigo carmine; white-light endoscopy with narrow-band imaging
ACG, 2018; Guideline [56]	CD	No specific recommendation			Colonoscopy with chromoendoscopy: high risk for colorectal neoplasia [†]
AGA, 2021; expert consensus [52]	IBD	8-10 yr; after a negative screening colonoscopy: 1-5 yr; concomitant PSC: From diagnosis	No specific recommendation	High risk for developing colorectal dysplasia ² ; persistent moderate-severe pouchitis, and/or pre-pouch ileitis: At least 1 yr	Dye spray chromoendoscopy; high-definition endoscopy with virtual chromoendoscopy
AOCC and APAC, 2021; expert consensus [57]	IBD	8 yr		UC patients with LGD in flat mucosae: In 3-6 mo	No specific recommendation
BSG, 2019; guideline [58]	IBD	8 yr; concomitant PSC: From diagnosis	Lower risk: Extensive colitis with no active inflammation; colitis affecting < 50% of the colon; intermediate risk: extensive colitis with mildly active inflammation; post-inflammatory polyps; CRC in an FDR older than 50 yr; higher risk: Extensive colitis with moderate-to-severely active inflammation; stricture or dysplasia in last 5 yr; history of PSC (including after orthotopic liver transplantation); CRC in a FDR younger than 50 yr	Lower risk: 5 yr; intermediate risk: 3 yr; higher risk: 1 yr	High-definition colonoscopy with chromoendoscopy
CCA, 2018; Guideline [59]	IBD	8-10 yr	Lower risk: Quiescent disease and no other risk factors; intermediate risk: Quiescent disease without high risk factors; family history of CRC in an FDR; higher risk: Chronic active inflammation; prior colorectal dysplasia; evidence of intestinal damage with foreshortened tubular colon, colonic stricture, or pseudopolyps; PSC; family history of CRC younger than 50 yr	Lower risk: 5 yr; Intermediate risk: 3 yr; higher risk: 1 yr	Colonoscopy with chromoendoscopy
CSG, 2018; Chinese consensus [53]	IBD	8-10 yr	No specific recommendation	UC: 8-10 yr; montreal type E2: 2 yr (15 yr after the onset of the disease); montreal type E3: 2 yr (8-10 yr after the onset of the disease); 1 yr (after 20 yr); concomitant PSC: 1 yr	No specific recommendation
ECCO, 2017; guideline [55]	UC	Over 8 yr	Lower risk: Neither intermediate nor high-risk features; intermediate risk: Extensive colitis with mild or moderate active inflammation; post-inflammatory polyps; CRC in a FDR older than 50 yr; higher risk: Extensive colitis with severe active inflammation; stricture or dysplasia in last 5 yr; PSC	Lower risk: 5 yr; intermediate risk: 2-3 yr; higher risk: 1 yr	High-definition endoscopy; chromoendoscopy with targeted biopsies
ECCO, 2019; guideline [60,61]	IBD	No specific recommendation	Same with BSG Guideline (2019)	Lower risk: 5 yr; intermediate risk: 2-3 yr; higher risk: 1 yr	
JSG, 2020; Guideline [62]	IBD	8 yr	No specific recommendation		Targeted biopsies
NCCN, 2022; Guideline [63]	IBD	8 yr	Low risk: No active inflammation; high risk: Extensive colitis with active inflammation; dysplasia; PSC; family history of CRC younger than 50 yr	Low risk: 2-3 yr; high risk: 1 yr; HGD or piecemeal resection: 3-6 mo	High-definition white light endoscopy; colonoscopy with chromoendoscopy
NICE, 2022; guideline	IBD	UC but not proctitis alone or CD involving	Same with BSG guideline (2019)	Low risk: 5 yr; intermediate risk: 3 yr;	Colonoscopy with chromoendoscopy

[64]	more than one segment of the colon: 10 yr	high risk: 1 yr	
WGO, 2015; IBD guideline [54]	8 yr	No specific recommendation	Magnification and chromoendoscopy

¹Personal history of dysplasia, primary sclerosing cholangitis (PSC).

²Prior colorectal cancer or dysplasia, PSC.

ACG: American College of Gastroenterology; AGA: American Gastroenterological Association; AOCC: Asian Organization for Crohn's and Colitis; APAG: Asia Pacific Association of Gastroenterology; BSG: British Society of Gastroenterology; CCA: Cancer Council Australia; CD: Crohn's disease; CRC: Colorectal cancer; CSG: Chinese Society of Gastroenterology; ECCO: European Crohn's and Colitis Organization; FDR: First-degree relative; HGD: High-grade dysplasia; IBD: Inflammatory bowel disease; LGD: Low-grade dysplasia; JSG: Japanese Society of Gastroenterology; NCCN: National Comprehensive Cancer Network; NICE: National Institute for Health and Care Excellence; PSC: Primary sclerosing cholangitis; UC: Ulcerative colitis; WGO: World Gastroenterology Organization.

suspicion of malignant lesions, CD complications, and ineffective medical treatment[53]. The World Gastroenterology Organization (WGO) guidelines recommend different procedures for patients with UC (*e.g.*, consider segmental resection in elderly patients with localized neoplasms or extensive comorbidities) and CD (*e.g.*, temporary diverting ileostomy/colostomy for severe perianal fistula) in different states[54].

Importantly, surgery appears to increase the risk of developing cancer. Patients with IBD have a higher risk of developing CRC after segmental colonic resection for CRC. During the 3-year follow-up period after initial surgery, 1.6% of IBD patients developed CRC compared to 0.7% of non-IBD patients. Furthermore, 6.3% of IBD patients developed tumors compared to 2.3% of non-IBD patients during the 15-year follow-up period after initial surgery[73]. Consequently, no guidelines recommend prophylactic colectomy to prevent cancer.

CHEMOPREVENTION IN CAC

Aminosalicylic acid

According to the widely accepted concepts, aminosalicylic acid (ASA) has been an essential drug in the treatment of mild to moderate UC. Several studies have investigated its potential value in the chemoprevention of CAC. Long-term use of 5-ASA compounds has been shown to reduce the risk of UC-associated CRC in both human[74] and animal models[75]. Three meta-analyses[76-78] and a large epidemiological study[79] confirmed a protective association between the application of 5-aminosalicylate compounds and CRC. However, in another meta-analysis of nonreferral populations, there appeared to be no protective effect of 5-ASA on CAC[80].

Despite some conflicting results, most studies have confirmed the chemopreventive effect of 5-ASA in preventing CAC. The chemopreventive effects of 5-ASA vary for different disease classifications and drug types: The risk of CAC is greatly reduced in UC patients but not significantly in CD patients; mesalazine significantly reduces the risk of CAC, but salazosulfapyridine does not show any protective effect[76,77]. The dose-effect relationship on the protective effect of mesalazine is apparent[77]. A daily dosage of mesalazine ≥ 1.2 g is more protective against colorectal neoplasia than < 1.2 g. A case-control study demonstrated that a cumulative mesalamine dose of over 4500 g led to a CRC risk reduction of 97.6% [81]. Given this evidence, the 2017 ECCO Consensus recommended the use of mesalazine for the chemoprevention of CRC in all patients with UC[55].

Immunomodulators

The antineoplastic effect of thiopurines is debatable due to inconsistent results across studies. A cohort study in the Netherlands found a significant protective effect of thiopurines on the risk of advanced neoplasia[82]. However, data from a meta-analysis[83] and a case-control study[84] have demonstrated that thiopurine use was not associated with a significantly lower risk of colorectal neoplasia. In addition, the effectiveness of thiopurines varies in different disease classifications and geographical regions. Thiopurine treatment was associated with a reduced risk of colorectal neoplasia in European studies but not in African and Asian studies; thiopurine treatment also reduces the risk of CAC, which is significant in patients with UC but not in patients with CD[85].

Although thiopurines may reduce the risk of CAC, they are also associated with an increased risk of cancer[86]. There was no excess risk of developing any cancers in individuals with older-onset IBD in a population-based study[87]. Nevertheless, a nested case-control study has identified that exposure to thiopurines for over 5 years is related to a significantly higher risk of nonmelanoma skin cancer and lymphoproliferative disorders[86] but unrelated to a higher risk of melanoma or colorectal cancer[88]. Therefore, given this evidence, the American College of Gastroenterology (ACG) guidelines recommended that chemopreventive medical therapy alone is not an appropriate way to prevent UC-associated CRC and is not a substitute for colonoscopy[51].

In addition to thiopurines, given the therapeutic effect of thalidomide in moderate UC and moderate CD, its efficacy in CAC is under investigation. Lu *et al*[89] demonstrated that thalidomide suppressed macrophage polarization in the tumor microenvironment, which not only relieved colonic inflammation to promote mucosal healing but also inhibited the development of CAC. These findings may shed light on the potential use of thalidomide for the chemoprevention of

Table 2 Summary of guidelines and consensus statements reporting on surgical management in inflammatory bowel disease

Society	Disease type	Absolute indication (surgery is recommended)	Relative indication (surgery can be considered)
ACG, 2019; guideline[51]	UC	Dysplasia in UC is not resectable or is multifocal	Moderately to severely active UC who are refractory or intolerant to medical therapy
ACG, 2018; guideline[56]	CD	No statements are provided	Intra-abdominal abscess
AGA, 2021; expert consensus [52]	IBD	Unresectable visible dysplasia or invisible multifocal or high-grade dysplasia on histology	No statements are provided
AOCC and APAG, 2021; expert consensus [57]	IBD	No statements are provided	
BSG, 2019; guideline[58]	UC	Patients with acute severe UC who have not responded within 7 d of rescue therapy with infliximab or ciclosporin, or those with deterioration or complications before that time (including toxic megacolon, severe hemorrhage or perforation): Subtotal colectomy and ileostomy, with preservation of the rectum; patients who have chronic active symptoms despite optimal medical therapy: Surgical resection of the colon and rectum	
	CD	Localized ileocaecal CD for those failing or relapsing after initial medical therapy, or in those preferring surgery to the continuation of drug therapy: Laparoscopic resection; patients with small bowel CD strictures shorter than 10 cm: Stricture-plasty/resection; patients with severe perianal CD refractory to medical therapy: Fecal stream diversion	
ASCRS, 2020 [71]; guideline	CD	Patients with severe acute colitis who do not adequately respond to medical therapy or who have signs or symptoms of impending or actual perforation; patients with a free perforation: surgical resection of the perforated segment	Patients who demonstrate an inadequate response to, develop complications from or are nonadherent with medical therapy; patients with symptomatic small-bowel or anastomotic strictures that are not amenable to medical therapy and/or endoscopic dilation; patients with strictures of the colon that cannot be adequately surveyed endoscopically; Resection; patients with penetrating Crohn's disease with abscess formation; patients with enteric fistulas that persist despite appropriate medical therapy
CSG 2018; Chinese consensus [53]	UC	Massive hemorrhage, perforation, malignancy, and high suspicion of malignant pathology	Severe UC that is refractory to active medical treatment, and toxic megacolon refractory to medical treatment should; undergo surgical intervention early; poor efficacy of medical treatment and/or adverse drug reactions that have seriously affected patients' quality of life
	CD	CD complications ¹ , ineffective medical treatment ²	No statements are provided
ECCO, 2019; guideline[70]	UC	No statements are provided	Refractory and corticosteroid-dependent patients; patients with UC and a minimally affected rectum
ECCO, 2020; guideline[72]	CD	Patients with refractory pancolonic Crohn's disease without a history of perianal disease: Restorative proctocolectomy with IPAA; patients with a single involved colonic segment in CD: Segmental colectomy; patients with limited, nonstructuring, ileocaecal CD (diseased terminal ileum < 40 cm): Laparoscopic resection; Small-bowel strictures related to CD: Strictureplasty; patients with short (< 5 cm) strictures of the terminal ileum in CD: Endoscopic balloon dilatation or surgery; patients with CD and complex perianal fistulae: Ligation of the intersphincteric fistula tract	
JSG, 2020; guideline[62]	IBD	In severe cases of IBD and those with cancer or dysplasia; patients with symptoms caused by the primary disease that do not improve with medical treatment, side effects of medication, and extraintestinal complications (especially pyoderma gangrenosum)	
WGO, 2015; guideline[54]	UC	Medical treatment is not completely successful or in the presence of dysplasia	
	CD	Surgery should be considered as an alternative to medical treatment early in the disease course for short-segment CD limited to the distal ileum	

¹Intestinal obstruction, abdominal abscess, fistula formation, acute perforation, major bleeding, carcinogenesis.

²Severe Crohn's disease refractory to steroid therapy; patients with poor efficacy of medical treatment and/or adverse drug reactions that have seriously affected the quality of life.

IPAA: Ileal pouch-anal anastomosis; UC: Ulcerative colitis; IBD: Inflammatory bowel disease; CD: Crohn's disease; ACG: American College of Gastroenterology; AGA: American Gastroenterological Association; AOCC: Asian Organization for Crohn's and Colitis; BSG: British Society of Gastroenterology; CSG: Chinese Society of Gastroenterology; ECCO: European Crohn's and Colitis Organization; JSG: Japanese Society of

Gastroenterology; WGO: World Gastroenterology Organization.

CAC.

Biological agents

Biological agents commonly used in the guidelines for the treatment of IBD include antitumor necrosis factor- α (anti-TNF α) agent (Infliximab), $\alpha 4\beta 7$ integrin antibody (Vedolizumab), Janus kinase (JAK) inhibitor (Tofacitinib), and IL-12/IL-23 antagonist (Ustekinumab)[70]. The guidelines recommend these drugs as an alternative treatment for moderate to severe UC and moderate to severe CD. However, biological agents appear to have no chemopreventive effect on CAC. Two population-based studies, one from France[87] and the other from Canada[88], found no association between anti-TNF α exposure and CRC. Concerns about the carcinogenic risk of antineoplastic drugs are of significant importance. Fortunately, a meta-analysis showed that antineoplastic drugs do not increase the risk of CAC[90]. The evidence-based medical evidence on chemoprevention in the last few years is presented in Table 3[91-97].

Table 3 Summary of chemoprevention in colitis-associated colorectal cancer

Population	Agent	Efficacy of candidate chemopreventive drugs	Type of study
CAC[77]	5-ASA	Protective factors	Meta-analysis
CAC[78]	5-ASA	Protective factors	Meta-analysis
CAC[76]	Mesalamine; Sulfasalazine	Protective factors; No statistical effect	Meta-analysis
CAC[80]	5-ASA	No statistical effect	Meta-analysis
CAC[81]	Mesalamine	Protective factors	Case-control study
CAC[84]	5-ASA	Protective factors	Case-control study
GI cancer in IBD[91]	5-ASA	Protective factors	Cohort study
CAC[79]	5-ASA	Protective factors	Nested case-control study
CAC[87]	5-ASA	No statistical effect	A population-based study
CAC[85]	Thiopurines	Protective factors	Meta-analysis
CAC[83]	Thiopurines	No statistical effect	Meta-analysis
CAC[84]	Thiopurines	No statistical effect	Case-control study
Advanced neoplasia in IBD ¹ [82]	Thiopurines	Protective factors	Cohort study
CRC[88]			Nested case-control study
CRC[92]	Folic acid	No statistical effect	Meta-analysis
CRC[93]	Folic acid	No statistical effect	Meta-analysis
CAC[94]	Non-aspirin NSAIDs	No statistical effect	Meta-analysis
CRC[95]	Vitamin D	No statistical effect	Meta-analysis
Colorectal adenomas[96]	Calcium intake as a food and dairy product	Significantly decrease	Meta-analysis
CRC[93]	Calcium	No statistical effect	Meta-analysis
CAC[97]	Statin	No statistical effect	Cohort study

¹Advanced neoplasia: including high-grade dysplasia and colorectal cancer.

ASA: Aminosalicylates; NSAIDs: Nonsteroidal anti-inflammatory drugs; CAC: Colitis-associated colorectal cancer; CRC: Colorectal cancer; IBD: Inflammatory bowel disease.

NEW STRATEGIES IN CAC TREATMENT

Probiotics

Recent attention has focused on the anticancer activity of probiotics, despite the lack of data from large clinical trials. Although the protective effect of probiotics on CAC has not yet been reported, the use of probiotic supplements has been indicated to significantly reduce the risk of postoperative complications in patients undergoing CRC surgery[98]. Importantly, some studies appear to form the basis of future explorations into probiotics for the treatment of CAC. As mentioned earlier, genomic instability has been linked to carcinogenesis in IBD. *Bifidobacterium infantis* has been demonstrated to alleviate colonic inflammation by activating DNA repair pathways and enhancing genomic stability[99]. Lactic acid bacteria, which have been reported to be successfully used in managing sporadic CRC[100], have also been shown to have a potential chemopreventive effect on CAC. One study by Silveira *et al*[101] established the CAC murine model and found that *Lactobacillus bulgaricus* downregulated certain cytokine levels in the intestine and tumors and inhibited tumor growth.

Traditional Chinese medicines

Traditional Chinese medicines (TCMs) are a unique but helpful health resource in China. Many classic TCMs have a long history of adjunct therapy in patients with mild to moderate IBD and are still in use today[102]. Qingchang Wenzhong decoction[103] and Sini decoction[104], effective TCM prescriptions, have been indicated to inhibit colitis-associated carcinogenesis, possibly through the improvement of intestinal flora dysbiosis and the intestinal barrier.

Others

Improving microbial dysbiosis by modulating the gut microbiota is a novel strategy for the prevention and treatment of CRC. As mentioned above, probiotics have shown great potential in the prevention and treatment of CRC. Other approaches to gut microbiota modulation, such as prebiotics, postbiotics, and fecal microbiota transplantation (FMT), are theoretically promising for the prevention and treatment of CRC. Despite the lack of clinical evidence, two clinical trials of FMT in CRC are underway. It is anticipated that these drugs are effective in the prevention and treatment of CRC.

CONCLUSION

Compared to sporadic CRC, CAC has a unique carcinogenic process. Regular colonoscopic surveillance is an effective way to improve prognosis. There is no consensus on the role of immunomodulators and biological agents in the chemoprevention of CAC. Currently, ASA is the only effective chemopreventive agent. TCM, probiotics, and other gut microbiota modulators seem to be promising strategies for the prevention and treatment of CRC. Recent advances in CAC are based on the rapid development of various types of omics in the postgenomic era. Existing studies have attempted to explore the pathogenesis of CAC from different perspectives, including genetics, immunology, and microbiology. However, due to the complexity and sophistication of life activities, more efforts are needed to restore the findings from different levels to the process of cellular carcinogenesis.

FOOTNOTES

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