

# Chemoprevention of Colitis-Associated Dysplasia or Cancer in Inflammatory Bowel Disease

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## Article Info

Received October 16, 2021

Revised November 20, 2021

Accepted December 7, 2021

Published online June 7, 2022

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Part of the work was presented in the AOCC 2020 which was held in Korea from December 16 to 18, 2020.

The association between inflammatory bowel disease and colorectal cancer is well known. Although the overall incidence of inflammatory bowel disease has declined recently, patients with this disease still have a 1.7-fold increased risk of colorectal cancer. The risk factors for developing colorectal cancer include extensive colitis, young age at diagnosis, disease duration, primary sclerosing cholangitis, chronic colonic mucosal inflammation, dysplasia lesion, and post-inflammatory polyps. In patients with inflammatory bowel disease, control of chronic inflammation and surveillance colonoscopies are important for the prevention of colorectal cancer. The 2017 guidelines from the European Crohn's and Colitis Organisation suggest that colonoscopies to screen for colorectal cancer should be performed when inflammatory bowel disease symptoms have lasted for 8 years. Current evidence supports the use of chemoprevention therapy with mesalazine to reduce the risk of colorectal cancer in patients with ulcerative colitis. Other compounds, including thiopurine, folic acid, statin, and tumor necrosis factor- $\alpha$  inhibitor, are controversial. Large surveillance cohort studies with longer follow-up duration are needed to evaluate the impact of drugs on colorectal cancer risks. (*Gut Liver* 2022;16:840-848)

**Key Words:** Inflammatory bowel disease; Crohn disease; Ulcerative colitis

## INTRODUCTION

Inflammatory bowel disease (IBD), especially ulcerative colitis (UC), is associated with an increased risk of colorectal cancer (CRC).<sup>1-5</sup> A 2001 meta-analysis reported that the prevalence of CRC was approximately 3.7% in patients of UC patients and the cumulative risk after 10 and 30 years was 2% and 18%, respectively.<sup>6</sup> A recent population-based study demonstrated a lower incidence of CRC in UC patients of 0.06% to 0.15% and a lower cumulative risk of 2.1% to 7.5% after 30 years of UC.<sup>7-14</sup>

In IBD, chronic inflammation with oxidative stress may interact with genes involved in carcinogenic pathways.<sup>15</sup> Unlike sporadic CRC, the “inflammation-dysplasia-carcinoma” pathway causes a series of genetic alterations in IBD-related CRC.<sup>16</sup> Toll-like receptors and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) activate nuclear factor- $\kappa$ B (NF- $\kappa$ B),

an inflammatory factor. NF- $\kappa$ B induces transcription of genes involved in tumorigenesis, such as cyclooxygenase-2 (COX-2), inducible nitric oxide synthase, and angiogenic factors.<sup>17</sup> In the early phase of dysplasia, inflammation may induce apoptosis via tumor suppressor p53 pathways. Compared with sporadic CRC, the onset of p53 mutations is earlier in IBD-related CRC.<sup>18</sup> The final key gene in IBD-related CRC, just prior to carcinoma, is nonfunctional adenomatous polyposis coli. Unstable chromosomes or abnormalities of microsatellites may cause loss of adenomatous polyposis coli function.<sup>19</sup>

Strategies to reduce CRC in IBD patients include early diagnosis of colitis, control of chronic inflammation, and early detection of dysplasia via surveillance endoscopy. The effects of chemopreventives on CRC risk have been reported in a number of clinical studies.<sup>20</sup> In this review, the risk factors for CRC in patients diagnosed with IBD, sur-

veillance strategies, and chemoprevention of colitis-related CRC and dysplasia in IBD patients are discussed.

## 1. Risk factors of CRC for patients diagnosed IBD

The 2017 European Crohn's and Colitis Organisation (ECCO) consensus reported several risk factors for CRC in IBD patients.<sup>21</sup> The risk factors included disease duration<sup>6,8,22,23</sup> and extensive colitis.<sup>23</sup> Compared to the general population, the risk of CRC was 1.7-fold higher for proctitis, 2.8-fold higher for left side colitis, and 14.8-fold higher for pancolitis.<sup>24</sup> The histological extent was associated with high-grade dysplasia and CRC.<sup>25,26</sup> Non-polypoid (hazard ratio [HR], 8.6; 95% confidence interval [CI], 3.0 to 24.8) or dysplastic lesions more than 1 cm in size (HR, 3.8; 95% CI, 1.5 to 13.4) and a dysplasia lesion history (HR, 2.8; 95% CI, 1.2 to 6.5) were risk factors for developing high-grade dysplasia or CRC in another study.<sup>26</sup> The most consistent risk factor for CRC is primary sclerosing cholangitis (PSC), which increases the absolute risk of CRC by up to 31%.<sup>27-29</sup> Family history of CRC also increases the risk of CRC in patients with UC.<sup>30</sup> Inflammatory complications, such as post-inflammatory polyps, foreshortened colon, and strictures, are associated with CRC.<sup>31-33</sup> A recent meta-analysis showed that extensive disease (odds ratio [OR], 2.42; 95% CI, 2.00 to 2.92), post-inflammatory polyps (OR, 3.29; 95% CI, 2.41 to 4.48), low-grade dysplasia (OR, 10.85; 95% CI, 5.13 to 22.97), stricture (OR, 7.78; 95% CI, 3.74 to 16.14), aneuploidy (OR, 5.17; 95% CI, 2.28 to 11.71), UC (vs Crohn's disease) (OR, 1.50; 95% CI, 1.09 to 2.06), PSC (OR, 4.14; CI, 2.85 to 6.01), male gender (OR, 1.27; 95% CI, 1.12 to 1.44), and family history of CRC (OR, 2.62; 95% CI, 1.93 to 3.57) were risk factors for developing CRC or high-grade dysplasia in IBD patients.<sup>34</sup> Endoscopic inflammation (OR, 2.62; 95% CI, 0.84 to 8.17), histologic inflammation (OR, 1.98; 95% CI, 0.68 to 5.73), perianal disease (OR, 2.57; 95% CI, 0.92 to 7.15), disease duration (OR, 4.74; 95% CI, 0.36 to 63.06), p53 mutation (OR, 2.47; 95% CI, 0.72 to 8.48), appendectomy (OR, 1.57; 95% CI, 0.72 to 3.41), family history of IBD (OR, 1.13; 95% CI, 0.53 to 2.39), Caucasian race (OR, 1.11; 95% CI, 0.85 to 1.45), or IBD diagnosis less than 30 years (OR, 0.88; 95% CI, 0.41 to 1.89) were not significant risk factors for developing CRC or high-grade dysplasia in the same meta-analysis.

## 2. Surveillance colonoscopy

A 2018 Cochrane review of surveillance colonoscopy included five observational studies and 7,199 IBD patients; the review showed significantly reduced cancer detection in the surveillance group (OR, 0.58; 95% CI, 0.42 to 0.80;  $p < 0.001$ ). The surveillance group had a significantly lower ratio of CRC-related death (OR, 0.36; 95% CI, 0.19 to 0.69;

$p = 0.002$ ) in four pooled studies and a significantly elevated rate of early-stage CRC in two pooled studies (OR, 5.40; 95% CI, 1.51 to 19.30;  $p = 0.009$ ).<sup>35</sup> The 2017 ECCO guideline suggests that a colonoscopy to screen CRC should be performed after 8 years of IBD symptoms.<sup>21</sup> The next surveillance colonoscopy should be arranged in 1 year for patients with high-risk features, such as severe active inflammation, dysplasia, colon stricture, or PSC. The next surveillance should be scheduled at 2 to 3 years for patients with intermediate risk factors, including post-inflammatory polyps, mild-to-moderate active inflammation of extensive colitis, or patient's first-degree relative with CRC at age of 50 years and above. The next surveillance colonoscopy should be scheduled after 5 years in patients without high or intermediate risks.<sup>21</sup>

A 2019 meta-analysis to evaluate different colonoscopy methods for the detection of dysplasia in IBD patients included ten studies, and six studies were randomized controlled trials (RCTs). Three RCTs favored chromoendoscopy for the detection of dysplasia more than light endoscopy (relative risk [RR], 1.50; 95% CI, 1.08 to 2.10), and the results for chromoendoscopy were similar to high-definition white-light endoscopy (HDWLE) (RR, 1.36; 95% CI, 0.84 to 2.18).<sup>36</sup> In non-RCTs, chromoendoscopy was superior to both HDWLE and standard-definition white-light endoscopy (SDWLE) for the detection of dysplasia lesion in IBD patients (RR, 3.48; 95% CI, 2.11 to 5.73; SDWLE: RR, 6.85; 95% CI, 2.79 to 16.81; HDWLE: RR, 2.57; 95% CI, 1.41 to 4.68).<sup>36</sup> One RCT included targeted and random biopsies (quadrantic biopsies every 10 cm) for surveillance colonoscopy; the neoplasm detection rate was similar (target biopsy group, 11.4%; random biopsy group, 9.3%;  $p = 0.617$ ).<sup>37</sup> Chromoendoscopy with targeted biopsies was recommended in the 2017 ECCO consensus for the detection of dysplasia in IBD patients. Alternatively, when white-light colonoscopy is used, targeted and random biopsies should be collected for any visible lesions.<sup>21</sup> Endoscopic artificial intelligence with deep learning or machine learning is being developed in recently years.<sup>38-43</sup> Application of such technology is promising to assess mucosal healing and predict disease relapse for IBD patients.<sup>39,44</sup> The use of such technology may improve the ability of endoscopist to detect dysplasia for IBD patients.<sup>45</sup>

## CHEMOPREVENTION

### 1. Chemoprevention with 5-aminosalicylic acid

In 1994, Pinczowski *et al.*<sup>46</sup> first reported the chemopreventive effects of sulfasalazine in IBD patients. Three-month treatment with sulfasalazine significantly protected

UC patients from CRC. Interest in chemopreventive therapies for IBD patients was provoked by these findings. The structural analog of aspirin, 5-aminosalicylic acid (5-ASA), has chemopreventive activity via different pathways.<sup>47</sup> Induction of S phase arrest by 5-ASA improves DNA fidelity and, consequently, reduces mutation rates.<sup>48,49</sup> Nitric oxide synthase activity and the generation of reactive oxygen species are also reduced, protecting patients from free radical damage.<sup>50,51</sup> Suppression of the epidermal growth factor pathway and downregulation of c-Myc lead to apoptosis.<sup>52,53</sup> The Wnt/beta-catenin pathway is modulated and the tumor suppressor peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ) is upregulated by 5-ASA, leading to inhibition of cell proliferation.<sup>54</sup> Finally, 5-ASA inhibits the NF- $\kappa$ B pathway and blocks both COX-2-dependent and COX-2-independent cancer cell growth.<sup>55,56</sup>

In a case-control study nested in the CESAME cohort study, propensity scores were adjusted for 5-ASA treatment. The sub-analysis in patients diagnosed with IBD showed a protective effect for patients with long-standing extensive colitis (OR, 0.5; 95% CI, 0.2 to 0.9).<sup>57</sup> A population-based cohort study in Hong Kong included 2,103 IBD patients (857 Crohn's disease and 1,246 UC); this study showed no cancer risk reduction after adjustment for age, gender, and smoking status (adjusted HR, 1.22; 95% CI, 0.6 to 2.5).<sup>58</sup> Meta-analysis can provide recommendations from heterogeneous data. In a meta-analysis of 17 studies, 5-ASA was associated with a lower risk of developing CRC/dysplasia in UC patients in both population- and clinical-based studies (OR, 0.46; 95% CI, 0.34 to 0.61). The pooled analysis revealed no protective effects against CRC/dysplasia in Crohn's disease patients in either the clinical- or population-based studies (OR, 0.66; 95% CI, 0.42 to 1.03). This meta-analysis also analyzed the impact of different types and dosages of 5-ASA (mesalazine and sulfasalazine) on CRC/dysplasia development. Mesalazine at  $\geq 1.2$  g/day was more protective than lower dosages. However, sulfasalazine use showed no protective effects against CRC/dysplasia at either  $\geq 2.0$  g/day or  $< 2.0$  g/day. The most protective effects of 5-ASA were detected in patients from Asian countries (OR, 0.25; 95% CI, 0.14 to 0.47). The second most protective effect was found in European patients (OR, 0.55; 95% CI, 0.42 to 0.73). However, no significant protective effects of 5-ASA against CRC were detected in North American IBD patients (OR, 0.67; 95% CI, 0.44 to 1.02).<sup>59</sup> Two other meta-analyses showed similar results.<sup>60,61</sup> In a recent meta-analysis, a multivariable analysis of six studies showed a lower risk of CRC in patients treated with 5-ASA (pool OR, 0.51; 95% CI, 0.39 to 0.66). The 2017 ECCO consensus states that mesalamine compounds may decrease the incidence of CRC in UC.<sup>21</sup>

## 2. Chemoprevention with thiopurines

The anti-inflammatory thiopurines were used to maintain IBD patients during remission to avoid prolonged steroid use.<sup>62,63</sup> In a French long-term follow-up study of 19,486 patients, a decreased risk of CRC/high-grade dysplasia was observed in patients with long-term extensive colitis after treatment with thiopurines compared to patients who were never treated with thiopurines (HR, 0.28; 95% CI, 0.09 to 0.89).<sup>64</sup> However, in the same patient group, thiopurines were associated with an increased risk of lymphoproliferative malignancy (HR, 52.5). When comparing patients receiving thiopurines versus patients who had never received the drugs, the multivariate-adjusted analysis for lymphoproliferative disorder showed a hazard ratio of 5.28 (95% CI, 2.01 to 13.9;  $p=0.0007$ ).<sup>65</sup> Another meta-analysis of 76,999 patients to assess the correlation between thiopurine treatment and CRC risk in IBD patients showed significant protective effects in UC patients (OR, 0.67; 95% CI, 0.45 to 0.98). However, there was no significant protective effect in UC patients (OR, 1.06; 95% CI, 0.54 to 2.09).<sup>66</sup> Another meta-analysis of 11 cohort studies and 16 case-control studies, which included 95,397 IBD patients, showed a risk reduction in high-grade dysplasia and CRC both in case-control and cohort studies. In patients with high CRC risk, the chemopreventive effects were significant in patients with disease duration over 8 years with an OR of 0.47 in case-control studies (95% CI, 0.31 to 0.70) and a RR of 0.96 in cohort studies (95% CI, 0.94 to 0.98). However, protective effects in IBD patients with PSC or extensive colitis were not demonstrated in this study.<sup>67</sup> Despite the decreased risk of CRC in IBD patients, thiopurines may have carcinogenic effects. As a result, the 2017 ECCO consensus did not recommend for or against chemoprevention with thiopurines.<sup>21</sup>

## 3. Chemoprevention with statins

Statins are hydroxymethylglutaryl coenzyme A reductase inhibitors that decrease cholesterol synthesis and increase the removal of low-density lipoprotein. These drugs are widely used in patients with hyperlipidemia. Statins may also have a role in CRC prevention and treatment.<sup>68</sup> Several studies demonstrated the chemopreventive effects of statins on CRC via effects on inflammation-induced colon cancer proliferation, potential effects on vascular endothelial growth factor inhibitors, and effects on intracellular oxidative stress and apoptosis.<sup>69-72</sup> Nevertheless, studies assessing the effects of statins on CRC in IBD patients are scarce.

One study showed a risk reduction in IBD-related CRC (OR, 0.07; 95% CI, 0.01 to 0.78) and non-IBD-related CRC (OR, 0.49; 95% CI, 0.39 to 0.62) after long-term statin

use.<sup>73</sup> According to a multivariate analysis, statin treatment reduced the risk of CRC development in IBD patients (OR, 0.42; 95% CI, 0.28 to 0.62).<sup>74</sup> However, a cohort study from Mount Sinai Hospital showed no difference in CRC risk despite statin use (adjusted HR, 0.98; 95% CI, 0.43 to 2.25).<sup>75</sup> Therefore, the chemopreventive effects of statins in IBD patients remain controversial.

#### 4. Chemoprevention with ursodeoxycholic acid

Patients with both IBD and PSC have a 5- to 9-fold higher risk of CRC than the risk in patients with IBD alone.<sup>76-79</sup> High levels of bile acids in the colon may have carcinogen effects, resulting in the proliferation of colonic epithelial cells, which eventually leads to dysplasia or CRC.<sup>80,81</sup> Therefore, investigators hypothesized that ursodeoxycholic acid may decrease colonic dysplasia in patients with UC and PSC (OR, 0.18; 95% CI, 0.05 to 0.61).<sup>82</sup> In a recent meta-analysis including eight studies (five observational, three RCTs), ursodeoxycholic acid did not significantly protect against CRC (OR, 0.81; 95% CI, 0.41 to 1.61).<sup>80</sup> Nevertheless, a significant protective effect against developing CRC and/or high-grade dysplasia was detected (OR, 0.35; 95% CI, 0.17 to 0.73).<sup>80</sup>

#### 5. Chemoprevention with biologics

Biologics, such as anti-TNF- $\alpha$ , were first employed as induction therapy for severe colitis that was refractory to intravenous corticosteroid.<sup>62</sup> Cancer preventive effects of infliximab, an anti-TNF- $\alpha$ , were demonstrated in animal models. The early administration of infliximab induces significant anti-mutagenic actions, apoptosis of inflammatory cells, attenuation of TNF- $\alpha$  levels, and suppression of  $\beta$ -catenin accumulation, which all contribute to the attenuation of colonic tumor formation.<sup>83</sup> A Quebec claims database study from Canada<sup>84</sup> including 19,582 patients found anti-TNF exposure was not associated with an increased risk of CRC in IBD patients. In a Dutch case-control study from 78 general hospitals, chemopreventive effects on CRC were detected in response to anti-TNF- $\alpha$  treatment in IBD patients (OR, 0.09; 95% CI, 0.01 to 0.68;  $p=0.02$ ).<sup>85</sup> A large cohort study enrolled 225,090 individuals with Crohn's disease and 188,420 with UC between 1999 and 2020 from the multicenter database (Explorys) in the United States was the first to show the inverse association of anti-TNF therapy and CRC.<sup>86</sup> Anti-TNF- $\alpha$  treatment reduced the risk of developing CRC in Crohn's disease (OR, 0.69; 95% CI, 0.66 to 0.73;  $p<0.0001$ ) and UC patients (OR, 0.78; 95% CI, 0.73 to 0.83;  $p<0.0001$ ).<sup>86</sup> Further prospective studies are warranted to evaluate anti-TNF- $\alpha$  drugs as chemoprotective agents in patients with IBD. Current available guidelines do not recommend for or against chemopreven-

tion with anti-TNF- $\alpha$  or other newer biologic agents.<sup>62,87</sup>

#### 6. Chemoprevention with folic acid

Several solid tumors, including lung, breast, pancreas, and cervical, and CRCs, are associated with decreased folate levels.<sup>88,89</sup> Folate deficiency may occur in IBD patients due to poor nutrition, competitive inhibition of intestinal absorption by sulfasalazine, and excessive intestinal losses.<sup>90,91</sup> In one meta-analysis of 10 studies with 4,517 patients, folate supplementation had a protective effect against CRC development (pool HR, 0.58; 95% CI, 0.37 to 0.80).<sup>92</sup> Chemoprevention with folate is feasible due to low costs and good tolerability and safety. Further prospective studies are needed to define the chemopreventive influence of folate supplements.

#### 7. Chemoprevention with nonsteroidal anti-inflammatory drug

Nonsteroidal anti-inflammatory drugs (NSAIDs) are thought to decrease the risk of IBD-related CRC by blocking the COX-2 pathway.<sup>17</sup> A case-controlled study from 2006 reported decreased CRC risk in IBD patients using a multiple variable model (OR, 0.10; 95% CI, 0.03 to 0.33).<sup>93</sup> However, recent studies did not confirm these protective effects.<sup>85,94</sup> One meta-analysis in 2016 included eight studies with 14,917 patients. No significant effects of NSAIDs on CRC risk were detected. The pooled adjusted OR of CRC development after exposure to NSAIDs was 0.80 (95% CI, 0.39 to 1.21).<sup>95</sup> Despite the high heterogeneity in these studies, chemoprevention with NSAID did not exhibit protective effects.

#### 8. Chemoprevention with acetylsalicylic acid

The potential effects of acetylsalicylic acid (aspirin) on IBD-related CRC have been investigated. In three studies including 1,282 patients, no protective effect of aspirin against CRC development in IBD patients was detected (adjusted OR, 0.66; 95% CI, 0.06 to 1.39).<sup>95</sup> However, these studies did not record the accurate dose and duration of aspirin treatment. Favorable effects of aspirin were reported with longer duration of use (the risk reduction was 20% after 5 years of use and 30% after 10 years of use) and increasing dosage (100 mg/day conveys a risk reduction of 10%, and 325 mg/day conveys a risk reduction of 35%).<sup>96</sup> Currently, the evidence does not support the protective effect of aspirin against IBD-CRC.

#### 9. Guideline recommendations for chemoprevention

Table 1 summarizes the different consensus guidelines. The British Society of Gastroenterology (BSG),<sup>97</sup> ECCO,<sup>62</sup> and the Japanese Society of Gastroenterology recom-



**Table 1.** Summary of Consensus Guidelines for Chemoprevention

Consensus	5-ASA	Thiopurines	Other drugs
ECCO 2017	Evidence level 2	Insufficient evidence	Insufficient evidence
ACG 2019	Insufficient evidence	Insufficient evidence	Nil
BSG 2019	At least 2 g daily, strong recommendation, moderate-quality evidence	Weak recommendation, low-quality evidence	Insufficient evidence
JSGE 2020	Strong recommendation, low-quality evidence	Nil	Nil

ECCO, European Crohn's and Colitis Organisation; ACG, American College of Gastroenterology; BSG, British Society of Gastroenterology; JSGE, Japanese Society of Gastroenterology; 5-ASA, 5-aminosalicylic acid.

mended 5-ASA.<sup>98</sup> The recommendation was strong, but the evidence was moderate to low-quality. Thiopurine was suggested by the BSG.<sup>97</sup> However, the recommendation was weak and the evidence was low. The American College of Gastroenterology suggested good control of chronic inflammation and a surveillance strategy to prevent CRC development.<sup>99</sup> Despite several cohort studies and meta-analyses showing chemopreventive effects of 5-ASA and thiopurine against CRC, the data were inconsistent when adjusting for confounding factors, including inflammation severity.

## CONCLUSIONS

The overall prevalence of IBD-related CRC declined recently, but IBD patients still have a 1.7-fold increased risk of CRC. Controlled chronic inflammation and surveillance colonoscopy are important for the prevention of CRC in IBD patients. According to the 2017 ECCO consensus, the first colonoscopy should be scheduled 8 years after the onset of symptoms, and the next surveillance should be scheduled in 1 to 5 years according to the risk factors. Current evidence supports chemoprevention with mesalamine to reduce CRC among UC patients. Other compounds, including thiopurine, folic acid, statins, and TNF- $\alpha$  inhibitors, are controversial. An RCT to investigate the effects of chemoprevention is not feasible and would be unethical. However, large surveillance cohort studies with longer follow-up times are required to evaluate the impact of drugs on CRC risks.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

## ACKNOWLEDGEMENTS

The authors received research funds from Changhua Christian Hospital (109-CCH-IRP-008 and 110-CCH-IRP-020).

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## REFERENCES

1. Wei SC, Chang TA, Chao TH, et al. Management of ulcerative colitis in Taiwan: consensus guideline of the Taiwan Society of Inflammatory Bowel Disease. *Intest Res* 2017;15:266-284.
2. Yen HH, Hsu TC, Chen MW, Su PY, Chen YY. Clinical features and treatment of inflammatory bowel disease in a low-incidence area: a hospital-based retrospective cohort study in Taiwan. *Medicine (Baltimore)* 2021;100:e25090.
3. Yen HH, Su PY, Huang SP, et al. Evaluation of non-alcoholic fatty liver disease in patients with inflammatory bowel disease using controlled attenuation parameter technology: a Taiwanese retrospective cohort study. *PLoS One* 2021;16:e0252286.
4. Yen HH, Chen MW, Chang YY, Huang HY, Hsu TC, Chen YY. Predictive values of stool-based tests for mucosal healing among Taiwanese patients with ulcerative colitis: a retrospective cohort analysis. *PeerJ* 2020;8:e9537.
5. Yen HH, Weng MT, Tung CC, et al. Epidemiological trend in inflammatory bowel disease in Taiwan from 2001 to 2015: a nationwide populationbased study. *Intest Res* 2019;17:54-62.
6. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut* 2001;48:526-535.
7. Söderlund S, Brandt L, Lapidus A, et al. Decreasing time-trends of colorectal cancer in a large cohort of patients with

- inflammatory bowel disease. *Gastroenterology* 2009;136:1561-1567.
8. Jess T, Simonsen J, Jørgensen KT, Pedersen BV, Nielsen NM, Frisch M. Decreasing risk of colorectal cancer in patients with inflammatory bowel disease over 30 years. *Gastroenterology* 2012;143:375-381.
  9. Palli D, Trallori G, Bagnoli S, et al. Hodgkin's disease risk is increased in patients with ulcerative colitis. *Gastroenterology* 2000;119:647-653.
  10. Bernstein CN, Blanchard JF, Kliewer E, Wajda A. Cancer risk in patients with inflammatory bowel disease: a population-based study. *Cancer* 2001;91:854-862.
  11. Winther KV, Jess T, Langholz E, Munkholm P, Binder V. Long-term risk of cancer in ulcerative colitis: a population-based cohort study from Copenhagen County. *Clin Gastroenterol Hepatol* 2004;2:1088-1095.
  12. Jess T, Loftus EV Jr, Velayos FS, et al. Risk of intestinal cancer in inflammatory bowel disease: a population-based study from Olmsted county, Minnesota. *Gastroenterology* 2006;130:1039-1046.
  13. Jess T, Riis L, Vind I, et al. Changes in clinical characteristics, course, and prognosis of inflammatory bowel disease during the last 5 decades: a population-based study from Copenhagen, Denmark. *Inflamm Bowel Dis* 2007;13:481-489.
  14. Lutgens MW, van Oijen MG, van der Heijden GJ, Vleggaar FP, Siersema PD, Oldenburg B. Declining risk of colorectal cancer in inflammatory bowel disease: an updated meta-analysis of population-based cohort studies. *Inflamm Bowel Dis* 2013;19:789-799.
  15. Itzkowitz SH, Yio X. Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. *Am J Physiol Gastrointest Liver Physiol* 2004;287:G7-G17.
  16. Feagins LA, Souza RF, Spechler SJ. Carcinogenesis in IBD: potential targets for the prevention of colorectal cancer. *Nat Rev Gastroenterol Hepatol* 2009;6:297-305.
  17. McConnell BB, Yang VW. The role of inflammation in the pathogenesis of colorectal cancer. *Curr Colorectal Cancer Rep* 2009;5:69-74.
  18. Dirisina R, Katzman RB, Goretsky T, et al. p53 and PUMA independently regulate apoptosis of intestinal epithelial cells in patients and mice with colitis. *Gastroenterology* 2011;141:1036-1045.
  19. Mattar MC, Lough D, Pishvaian MJ, Charabaty A. Current management of inflammatory bowel disease and colorectal cancer. *Gastrointest Cancer Res* 2011;4:53-61.
  20. Bezzio C, Festa S, Saibeni S, Papi C. Chemoprevention of colorectal cancer in ulcerative colitis: digging deep in current evidence. *Expert Rev Gastroenterol Hepatol* 2017;11:339-347.
  21. Magro F, Gionchetti P, Eliakim R, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. *J Crohns Colitis* 2017;11:649-670.
  22. Choi CH, Rutter MD, Askari A, et al. Forty-year analysis of colonoscopic surveillance program for neoplasia in ulcerative colitis: an updated overview. *Am J Gastroenterol* 2015;110:1022-1034.
  23. Selinger CP, Andrews JM, Titman A, et al. Long-term follow-up reveals low incidence of colorectal cancer, but frequent need for resection, among Australian patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2014;12:644-650.
  24. Lennard-Jones JE, Morson BC, Ritchie JK, Williams CB. Cancer surveillance in ulcerative colitis. Experience over 15 years. *Lancet* 1983;2:149-152.
  25. Mathy C, Schneider K, Chen YY, Varma M, Terdiman JP, Mahadevan U. Gross versus microscopic pancolitis and the occurrence of neoplasia in ulcerative colitis. *Inflamm Bowel Dis* 2003;9:351-355.
  26. Choi CH, Ignjatovic-Wilson A, Askari A, et al. Low-grade dysplasia in ulcerative colitis: risk factors for developing high-grade dysplasia or colorectal cancer. *Am J Gastroenterol* 2015;110:1461-1471.
  27. Claessen MM, Lutgens MW, van Buuren HR, et al. More right-sided IBD-associated colorectal cancer in patients with primary sclerosing cholangitis. *Inflamm Bowel Dis* 2009;15:1331-1336.
  28. Jayaram H, Satsangi J, Chapman RW. Increased colorectal neoplasia in chronic ulcerative colitis complicated by primary sclerosing cholangitis: fact or fiction? *Gut* 2001;48:430-434.
  29. Kappelman MD, Farkas DK, Long MD, et al. Risk of cancer in patients with inflammatory bowel diseases: a nationwide population-based cohort study with 30 years of follow-up evaluation. *Clin Gastroenterol Hepatol* 2014;12:265-273.
  30. Nuako KW, Ahlquist DA, Mahoney DW, Schaid DJ, Siems DM, Lindor NM. Familial predisposition for colorectal cancer in chronic ulcerative colitis: a case-control study. *Gastroenterology* 1998;115:1079-1083.
  31. Koutroubakis IE, Regueiro M, Schoen RE, et al. Multiyear patterns of serum inflammatory biomarkers and risk of colorectal neoplasia in patients with ulcerative colitis. *Inflamm Bowel Dis* 2016;22:100-105.
  32. Sonnenberg A, Genta RM. Epithelial dysplasia and cancer in IBD strictures. *J Crohns Colitis* 2015;9:769-775.
  33. Fumery M, Pineton de Chambrun G, Stefanescu C, et al. Detection of dysplasia or cancer in 3.5% of patients with inflammatory bowel disease and colonic strictures. *Clin Gastroenterol Hepatol* 2015;13:1770-1775.
  34. Wijnands AM, de Jong ME, Lutgens M, et al. Prognostic

- factors for advanced colorectal neoplasia in inflammatory bowel disease: systematic review and meta-analysis. *Gastroenterology* 2021;160:1584-1598.
35. Bye WA, Ma C, Nguyen TM, Parker CE, Jairath V, East JE. Strategies for detecting colorectal cancer in patients with inflammatory bowel disease: a Cochrane systematic review and meta-analysis. *Am J Gastroenterol* 2018;113:1801-1809.
  36. Feuerstein JD, Rakowsky S, Sattler L, et al. Meta-analysis of dye-based chromoendoscopy compared with standard- and high-definition white-light endoscopy in patients with inflammatory bowel disease at increased risk of colon cancer. *Gastrointest Endosc* 2019;90:186-195.
  37. Watanabe T, Ajioka Y, Mitsuyama K, et al. Comparison of targeted vs random biopsies for surveillance of ulcerative colitis-associated colorectal cancer. *Gastroenterology* 2016;151:1122-1130.
  38. Yen HH, Wu PY, Su PY, et al. Performance comparison of the deep learning and the human endoscopist for bleeding peptic ulcer disease. *J Med Biol Eng* 2021;41:504-513.
  39. Huang TY, Zhan SQ, Chen PJ, Yang CW, Lu HH. Accurate diagnosis of endoscopic mucosal healing in ulcerative colitis using deep learning and machine learning. *J Chin Med Assoc* 2021;84:678-681.
  40. Correia FP, Lourenço LC. Artificial intelligence application in diagnostic gastrointestinal endoscopy-Deus ex machina? *World J Gastroenterol* 2021;27:5351-5361.
  41. Chang YY, Li PC, Chang RF, et al. Deep learning-based endoscopic anatomy classification: an accelerated approach for data preparation and model validation. *Surg Endosc* 2022;36:3811-3821.
  42. Yen HH, Wu PY, Chen MF, Lin WC, Tsai CL, Lin KP. Current status and future perspective of artificial intelligence in the management of peptic ulcer bleeding: a review of recent literature. *J Clin Med* 2021;10:3527.
  43. Chang YY, Yen HH, Li PC, et al. Upper endoscopy photodocumentation quality evaluation with novel deep learning system. *Dig Endosc* 2022;34:994-1001.
  44. Gutierrez Becker B, Arcadu F, Thalhammer A, et al. Training and deploying a deep learning model for endoscopic severity grading in ulcerative colitis using multicenter clinical trial data. *Ther Adv Gastrointest Endosc* 2021;14:2631774521990623.
  45. Maeda Y, Kudo SE, Ogata N, et al. Can artificial intelligence help to detect dysplasia in patients with ulcerative colitis? *Endoscopy* 2021;53:E273-E274.
  46. Pinczowski D, Ekblom A, Baron J, Yuen J, Adami HO. Risk factors for colorectal cancer in patients with ulcerative colitis: a case-control study. *Gastroenterology* 1994;107:117-120.
  47. Lyakhovich A, Gasche C. Systematic review: molecular chemoprevention of colorectal malignancy by mesalazine. *Aliment Pharmacol Ther* 2010;31:202-209.
  48. Luciani MG, Campregher C, Fortune JM, Kunkel TA, Gasche C. 5-ASA affects cell cycle progression in colorectal cells by reversibly activating a replication checkpoint. *Gastroenterology* 2007;132:221-235.
  49. Gasche C, Goel A, Natarajan L, Boland CR. Mesalazine improves replication fidelity in cultured colorectal cells. *Cancer Res* 2005;65:3993-3997.
  50. Mantena SK, Unnikrishnan MK, Joshi R, Radha V, Devi PU, Mukherjee T. In vivo radioprotection by 5-aminosalicylic acid. *Mutat Res* 2008;650:63-79.
  51. Nandi J, Saud B, Zinkievich JM, Palma DT, Levine RA. 5-aminosalicylic acid improves indomethacin-induced enteropathy by inhibiting iNOS transcription in rats. *Dig Dis Sci* 2008;53:123-132.
  52. Monteleone G, Franchi L, Fina D, et al. Silencing of SH-PTP2 defines a crucial role in the inactivation of epidermal growth factor receptor by 5-aminosalicylic acid in colon cancer cells. *Cell Death Differ* 2006;13:202-211.
  53. Chu EC, Chai J, Ahluwalia A, Tarnawski AS. Mesalazine downregulates c-Myc in human colon cancer cells. A key to its chemopreventive action? *Aliment Pharmacol Ther* 2007;25:1443-1449.
  54. Bos CL, Diks SH, Hardwick JC, Walburg KV, Peppelenbosch MP, Richel DJ. Protein phosphatase 2A is required for mesalazine-dependent inhibition of Wnt/beta-catenin pathway activity. *Carcinogenesis* 2006;27:2371-2382.
  55. Stolfi C, Pellegrini R, Franze E, Pallone F, Monteleone G. Molecular basis of the potential of mesalazine to prevent colorectal cancer. *World J Gastroenterol* 2008;14:4434-4439.
  56. Song M, Xia B, Li J. Effects of topical treatment of sodium butyrate and 5-aminosalicylic acid on expression of trefoil factor 3, interleukin 1beta, and nuclear factor kappaB in trinitrobenzene sulphonic acid induced colitis in rats. *Postgrad Med J* 2006;82:130-135.
  57. Carrat F, Seksik P, Colombel JF, Peyrin-Biroulet L, Beaugerie L; CESAME Study Group. The effects of aminosaliclates or thiopurines on the risk of colorectal cancer in inflammatory bowel disease. *Aliment Pharmacol Ther* 2017;45:533-541.
  58. Mak J, So J, Tang W, et al. Cancer risk and chemoprevention in Chinese inflammatory bowel disease patients: a population-based cohort study. *Scand J Gastroenterol* 2020;55:279-286.
  59. Qiu X, Ma J, Wang K, Zhang H. Chemopreventive effects of 5-aminosalicylic acid on inflammatory bowel disease-associated colorectal cancer and dysplasia: a systematic review with meta-analysis. *Oncotarget* 2017;8:1031-1045.
  60. Bonovas S, Fiorino G, Lytras T, Nikolopoulos G, Peyrin-Biroulet L, Danese S. Systematic review with meta-analysis: use of 5-aminosalicylates and risk of colorectal neoplasia in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2017;45:1179-1192.
  61. O'Connor A, Packey CD, Akbari M, Moss AC. Mesalamine,

- but not sulfasalazine, reduces the risk of colorectal neoplasia in patients with inflammatory bowel disease: an agent-specific systematic review and meta-analysis. *Inflamm Bowel Dis* 2015;21:2562-2569.
62. Harbord M, Eliakim R, Bettenworth D, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: current management. *J Crohns Colitis* 2017;11:769-784.
  63. Torres J, Bonovas S, Doherty G, et al. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. *J Crohns Colitis* 2020;14:4-22.
  64. Beaugerie L, Svrcek M, Seksik P, et al. Risk of colorectal high-grade dysplasia and cancer in a prospective observational cohort of patients with inflammatory bowel disease. *Gastroenterology* 2013;145:166-175.
  65. Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet* 2009;374:1617-1625.
  66. Lu MJ, Qiu XY, Mao XQ, Li XT, Zhang HJ. Systematic review with meta-analysis: thiopurines decrease the risk of colorectal neoplasia in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2018;47:318-331.
  67. Zhu Z, Mei Z, Guo Y, et al. Reduced risk of inflammatory bowel disease-associated colorectal neoplasia with use of thiopurines: a systematic review and meta-analysis. *J Crohns Colitis* 2018;12:546-558.
  68. Dobrzycka M, Spychalski P, Łachiniński AJ, Kobiela P, Jędrusik P, Kobiela J. Statins and colorectal cancer: a systematic review. *Exp Clin Endocrinol Diabetes* 2020;128:255-262.
  69. Qi XF, Kim DH, Yoon YS, et al. Involvement of oxidative stress in simvastatin-induced apoptosis of murine CT26 colon carcinoma cells. *Toxicol Lett* 2010;199:277-287.
  70. Bergman M, Salman H, Djaldetti M, Bessler H. Statins as modulators of colon cancer cells induced cytokine secretion by human PBMC. *Vascul Pharmacol* 2011;54:88-92.
  71. Ishikawa S, Hayashi H, Kinoshita K, et al. Statins inhibit tumor progression via an enhancer of zeste homolog 2-mediated epigenetic alteration in colorectal cancer. *Int J Cancer* 2014;135:2528-2536.
  72. Lim T, Lee I, Kim J, Kang WK. Synergistic effect of simvastatin plus radiation in gastric cancer and colorectal cancer: implications of BIRC5 and connective tissue growth factor. *Int J Radiat Oncol Biol Phys* 2015;93:316-325.
  73. Samadder NJ, Mukherjee B, Huang SC, et al. Risk of colorectal cancer in self-reported inflammatory bowel disease and modification of risk by statin and NSAID use. *Cancer* 2011;117:1640-1648.
  74. Ananthakrishnan AN, Cagan A, Cai T, et al. Statin use is associated with reduced risk of colorectal cancer in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2016;14:973-979.
  75. Shah SC, Glass J, Giustino G, et al. Statin exposure is not associated with reduced prevalence of colorectal neoplasia in patients with inflammatory bowel disease. *Gut Liver* 2019;13:54-61.
  76. Singh S, Edakkanambeth Varayil J, Loftus EV Jr, Talwalkar JA. Incidence of colorectal cancer after liver transplantation for primary sclerosing cholangitis: a systematic review and meta-analysis. *Liver Transpl* 2013;19:1361-1369.
  77. Khaderi SA, Sussman NL. Screening for malignancy in primary sclerosing cholangitis (PSC). *Curr Gastroenterol Rep* 2015;17:17.
  78. Boonstra K, Weersma RK, van Erpecum KJ, et al. Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis. *Hepatology* 2013;58:2045-2055.
  79. Soetikno RM, Lin OS, Heidenreich PA, Young HS, Blackstone MO. Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis: a meta-analysis. *Gastrointest Endosc* 2002;56:48-54.
  80. Singh S, Khanna S, Pardi DS, Loftus EV Jr, Talwalkar JA. Effect of ursodeoxycholic acid use on the risk of colorectal neoplasia in patients with primary sclerosing cholangitis and inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm Bowel Dis* 2013;19:1631-1638.
  81. Nagengast FM, Grubben MJ, van Munster IP. Role of bile acids in colorectal carcinogenesis. *Eur J Cancer* 1995;31A:1067-1070.
  82. Tung BY, Emond MJ, Haggitt RC, et al. Ursodiol use is associated with lower prevalence of colonic neoplasia in patients with ulcerative colitis and primary sclerosing cholangitis. *Ann Intern Med* 2001;134:89-95.
  83. Kim YJ, Hong KS, Chung JW, Kim JH, Hahm KB. Prevention of colitis-associated carcinogenesis with infliximab. *Cancer Prev Res (Phila)* 2010;3:1314-1333.
  84. Kopylov U, Vutcovici M, Kezouh A, Seidman E, Bitton A, Afif W. Risk of lymphoma, colorectal and skin cancer in patients with IBD treated with immunomodulators and biologics: a Quebec claims database study. *Inflamm Bowel Dis* 2015;21:1847-1853.
  85. Baars JE, Looman CW, Steyerberg EW, et al. The risk of inflammatory bowel disease-related colorectal carcinoma is limited: results from a nationwide nested case-control study. *Am J Gastroenterol* 2011;106:319-328.
  86. Alkhayyat M, Abureesh M, Gill A, et al. Lower rates of colorectal cancer in patients with inflammatory bowel disease using anti-TNF therapy. *Inflamm Bowel Dis* 2021;27:1052-1060.
  87. Raine T, Bonovas S, Burisch J, et al. ECCO guidelines on therapeutics in ulcerative colitis: medical treatment. *J Crohns Colitis* 2022;16:2-17.



88. Freudenheim JL, Graham S, Marshall JR, Haughey BP, Cholewinski S, Wilkinson G. Folate intake and carcinogenesis of the colon and rectum. *Int J Epidemiol* 1991;20:368-374.
89. Wien TN, Pike E, Wisløff T, Staff A, Smeland S, Klemp M. Cancer risk with folic acid supplements: a systematic review and meta-analysis. *BMJ Open* 2012;2:e000653.
90. Potack J, Itzkowitz SH. Colorectal cancer in inflammatory bowel disease. *Gut Liver* 2008;2:61-73.
91. Swinson CM, Perry J, Lumb M, Levi AJ. Role of sulphasalazine in the aetiology of folate deficiency in ulcerative colitis. *Gut* 1981;22:456-461.
92. Burr NE, Hull MA, Subramanian V. Folic acid supplementation may reduce colorectal cancer risk in patients with inflammatory bowel disease: a systematic review and meta-analysis. *J Clin Gastroenterol* 2017;51:247-253.
93. Velayos FS, Loftus EV Jr, Jess T, et al. Predictive and protective factors associated with colorectal cancer in ulcerative colitis: a case-control study. *Gastroenterology* 2006;130:1941-1949.
94. Rubin DT, Huo D, Kinnucan JA, et al. Inflammation is an independent risk factor for colonic neoplasia in patients with ulcerative colitis: a case-control study. *Clin Gastroenterol Hepatol* 2013;11:1601-1608.
95. Burr NE, Hull MA, Subramanian V. Does aspirin or non-aspirin non-steroidal anti-inflammatory drug use prevent colorectal cancer in inflammatory bowel disease? *World J Gastroenterol* 2016;22:3679-3686.
96. Bosetti C, Santucci C, Gallus S, Martinetti M, La Vecchia C. Aspirin and the risk of colorectal and other digestive tract cancers: an updated meta-analysis through 2019. *Ann Oncol* 2020;31:558-568.
97. Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut* 2019;68(Suppl 3):s1-s106.
98. Nakase H, Uchino M, Shinzaki S, et al. Evidence-based clinical practice guidelines for inflammatory bowel disease 2020. *J Gastroenterol* 2021;56:489-526.
99. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol* 2019;114:384-413.