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*REVIEW*

# Inflammatory bowel disease-related colorectal cancer: Past, present and future perspectives

Snehali Majumder, Uday Nagesh Shivaji, Rangarajan Kasturi, Alben Sigamani, Subrata Ghosh, Marietta Iacucci

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## Abstract

Inflammatory bowel disease-related colorectal cancer (IBD-CRC) is one of the most serious complications of IBD contributing to significant mortality in this cohort of patients. IBD is often associated with diet and lifestyle-related gut microbial dysbiosis, the interaction of genetic and environmental factors, leading to chronic gut inflammation. According to the "common ground hypothesis", microbial dysbiosis and intestinal barrier impairment are at the core of the chronic inflammatory process associated with IBD-CRC. Among the many underlying factors known to increase the risk of IBD-CRC, perhaps the most important factor is chronic persistent inflammation. The persistent inflammation in the colon results in increased proliferation of cells necessary for repair but this also increases the risk of dysplastic changes due to chromosomal and microsatellite instability. Multiple pathways have been identified, regulated by many positive and negative factors involved in the development of cancer, which in this case follows the 'inflammation-dysplasia-carcinoma' sequence. Strategies to lower this risk are extremely important to reduce morbidity and mortality due to IBD-CRC, among which colonoscopic surveillance is the most widely accepted and implemented modality, forming part of many national and international guidelines. However, the effectiveness of surveillance in IBD has been a topic of

much debate in recent years for multiple reasons — cost-benefit to health systems, resource requirements, and also because of studies showing conflicting long-term data. Our review provides a comprehensive overview of past, present, and future perspectives of IBD-CRC. We explore and analyse evidence from studies over decades and current best practices followed globally. In the future directions section, we cover emerging novel endoscopic techniques and artificial intelligence that could play an important role in managing the risk of IBD-CRC.

**Key Words:** Inflammatory bowel disease; Colorectal cancer; Colitis-associated cancer; Surveillance in inflammatory bowel disease; Dye-spray colonoscopy; Adenomas; Dysplasia; Colectomy

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**Core Tip:** The focus of the review is on the evolution of inflammatory bowel disease-related colorectal cancer (IBD-CRC) based on literature over the past decades to the present day. We provide a comprehensive overview of risk factors associated with IBD-CRC, molecular pathways identified and current strategies used to reduce incidence globally. We also touch upon the history of surveillance practice, its effectiveness, and the latest guidance on IBD surveillance by international societies. In a section on future directions, we discuss introduction of novel endoscopic technologies, artificial intelligence, and potential use of microbiota modulation, all of which could help reduce the risk of IBD-CRC.

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## INTRODUCTION

Chronic inflammation is known to be a major risk factor in the pathogenesis of cancer. Inflammatory bowel disease (IBD) is a chronic inflammatory condition affecting the gastrointestinal (GI) tract and IBD-related colorectal cancer (IBD-CRC) is one of its major and serious complications. Although only 1%-2% of IBD patients develop IBD-CRC, it contributes to about 15% of IBD-related mortality[1]. As per current long-term epidemiological data, the risk of CRC in IBD patients is high, particularly in patients with extensive ulcerative colitis (UC). Eaden *et al*[2] in their meta-analysis of 116 studies found that the incidence of IBD-CRC was 2%, 8% and 18% at 10, 20, and 30 years after the onset of UC, respectively. The role of Crohn's disease (CD) in the development of CRC is debatable and considered modest in comparison to UC. Canavan *et al*[3] in their meta-analysis estimated cumulative risk of 2.9% at 10 years, 5.6% at 20 years, and 8.3% at 30 years in patients with CD. However, factors like patient selection, sample size, duration of follow-up, completeness of case recruitment, and geographical differences may have influenced these estimates.

The severity of inflammation is a significant risk factor that increases the risk of IBD-CRC. Inflammation-related oxidative stress leading to genomic instability is considered the main trigger for the development of CRC. Studies on colonic tissue in IBD-CRC at the cellular and molecular level have found that the sequence of development of carcinogenesis is different from that observed in sporadic cancer in the non-inflamed colon. IBD-associated carcinogenesis follows an 'inflammation-dysplasia-carcinoma' sequence instead of the 'adenoma-carcinoma' sequence seen in sporadic CRC[4].

In this review article, we present a comprehensive overview of the literature on the epidemiology of IBD-CRC over decades, risk factors and pathogenesis including molecular pathways implicated. In addition, we present preventive strategies, current evidence for surveillance, the evolution of surveillance techniques with time, chemoprevention and explored which endoscopic technologies are likely to become standard for surveillance in the future. We have also touched upon the emergence of using diet and faecal microbiota modulation as a potential strategy in the future.

### *Trends in the incidence of IBD related CRC over decades*

Many recent population-based studies and meta-analyses have shown that the risk of IBD-CRC is lower than what has been previously reported, most of which were from studies done in tertiary referral centres. One probable reason for this difference could be that recent studies are more focused on selecting the right study population (included more severe cases), sample size and are more thorough with follow-up; completeness of study recruitment and geographical differences were perhaps taken into consideration while analysing their findings. The details of the study results that reported the

incidence of IBD-CRC over the last four decades are summarized in Table 1.

## RISK FACTORS OF IBD RELATED CRC

The risk factors of IBD-CRC can be broadly classified as factors that are genetic or familial and factors related to diet and lifestyle. These are illustrated in Figure 1A.

### *Age and disease duration*

The association between disease duration in IBD and probability of CRC is controversial. Studies published over the decades report different conclusions. Several studies have found that the incidence of IBD-CRC is higher among patients who develop IBD at a young age making duration of disease an important risk factor[2,5,6]. Another surveillance study published in 2015 by investigators at St Mark's Hospital, London followed up 1375 UC patients for 15234 patient-years (median, 11 years per patient) and IBD-CRC was detected in 72 patients [incidence rate (IR), 4.7 per 1000 patient-years]. Although the IR of early IBD-CRC was noted to have increased by 2.5-fold in the current decade compared with the past decade ($P$ = 0.045) it is reassuring that the 10-year survival rate was high (79.6%)[7]. A number of studies have concluded that in Crohn's colitis risk of CRC is similar to UC if the extension and duration of the disease are comparable[8,9].

### *Geographic variation risk*

In a meta-analysis, Zhou *et al*[10] found that Oceania has a higher incidence than other continents. In Asia, it was found that the risk of CRC among UC patients increased after 10-20 years of disease duration, whereas in Europe, the risk of CRC in UC showed no statistical difference in disease duration for 1-9 years, 10-20 years, 21-30 years, or more than 30 years. In North America, the risk of CRC among UC patients increased significantly after more than 30 years of disease detection.

### *Gender*

Gender is reported to be an important risk factor for IBD-CRC. In a large population-based cohort ($n$ = 7607) of individuals diagnosed with IBD from 1954 to 1989, the risk of CRC was found to be 60% higher in males aged < 45 years at diagnosis, with a relative risk (RR) of 1.6 [95% confidence interval (CI): 1.2-2.2] compared to females[11]. Similar findings were noted in a meta-analysis conducted by Jess *et al*[12] where men had a greater risk with a standardized IR (SIR) of 2.6 (95%CI: 2.2-3.0) compared to women (SIR of 1.9; 95%CI: 1.5-2.3).

### *Extensive UC*

In a study published in 1994, Gillen *et al*[13] reported a 19-fold increase in the risk of CRC in extensive UC compared to the general population (matched for age, sex, and disease duration). Similar findings were reported by Zhou *et al*[10] in a large meta-analysis that included 58 studies and 267566 UC patients; they found that disease extent-specific risk estimates for CRC in UC were reported in 21 of the 58 studies and that extensive UC and left-sided UC had a higher risk of CRC (SIR: 1.42, 95%CI: 0.83-2.42; SIR: 0.56, 95%CI: 0.38-0.83 respectively) compared to proctitis (SIR: 0.18, 95%CI: 0.01-0.03).

### *Primary sclerosing cholangitis*

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease and a significant proportion of patients with PSC also develop IBD[14], often characterized by pancolitis, rectal sparing, backwash ileitis, and importantly, a threefold increased risk of colorectal dysplasia[15,16]. PSC with CD phenotype has been observed to be less severe than PSC with underlying UC[15-17].

A multicentric retrospective cohort study involving 277 PSC-IBD patients found that the IR of CRC since PSC diagnosis at 3.3 cases per 1000 patient-years (95%CI: 1.9-5.6), with an IR of 61 PSC cases per 100000 IBD patient-years. Of these, 69.7% were male, 67.5% had UC, and the mean age at PSC diagnosis was 40 ± 16 years. PSC-IBD patients with symptoms of PSC at diagnosis were noted to have an increased risk of CRC[16].

### *Gut microbial dysbiosis*

Recent evidence suggests that intestinal microbiota; particularly the bacterial component plays a fundamental role in the health and progression of diseases such as IBD and CRC. The factors that are known to influence the gut microbiome are illustrated in Figure 1B.

The development of IBD is often associated with altered microbial communities (dysbiosis) in the gut, interaction of genetic and environmental factors leading to chronic inflammation in the intestine. According to the "common ground hypothesis", microbial dysbiosis and a leaky gut (due to intestinal barrier impairment)[18-20] are at the core of the chronic inflammatory process associated with IBD-CRC [21]. Several studies involving patient and gnotobiotic mouse models[22,23] have substantiated this hypothesis[24].

**Table 1 The difference in the incidence of inflammatory bowel disease related colorectal cancer, past and present**

| Epidemiology | | CRC in ulcerative colitis | CRC in indeterminate colitis | CRC in Crohn's disease |
|---|---|---|---|---|
| Annual incidence | Past | Stewénius *et al*[111], 1995, 1.4/1000 PYD; Eaden *et al*[2], 2001, 2/1000 PYD-after 10 yr of initial onset; 7/1000 PY (patients with extensive colitis 90%) 30 yr of initial onset; Castaño-Milla *et al*[112], 2012, 1.01/1000 PYD - after 10 yr of initial onset; 3.75/1000 PYD - after 20 yr of initial onset; 5.85/1000 PYD - after 30 yr of initial onset | Stewénius *et al*[111], 1995, 2.4/1000 PYD | Olén *et al*[113], 2020, a Scandinavian population-based cohort study 0.31 per 1000 PY(1968); Laukoetter *et al*[114], 2011, 0.5/1000 PYD |
| | Present | Fumery *et al*[115], 2017, the annual incidence of CRC was 0.8% (95%CI: 0.4-1.3) | | Olén *et al*[113], 2020, a Scandinavian population-based cohort study 0.47 per 1000 person-years (2017) |
| Risk | Past | Eaden *et al*[2], 2001, 0.3% after 30 yr of initial onset | | Canavan *et al*[3], 2006, 2.9% after 10 yr of initial onset; 5.6% after 20 yr; 8.3% after 30 yr. Friedman *et al*[116], 2008, 7% by 10th surveillance (patients with extensive colitis 90%). Basseri *et al*[117], 2012, 5.6% by 10$^{th}$ surveillance (patients with extensive colitis 55%) |
| | Present | Fumery *et al*[115], 2017, the risk of CRC was higher when LGD was diagnosed by an expert gastrointestinal pathologist (1.5%) than by community pathologists (0.2%). Factors significantly associated with dysplasia progression were concomitant: PSC (OR, 3.4; 95% CI: 1.5-7.8); Invisible dysplasia (*vs* visible dysplasia; OR, 1.9; 95% CI: 1.0-3.4), distal location (*vs* proximal location; OR, 2.0; 95% CI: 1.1-3.7); Multifocal dysplasia (*vs* unifocal dysplasia; OR, 3.5; 95% CI: 1.5-8.5) | Keller *et al*[118], 2019, IBD-CRC is responsible for approximately 2% of the annual mortality from CRC overall, but 10%-15% of the annual deaths in IBD patients | Olén *et al*[113], a Scandinavian population-based cohort study. Patients with Crohn's disease who were diagnosed with CRC were at increased risk of CRC mortality compared with reference individuals also diagnosed with CRC [HR 1.42 (1.16-1.75) when adjusted for tumour stage] |

PYD: Patient year days; LGD: Low-grade dysplasia; CRC: Colorectal cancer; IBD-CRC: Inflammatory bowel disease-related colorectal cancer; PSC: Primary sclerosing cholangitis; HR: Hazard ratio; OR: Odds ratio; CI: Confidence interval.

Studies have shown high densities of mucosa-associated bacteria[21,25], with the ability to produce a greater mass of biofilm and extracellular matrix were present in IBD patients[26]. These mucosae associated highly virulent bacteria are suspected to play a pivotal role in gut inflammation and tumorigenesis[21]. Some of the common gut commensals like *Helicobacter pylori*[27], *Fusobacterium nucleatum*[28], *Bacteriodes fragilis*[29], and *Campylobacter* species[30] have been implicated in gastric tumorigenesis and CRC[23]. In a study by Gevers *et al*[31] on new-onset treatment-naïve pediatric patients with CD and UC, an abundance of *Enterobacteriaceae*, *Bacteroides/Prevotella*, *Veillonellaceae*, and *Fusobacteriaceae* were seen in ileal and colonic biopsies. Although the role of microbial and host factors in disease pathogenesis has not been established in chronic gut inflammation and IBD-CRC, it can be hypothesized that the combined effect of host barrier defects and bacterial invasiveness may evoke a massive amount of immune hyperactivation in the gut mucosa. This is likely to ultimately lead to a vicious cycle of chronic inflammation driven by the malignant transformation of the gut epithelium[21].

## PATHOGENESIS OF CRC IN IBD

### *Molecular pathways and mechanisms*

The molecular pathogenesis of IBD-CRC is very different from sporadic CRC[32]. With the advent of molecular technology in recent years, the pathophysiology of the development of IBD-CRC has been extensively studied, and has led to better understanding of molecular mechanisms and identification of new biomarkers[32-34].

Numerous positive and negative regulators in the development of IBD-CRC have been identified which are illustrated in Figure 2. The process of development of IBD-CRC is triggered probably due to chromosomal and microsatellite instability through well-defined pathways (*Wnt* pathway, CIMP pathway), causing mucosal dysplasia[32]. The involvement of these pathways suggests that persistent inflammation plays a prominent role in carcinogenesis. The changes occurring in the micro-environment due to chronic inflammation are thought to be responsible for the increased risk. The chronic proliferation necessary to repair epithelial layer damage (caused by constant inflammation) enhances the risk of dysplasia[35]. Although multiple cytokines and pathways have been identified in the pathogenesis of IBD-CRC[32-34], it continues to be a topic of ongoing research. Further research will not only enhance our understanding but also help identify non-invasive biomarkers and targets of therapy. A summary of currently known molecular mechanisms is summarized in Table 2.

**Table 2 Cytokines implicated in tumorigenesis in the colon**

| Cytokines | The mechanism | Potential target of therapy? | Ref. |
|---|---|---|---|
| TNF-α | Triggers systemic inflammation and is one of the cytokines that make up the acute phase reaction in IBD and other chronic inflammatory diseases TNF-α regulates the induction MACC1 *via* the NF-κB subunit p65 and the transcription factor *c-Jun* in CRC cells | Yes: Anti TNF used to control inflammation in IBD; hence may reduce incidence of CRC but this is debatable | Pache *et al*[119], Kobelt *et al*[120] |
| IL-6 family | In the chronic phase of inflammation, IL-6 is able to activate almost all the cells of the body: trans-signalling-Increased formations of IL-6-sIL-6R complexes interact with gp130 on the membrane of CD4+T-cells and leads to an increased expression and nuclear translocation of STAT3, which causes the induction of anti-apoptotic genes, *e.g.*, *Bcl-xl*. This leads to resistance of lamina propria T-cells to apoptosis. T-cell expansion contributes to chronic intestinal inflammation | No: Anti IL-6 antibodies not successfully used in IBD. Unlikely to be useful in reducing risk of IBD-CRC | Atreya and Neurath[121], Allocca *et al*[122], Coskun *et al*[123], Danese *et al*[124] |
| IL-11 | IL-11 belongs to the IL-6 family of cytokines. IL-11 has pro-tumorigenic activities such as proliferation, self-renewal, invasion and angiogenesis | No: No evidence to suggest it could be used as therapeutic agent. Could be useful as a diagnostic and prognostic biomarker | Murakami *et al*[125], Johnstone *et al*[126], Ren *et al*[127], Unver and McAllister[128], Pastor *et al*[129], Putoczki *et al*[130] |
| IL-17 | IL-7 is a cytokine that helps the long-term survival of Th17 cells and innate lymphoid cells that express the transcription factor RORγt. It is suspected to be important for maintaining populations of T cells that induce and induce mucosal inflammation in IBD. IL-7 also maintains NKT cells that produce IL-17, using the PI3K/AKT/*mTOR* pathway | No: Anti-IL-17 medications are associated with IBD exacerbation | Hohenberger *et al*[131], Moschen *et al*[132] |
| IL-21 | IL21 plays a dual role: IL-21 deficiency as a novel cause of early-onset IBD in human subjects accompanied by defects in B-cell development. Reduced numbers of circulating CD19 (+) B cells, including IgM (+) naive and class-switched IgG memory B cells, with a concomitant increase in transitional B-cell numbers. IL-21 Overproduction: IL-21 plays an important role in sustaining tissue-damaging immune responses | Yes: Could be used as a potential new therapeutic target in CD but unclear if it will influence IBD-CRC | Di Fusco *et al*[133], Salzer *et al*[134] |
| IL-23 | IL-23R signalling affects disease susceptibility increased production of IL-23 by macrophages, dendritic cells or granulocytes has been observed in various mouse models of colitis, colitis-associated cancer and IBD patients | Yes: Currently in clinical trials for CD but too early to comment on effect on IBD-CRC | Moschen *et al*[132], Neurath[135] |

NKT: Natural killer cells; MACC1: MET transcriptional regulator; UC: Ulcerative colitis; IBD-CRC: Inflammatory bowel disease-related colorectal cancer; AKT/PKB: Protein kinase B; IL: Interleukins; TNF-α: Tumor necrosis factor-α; RORγ: DNA-binding transcription factor; *mTOR*: Mechanistic target of rapamycin; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K: Phosphoinositide 3-kinases; gp130: Glycoprotein 130; *Bcl-xl*: B-cell lymphoma-extra large; *c-Jun*: c-Jun proto-oncogene; p65: Nuclear factor NF-kappa-B p65 subunit.

### *TP53 and KRAS mutations*

Earlier studies have found *TP53* and *KRAS* mutations in IBD-CRC and sporadic CRC. However, the molecular pathway towards the progression of carcinogenesis is different[32,36,37]. Recent studies have shown that *TP53* mutations were detected among 70% of sporadic colorectal carcinomas[38] and that both loss and gain of function of *TP53* might promote malignancy at the late phase of carcinogenesis [39].

It has been reported that the adenomatous polyposis coli (*APC*) and *KRAS* mutations were significantly less common in IBD-CRCs than in sporadic CRCs (15% *vs* 53%, $P < 0.001$ and 20% *vs* 38%, $P = 0.02$, respectively)[38].

### *STAT3 and IL-6/p-STAT3 pathway*

The signal transducer and activator of transcription 3 (STAT3) pathway has been identified as an important one in the development of both sporadic CRC as well as IBD-CRC (Figure 3A). The exact mechanism is still not very well understood but it is reported to be due to signalling protein dysregulation and constitutive activation of STAT3[33,40]. Corvinus *et al*[41] showed in their murine model that constitutive STAT3 activation was persistent and important in CRC cells, possibly triggered by IL-6. Further, studies by other investigators have reported subsequently that STAT3 activation is associated with invasion, survival, and growth of CRC cells in mice *in vivo*[40,42]. Lin *et al*[40] have also demonstrated using both *in vitro* and *in vivo* models that blockade of IL-6/p-STAT3 (phosphorylated-STAT3) using an inhibitor suppressed tumour cell growth in colon cancer cells.

In human colonic tissue, patients with active colitis had significantly more IL-6 and p-STAT3-positive epithelial cells than both inactive UC and controls; in addition, they found that the proportion of suppressor of cytokine signalling 3 (SOCS3)-positive cells was lower in patients with dysplastic lesions and CRC. A study by Gui *et al*[43] that compared the expression of IL-6, STAT3, and SOCS3 in adenomas from IBD and non-IBD patients found significantly lower IL6, lower IL6R, higher STAT3, and lower SOCS3 expression in IBD associated dysplastic lesions.

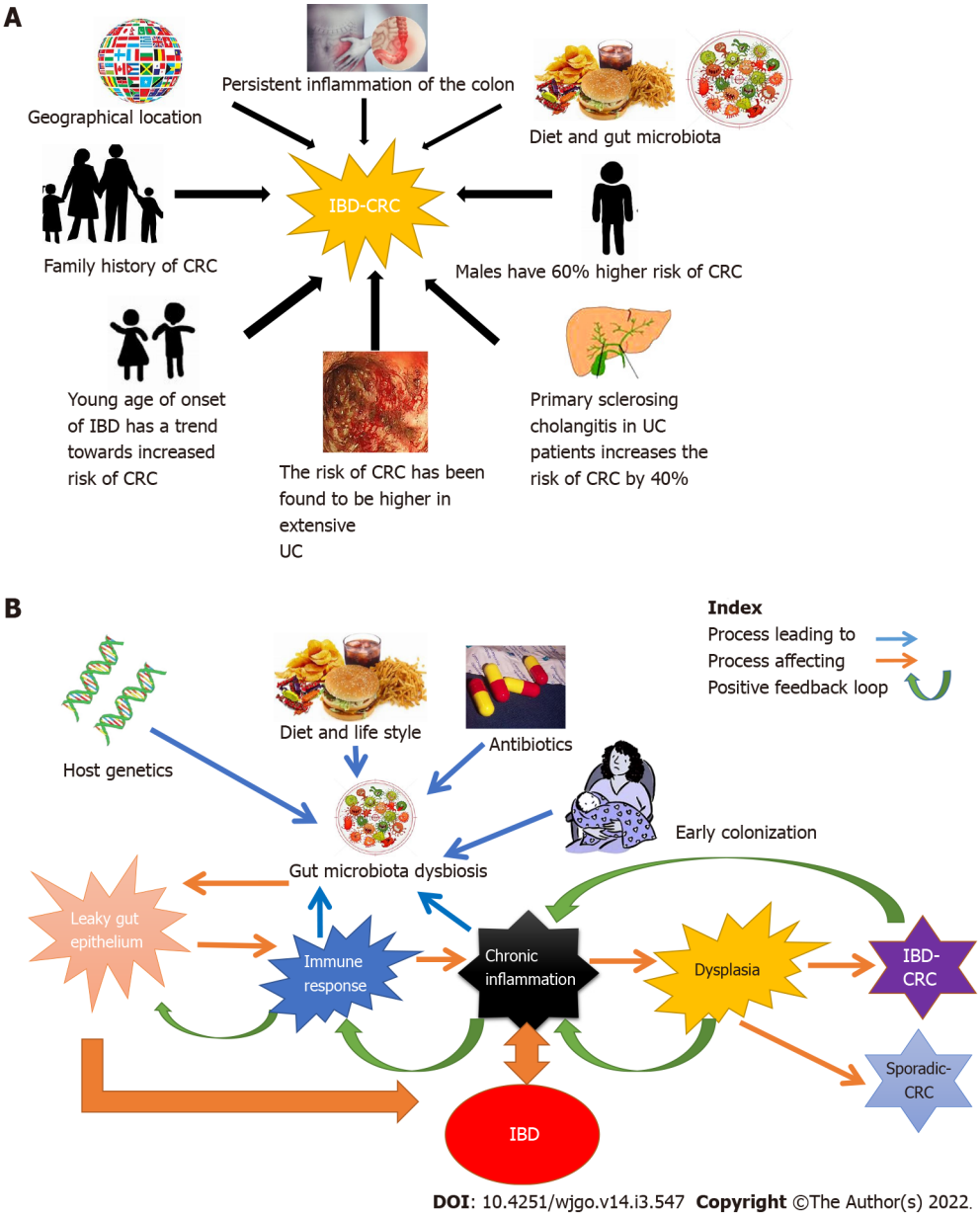


**Figure 1 Risk factors leading to the development of inflammatory bowel disease-related colorectal cancer and the role of gut microbiota in inflammatory bowel disease-related colorectal cancer.** A: Risk factors leading to the development of inflammatory bowel disease-related colorectal cancer (IBD-CRC). Risk factors are classified as familial and genetic. The factors are depicted in clockwise order: Genetic factors include a person's genetic makeup, family history of IBD and rarely monogenic causes of IBD. Younger age at diagnosis, male gender and durations of the disease has been identified as strong risk factors for IBD-CRC in longitudinal studies. The geographical location of the person, their diet, lifestyle, underlying diseases like extensive or left-sided ulcerative colitis, Primary sclerosing cholangitis, and other conditions causing persistent colon inflammation, are also known to increase the risk of development of IBD-CRC; B: Role of gut microbiota in IBD-CRC. Multiple factors such as diet, antibiotic use, and mode of birth and host genetic makeup influence/modulate the gut microbiota. This can lead to microbial dysbiosis mediated intestinal tissue damage causing intestinal barrier leak and mobilization of gut microbiota into host mucosa. The gut microbiota mediated break in the mucosal barrier, in turn, triggers an aggravated immune response leading to chronic inflammation. IBD, driven by an aberrant autoimmune response also leads to inflammation of the gut. This chronic inflammatory state leads to tissue damage causing dysplasia that can progress to cancer over time. CRC: Colorectal cancer; IBD: Inflammatory bowel disease; UC: Ulcerative colitis.

Overall, dysregulation of this signalling pathway plays an important role in triggering neoplasia. STAT3 pathway driven by IL-6 continues to be a topic of ongoing research and likely to be an attractive target with therapeutic potential.

### *The Wnt pathway*

The canonical *Wnt*-pathway (β-catenin mediated *Wnt*-signalling) regulates the proliferation and differentiation of colonic stem cells in the normal colon[44,45]. However, the loss of *APC* gene results in the shift of β-catenin from membrane to the nucleus. This causes increased transcription of cyclin D1 and *c-myc* genes, leading to carcinogenesis (Figure 3B)[32,46]. Claessen *et al*[32] in their study reported that the *Wnt* pathway was activated in the early phase of colitis-associated CRC, and in about 50% of IBD-

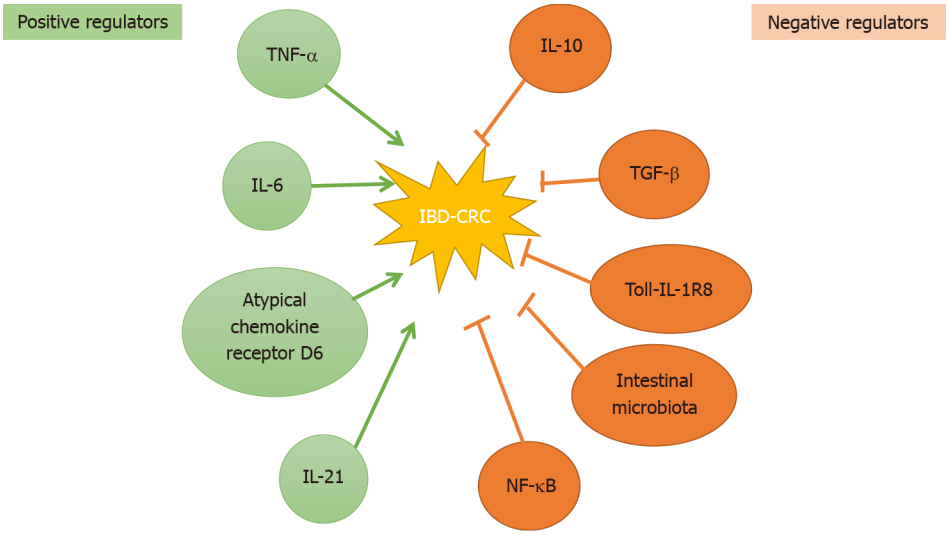


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**Figure 2 Molecular regulators of development of inflammatory bowel disease-related colorectal cancer.** Over the years numerous biological molecules and pathways have been identified that positively or negatively regulate the development of inflammatory bowel disease-related colorectal cancer. Microbial dysbiosis in conjunction with cytokines [tumor necrosis factor-α, interleukin (IL)-6 and IL-21] and chemokines (atypical chemokine receptor D6) drive intestinal immune response, in turn leading to chronic inflammation, tissue injury, dysplasia and cancer. The negative regulators including cytokines IL-10 and transforming growth factor-β, nuclear factor-kappa beta, Toll-like receptors, along with healthy gut microbiota prevent gut inflammation-mediated tissue injury and promote healing of damaged tissue. NF-κβ: Nuclear factor-kappa beta; TNF-α: Tumor necrosis factor-α; TGF-β: Transforming growth factor β; IL: Interleukin; CRC: Colorectal cancer; IBD: Inflammatory bowel disease.

associated neoplasia cases. Another significant finding was that the pathway was also activated in the surrounding regions of dysplasia associated with IBD, a phenomenon termed as "field-cancerization" [32]. They suggest that estimation of β-catenin can be used as a biomarker for colonic field cancerization, facilitating early detection of neoplasia during colonic surveillance[32]. It has been shown in other studies that β-catenin could potentially be used as a marker of survival[47,48] and prognosis[47].

### *Dysplasia*

CRC results from a series of genetic mutations that alter the normal growth pattern of cells, as a consequence of which, affected cells acquire a growth advantage over other cells. This aberration leads to morphological changes termed dysplasia. It was postulated that colorectal dysplasia could represent a premalignant lesion in IBD as early as 1949 by Warren and Sommers[49] and some years later in 1967 important observations that dysplasia originated from nonpolypoid mucosa were also reported by another group.

Historically, an elevated lesion containing dysplasia was referred to as a dysplasia-associated lesion or mass (DALM)[50]. The diagnosis of DALM became complicated over time because of the inconsistent criteria used in describing IBD-related dysplasia. The term DALM was also was being inaccurately always linked to colectomy[50]. However, with the advent of fibre optic endoscopic visualization techniques and improvement in localized surgical resection procedures the definition, classification, and management of dysplasia became more systematic[50-52]. The SCENIC guidelines in 2015 made important recommendations to standardize how lesions are described during surveillance. It was recommended that the term DALM be abandoned[53]. The term dysplasia redefined as an abnormal growth of cells, tissues, or organs leading to the development of abnormal histological or anatomical structures has now replaced the previously used term DALM[52] dysplasia is categorized as low-grade dysplasia (LGD) and high-grade dysplasia (HGD) based on the degree of histological abnormalities.

The identification of dysplastic changes is important as this is an important stage in the development of cancer and considered a strong predictor of CRC in IBD. Chronic intestinal inflammation is the primary risk factor that leads to LGD, which can then progress to HGD and eventually CRC[54] (Figure 4). This sequence of events is thought to be accelerated in IBD-CRC compared to sporadic CRC [54]. In a study de Jong *et al*[55] investigated the long-term risk of HGD and CRC following the development of LGD using a nationwide database identifying a large IBD patient cohort. The risk factors for advanced neoplasia progression were found to be age > 55 years at the time of LGD detection, male gender and follow-up at a tertiary IBD referral centre. The study also found that the incidence rate of progression to advanced neoplasia was 22% after 15 years of detection of IBD. Dysplasia in colonic strictures and epithelial dysplasia are both well-documented risk factors and considered to be precursors to the development of IBD-CRC[55,56]. In a case-control study among 53568 IBD patients undergoing colonoscopy, Sonnenberg and Genta[56] found that the prevalence of dysplasia was 3.22% and 2.08% in UC and CD respectively [odds ratio (OR) = 0.75, 95%CI: 0.65-0.86],

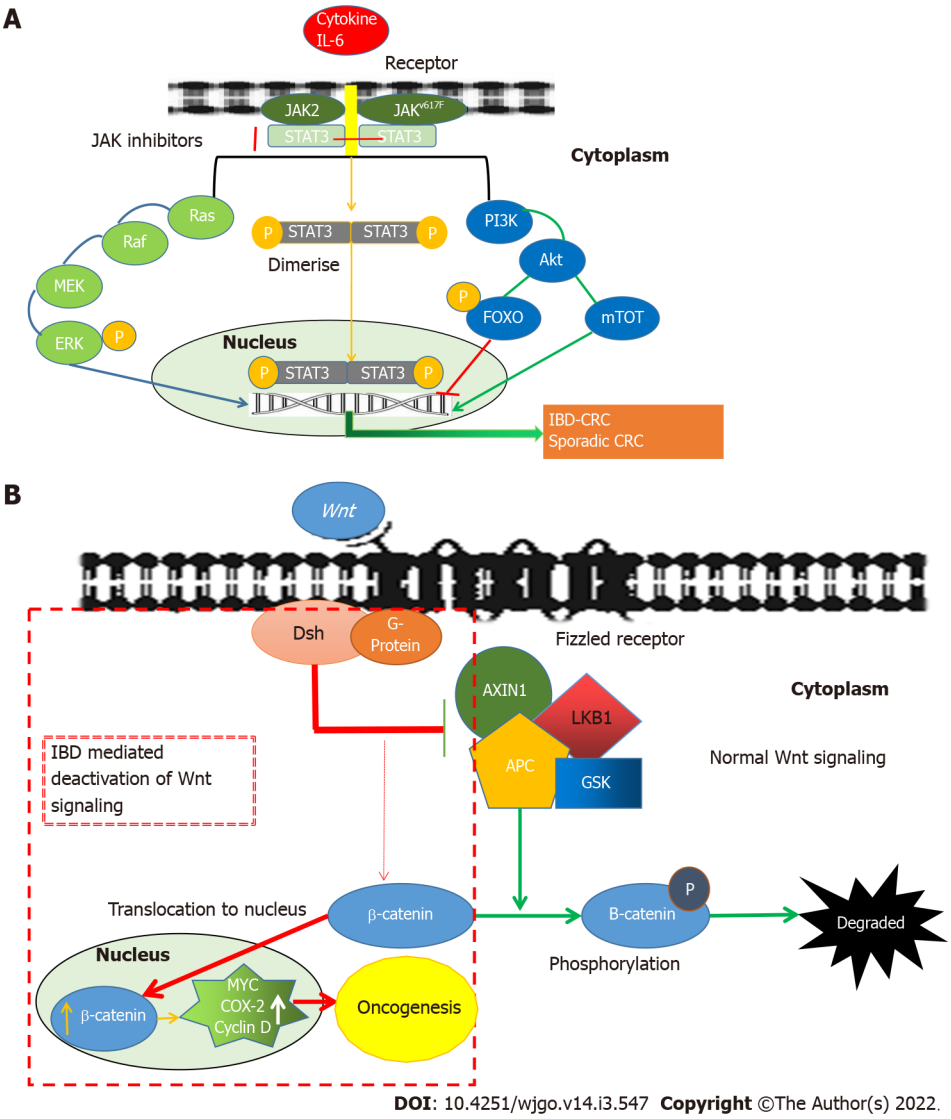


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**Figure 3 The inflammatory pathways leading to the development of IBD-related colorectal cancer.** A: The role of the JAK/STAT3 pathway in the development of IBD-related colorectal cancer. Various *in vivo* and *in vitro* models have shown that the JAK/STAT3 pathway plays a vital role in oncogenesis. The signal transduction of IL-6 involves the activation of JAK, activating transcription factors of the signal transducers and activators of STAT3. This is followed by its phosphorylation, dimerization and nuclear translocation of STAT3, initiating transcription of STAT3 target genes (including cyclin D1, *Bcl-xL*, *c-myc*, *Mcl1*, surviving and VEGF) leading to carcinogenesis. PI3K mediated activation of Forkhead box O3 (*FOXO*) leads to inhibition of gene transcription, whereas PI3K mediated activation of *mTOT* leads to oncogene transcription-mediated development of oncogenesis; B: The canonical *Wnt*-pathway in the development of IBD-related colorectal cancer. The canonical *Wnt*-pathway (*β-catenin* mediated *Wnt*-signaling) regulates proliferation and differentiation of the colonic stem cell in the normal colon. However, the loss of the adenomatous polyposis coli (*APC*) gene results in the shift of β-catenin from the membrane to the nucleus leading to increased transcription of cyclin D1 and *c-myc* genes thereby triggering carcinogenesis. IBD: Inflammatory bowel disease; CRC: Colorectal cancer; JAK: Juan kinase; P: Phosphorylation; STAT3: Signal transducer and activator of transcription proteins 3; PI3K: Phosphoinositide-3-kinases; Akt: RAC-alpha serine/threonine-protein kinase; FOXO: Forkhead box; *mTOT*: Mechanistic target of rapamycin; Ras: Small GTPase; Raf: Rapidly accelerated fibrosarcoma; MEK: Mitogen-activated extracellular signal-regulated kinase; ERK: Extracellular-signal-regulated kinase; Wnt: Wingless and int-1; Dsh: Dishevelled; AXIN: Axin-related protein 1; LKB1: Liver kinase B1; APC: Anaphase-promoting complex; GSK: Glycogensynthase kinase; MYC: *C-myc*; COX-2: Cyclooxygenase-2.

with a small increase in the prevalence of dysplasia within a stricture. The prevalence of cancer was higher in IBD patients with stricture compared to that without-0.78% and 0.11%, respectively (OR = 6.87, 95%CI: 3.30-12.89). A thirty-six-year analysis of a colonoscopic surveillance program found that in patients with UC who had undergone a colectomy due to HGD, 46% had a cancerous growth in the colon[57], thereby suggesting that the presence of HGD confers a high risk of synchronous cancer in the colon. Overall, dysplasia is a well-established histological stage in the development of IBD-CRC, and its detection during colonoscopy should prompt appropriate management to prevent progression to CRC. Surveillance programs are intended for the early detection of dysplastic lesions and strictures. In high-risk patients, surveillance helps in tracking disease progression in IBD patients. The intervals at which surveillance should take place vary from region to region, and based on guidelines by national societies. The British Society of Gastroenterology (BSG) recommends an intensified surveillance endoscopy program or a colectomy after the first 5 years of detection of LGD[58]. Other recommendations include

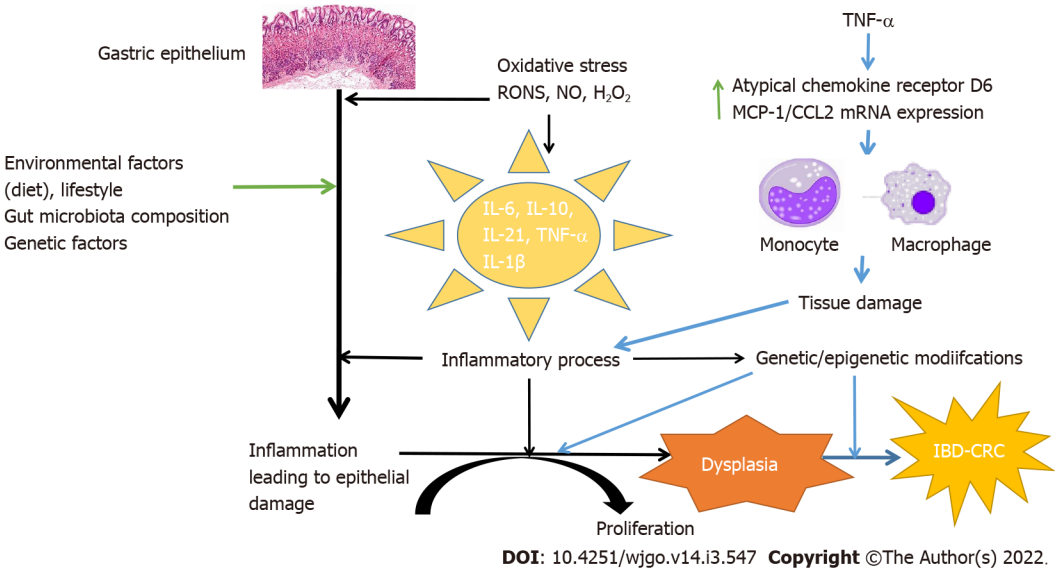


**Figure 4 Pathophysiology of inflammatory bowel disease-related colorectal cancer.** The pathophysiology of inflammatory bowel disease-related colorectal cancer (IBD-CRC) is different from sporadic IBD. IBD-CRC follows an "inflammation-dysplasia-carcinoma" sequence instead of the "adenoma-carcinoma" sequence as is seen in sporadic CRC. The pathophysiology associated with inflammation is at the heart of IBD-CRC. Various factors including genetic, familial along with numerous positive and negative molecular regulators and pathways have been identified which influence the development and maintenance of an inflammatory state. Inflammation leads to aberrant immune response leading to a chronic inflammatory state and gut tissue damage. Tissue damage and inflammation lead to dysplasia mediated carcinogenesis. CRC: Colorectal cancer; IBD: Inflammatory bowel disease; TNF-α: Tumor necrosis factor-α.

re-evaluation by a second pathologist if LGD is detected and further assessment by an expert endoscopist. The details of surveillance techniques are discussed in detail in the next section.

## STRATEGIES USED TO REDUCE THE INCIDENCE OF CRC IN IBD

### *Surveillance colonoscopy*

**Surveillance in IBD — the evolution of guidance and practice over time:** Surveillance in IBD could be described as the process of careful examination of the colon to detect early mucosal changes that may herald possible neoplasia. The mucosal changes/lesions (dysplasia of varying degrees) or adenomas provide an opportunity for early diagnosis and management of these lesions. There have been multiple studies in the past which have supported the use of surveillance as a tool to reduce cancer incidence in IBD. With the wider adoption of surveillance programmes over many years, long-term data have been in favour of regular surveillance of at-risk patients[7,59]. Over the last 2 decades, the practice of surveillance in IBD has largely been in line with guidance, which was mainly based on their large meta-analysis on the risk of IBD related CRC in 2001[2]. This landmark study, in particular, helped strengthen guidelines for regular surveillance. The summaries of recommendations are: Screening colonoscopy after 8-10 years that will also clarify disease extent for all patients; Regular surveillance to begin after 8-10 years for pancolitis and after 15-20 years for the left-sided disease; Reduced screening interval with increasing disease duration (due to increased risk in pancolitis); In the second decade of disease a colonoscopy to be conducted every three years, every two years for the third decade, and yearly by the fourth decade of disease; Two to four random biopsy specimens every 10 cm should be taken from the entire colon with additional samples of suspicious areas; Patients with PSC (including those with an orthotopic liver transplant) represent a subgroup at higher risk of cancer and they should have an annual colonoscopy.

These recommendations have been adopted by both the BSG and European Crohn's and Colitis Organisation (ECCO), with some minor differences and recent updates[60,61]. The core recommendations for surveillance remained stagnant for about twenty years. Recent advances in endoscopic technology and the use of new methods have meant that surveillance practices have started to change but can vary depending on the centre, availability of equipment, and expertise. The introduction of new technology has been matched by sound recommendations by the SCENIC guidelines and availability of newer endoscopic classification systems to help clinicians describe IBD-related dysplastic lesions whilst using these techniques. *e.g.*, the Frankfurt Advanced Chromoendoscopic IBD LEsions (FACILE) classification that has been developed, validated, and shown to be reproducible[62].

Although the SCENIC guidelines do not recommend routine use of Narrow Band Imaging (NBI) for surveillance, recent studies have shown that this could be a reliable modality. A large multicentre study by Watanabe *et al*[63] randomised 263 surveillance patients to either chromoendoscopy or surveillance

using NBI. The results showed no significant difference in lesion detection rates (10.7% *vs* 11.9%) and the duration of procedure was shorter with NBI (by 4 min; $P < 0.001$)[63]. Further, a study by Bisschops *et al*[64] found NBI to be significantly better than high definition chromoendoscopy images to differentiate neoplastic from non-neoplastic lesions among experts. The results of these studies indicate that the NBI may have a potential role in surveillance in the future and is likely to find a place in updated guidelines.

### How effective is surveillance?

The effectiveness of surveillance in IBD has been a topic of much debate over years for multiple reasons — cost-benefit to health systems, resource requirements, and also because studies show many conflicting data.

A Cochrane review by Collins *et al*[65] from 2006 looked into the effectiveness of surveillance in reducing the death rate from CRC in IBD. This study included a combination of prospective and retrospective studies that looked at the impact of surveillance on IBD-CRC. They reported on direct and indirect evidence to answer the question of the effectiveness of surveillance. The details of the studies included are given in Table 3. In summary, one study showed a dose-response to survival wherein a higher number of surveillance procedures were protective and increased survival, one showed that surveillance picked up CRC at an earlier stage and 5-year survival was better in the surveillance group compared to the non-surveillance group and another showed improved survival in the surveillance group compared to non-surveillance, but no improvement in mortality due to CRC. Some other studies have tried to estimate the economic benefits of surveillance. However, these models were calculated for sporadic cancers, and conclusions extended to IBD-CRC. It was shown that screening programs for normal individuals in the community have financial gains and therefore an argument has been made in favour of surveillance of high-risk patients with IBD. A more recent systematic review and meta-analysis by Bye *et al*[66] included observational studies of patients that included patients undergoing surveillance. Their pooled analysis showed a reduction in IBD-CRC in patients undergoing surveillance by 42% and IBD-CRC-related death by 64%, compared to those who did not undergo surveillance[66]. Current literature appears to favour surveillance and therefore it is part of standard service provision in many endoscopy centres.

### Impact of using different biopsy techniques and endoscopic modalities

Random biopsies during surveillance colonoscopy had been standard practice, which was a labour-intensive process not only for the endoscopist but also the pathologist. Studies that looked at accuracy of targeted biopsies changed the landscape of surveillance making it more efficient without compromising on the accuracy of detecting neoplasia.

### Targeted biopsies and white light endoscopy

In a key prospective exploratory trial, Watanabe *et al*[67] randomised chronic UC patients undergoing surveillance to either have targeted biopsies (from lesions detected) or step-wise multiple biopsies (random biopsies every 10 cm). The patients underwent high-definition white-light endoscopy (HD-WLE) in most cases. The investigators found that the detection of neoplasia was significantly higher in the target biopsy group compared to random biopsies (6.9% *vs* 0.5%), with a lower mean number of biopsies in the targeted group (34.8 *vs* 3.1; $P < 0.001$) and shorter examination time, concluding that targeted biopsies were as effective as random biopsies and more cost-effective[67]. This finding has been suggested in other studies, thereby indicating random biopsies could still be useful in select high risk patients, in line with the 2019 European Society of Gastrointestinal Endoscopy (ESGE) recommendations [68].

### Dye-chromoendoscopy

Dye-chromoendoscopy (DCE) is currently the standard of care for surveillance colonoscopy in IBD as it has been reported to aid the detection of subtle mucosal lesions. A prospective randomised trial that compared DCE using methylene blue with conventional endoscopy reported more accurate findings with better ability to differentiate between neoplastic and non-neoplastic lesions in patients with long-standing UC. Another prospective study by Marion *et al*[69] in 2008 compared the same techniques with randomised and targeted biopsies in a cohort of 102 patients with IBD. DCE detected significantly higher number of dysplastic lesions compared to random biopsies[69]. A large systematic review and network meta-analysis found DCE to have a significantly higher diagnostic yield for neoplastic lesions compared to WLE[70]. This technique is therefore recommended for surveillance endoscopy by the ESGE.

### Virtual chromoendoscopy

Virtual electronic chromoendoscopy (VCE) or dyeless virtual chromoendoscopy uses image enhanced technology (I scan) that has been introduced in recent years but already increasingly adopted by expert endoscopists for surveillance colonoscopy. A retrospective study by Gasia *et al*[71] compared various technologies namely standard WLE, high definition WLE, DCE, VCE, and also strategies of targeted

**Table 3 Summary of studies over decades reporting on surveillance in inflammatory bowel disease**

| Ref. | Number of patients and cohort | Results | Conclusions benefit-yes/no |
|---|---|---|---|
| Rosenstock *et al*[136], 1985, Retrospective Review | 248 chronic UC patients | In this cohort of patients: Overall incidence of HGD was 6%; HGD or carcinoma found in 24 procedures in 16 patients, mean disease duration of 16 yr, 15 patients had HGD; DALM most consistent indicator of carcinoma. > 95% of cancers 6 recognized at colonoscopy | The presence/absence of dysplasia a reliable histological marker that correlates with the presence/absence of cancer in UC. DALM with HGD had the strongest indication for surgery. Benefit- yes |
| Lashner *et al*[137], 1990, Prospective surveillance programme | 99 patients with pancolitis | In this cohort of patients: Both groups comparable in terms of age at onset, disease duration and gender; Total 8 fewer deaths in the surveillance group ($P < 0.05$); Colectomy was less common and was performed 4 yr later in the surveillance group ($P < 0.05$) | Screening in UC associated with improved survival and delayed colectomy. Findings did not show improvement in cancer-related survival. Benefit-equivocal |
| Löfberg *et al*[138], 1990, 15-yr Prospective surveillance programme | 72 UC, 12 patients developed definite dysplasia | In this cohort of patients: LGD detected in 7 patients; HGD in 4 and 1 Dukes' Stage-A cancer at operation; The cumulative risk of developing at least LGD was 14% after 25 yr of disease; Abnormal, aneuploid DNA content detected in biopsies of 12/59 patients (20.3%) this correlated significantly with LGD and HGD | Long-term use of surveillance in UC is reliable in detecting dysplasia and identify patients for prophylactic surgery. Benefit-yes; Earlier detection of neoplasia |
| Nugent *et al*[139], 1991, 13-yr Prospective surveillance programme | 213 UC patients | In this cohort of patients: A total of 15 patients underwent colectomy; A total of 7 patients had unsuspected carcinoma at various stages; Dysplasia detected among 11 patients; No difference in the prevalence of dysplasia between left-sided v/s extensive disease; No carcinoma detected among 175 patients without dysplasia on initial biopsies | Surveillance programme effective aid in reducing the risk of carcinoma in UC. Short term risk of CRC low if biopsy negative. Colectomy deferred in this group. Benefit-yes |
| Lynch *et al*[140], 1993, Prospective surveillance(between 1978 and 1990) | 160 UC patients | In this cohort of patients: A total of 739 colonoscopies carried out (4.6 colonoscopies/per patient); A 709 patient-years follow-up was carried out; In 1 patient Dukes's A cancer was detected; IBD-CRC caused the death of 1 patient; Overall, 9 IBD-CRC cases were diagnosed during the study period but only 1 case was detected by way of the surveillance programme | Results of this large study with long follow-up cast doubts on the effect-iveness of the surveillance programmes in detecting CRC in patients with UC. Benefit-no |
| Jonsson *et al*[141], 1994, Prospective, longitudinal study between 1977 and 1991 | 131 patients with UC | In this cohort of patients: A total of 632 colonoscopies performed, dysplasia was diagnosed in 24 (4 HGD), other than those with cancer; CRC diagnosed in 4 patients, of whom 2 included in the programme with a diagnosis of cancer; CRC and dysplasia are seen mainly in the left colon and in pancolitis patients | The surveillance programme was resource consuming and the cost-benefit must be questioned. Benefit-no. No cost-benefit as per authors |
| Karlén *et al*[142], 1998, Prospective case-control study | 4664 patients with UC, 142 patients with definite UC | In this cohort of patients: In 2 out of 40 patients with UC and 18/102 controls had at least one-surveillance colonoscopy (RR 0.29, 95% CI: 0.06-1.31); Out of 12 controls, only one patient with UC had two or more surveillance colonoscopies (RR 0.22, 95%CI: 0.03-1.74), indicating a protective dose-response relation | Surveillance may be associated with decreased risk of death from CRC in patients with long-standing UC. Benefit-yes. May improve survival |
| Friedman *et al*[143], 2001, Prospective Longitudinal study | 259 patients with chronic Crohn's colitis | In this cohort of patients: A total of 663 examinations were performed on 259 patients; The median interval between examinations was 24 mo; More frequent examinations were carried out(1-6 mo) in patients with dysplasia; Dysplasia or cancer was detected in 16% (10 indefinite, 23 LGD, 4 HGD and 5 cancers); Definite dysplasia or cancer was associated with age > 45 yr and had increased symptoms | Colonoscopic surveillance should be strongly considered in chronic extensive Crohn's colitis. Benefit-yes. May improve survival |
| Biasco *et al*[144], 2002, Prospective Longitudinal study (20 yr duration) | 65 patients with UC > 7 yr | In this cohort of patients: A total of 23 (35.3%) patients had surgery; A total of 29 (44.66%) patients discontinued the programme; Only 11 (16.9%) patients have remained in the programme | Results cast some doubts on the significance of such a programme and on its long-term feasibility. Benefit-no. Long-term feasibility doubtful |
| Hata *et al*[145] 2003, Retrospective January 1979 and December 2001 | 217 UC patients | In this cohort of patients: A total of 15 patients were detected to have definite dysplasia; Among 5/15 proved to have invasive cancer in resected specimens; cumulative risk for development of definite dysplasia at 10, 20 and 30 yr was 3.1%, 10.0%, and 15.6% respectively; A cumulative risk for the development of invasive cancer at 10, 20, and 30 yr was 0.5%, 4.1%, and 6.1%, respectively | The surveillance programme is useful for detecting IBD-CRC and survival may be improved by surveillance colonoscopy. Benefit-yes. May improve survival |

UC: Ulcerative colitis; IBD-CRC: Inflammatory bowel disease related colorectal cancer; LGD: Low-grade dysplasia; HGD: High-grade dysplasia; DALM: Dysplasia-associated lesion/mass; RR: Relative risk; CI: Confidence interval.

biopsies *vs* random. They found targeted biopsies to be better at neoplasia detection across all technologies except standard WLE. In a prospective randomised trial by the same investigating group, Iacucci *et al*[72] randomised patients with long-standing colitis into three arms: WLE, DCE, and VCE. In this non-inferiority study, VCE was found to be non-inferior to DCE in the detection of all neoplastic lesions. ESGE now strongly recommends the use of VCE or dye-spray with targeted biopsies for surveillance of

colon with quiescent disease[68].

### Chemoprevention of CRC

Chemoprevention in cancer is a term used for the use of pharmacological agents to reduce or delay the risk of carcinogenesis or progression of the disease[73,74]. Although there have been multiple drugs investigated for their potential, mesalazine currently has the largest evidence base to support its use for chemoprevention in CRC[74-76].

**Mesalazine:** Mesalazine or 5-aminosalicylic acid (5-ASA), a structural analogue of aspirin, has been used for many decades as first-line therapy for mild-to-moderate UC in oral and topical forms. In addition to its anti-inflammatory properties, it has received much attention for its chemopreventive effects. The drug appears to exert its effects through multiple mechanisms. A systematic review that looked into molecular mechanisms of chemoprevention of CRC was published in 2009. Lyakhovich and Gasche[74] in this study summarised that 5-ASA inhibits cyclooxygenase-2 (COX-2)/prostaglandin E2 synthesis, decreases the transcriptional activity of NF-κB by modulating RelA/p65 phosphorylation, and interferes with the Wnt pathway through protein phosphatase 2A. Multiple other systematic reviews have reported on the chemoprotective effects of 5-ASA. Velayos *et al*[77] included nine studies with 1932 UC patients in their systematic review and meta-analysis and reported a protective effect of 5-ASA in IBD-CRC and CRC/dysplasia. A large meta-analysis by Qiu *et al*[76] comprising of 26 studies with > 15000 patients (UC + CD) reported a chemopreventive effect on CRC but not dysplasia. A dose of > 1.2 g/d was effective to reduce the risk. Another meta-analysis reported that 5-ASA was protective against CRC and dysplasia with a strong protective effect noted in UC but a non-significant effect in CD [78].

With many reporting on the mechanisms of 5-ASA in reducing the risk of CRC, it is plausible that it has a chemopreventive effect in IBD and can be used in this cohort of patients.

**Thiopurines:** Thiopurines have been used for many decades in the management of IBD. There have been no randomised studies to investigate the efficacy of thiopurine therapy and current evidence is from cohort, case-control or population-based studies, with conflicting reports. A systematic review by Jess *et al*[79] in 2014 reported no protective effect of thiopurine therapy on CRC in IBD patients. The studies included carried heterogeneity and included clinic-based cohort and case-control studies, but no population-based studies. The lack of protective effect may be explained due to the inclusion of studies with patients at a severe spectrum of disease[79].

Another systematic review and meta-analysis by Lu *et al*[80] reported in 2018 on 24 observational studies involving 76999 participants to evaluate the risks of developing CRC in IBD patients on thiopurines. The authors found an overall protective effect of thiopurine use on CRC in patients with IBD (OR = 0.63, 95%CI: 0.46-0.86) in a pooled estimate and the effect was significant in UC patients (OR = 0.67, 95%CI: 0.45-0.98), but not in CD patients (OR = 1.06, 95%CI: 0.54-2.09). Interestingly, the authors also reported that the protective effect was limited to clinic-based and case-control studies but no population-based studies.

**Aspirin/non-steroidal anti-inflammatory drugs:** Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) have been studied for their chemo-preventive properties in the context of sporadic CRC. The elevated levels of COX-2 expression found in most CRC meant that NSAIDs and selective COX-2 inhibitors (COXIBs)[81] carry the potential for use in chemoprevention. A large, randomised study reported a reduction in metastatic disease in CRC with aspirin use[82]. Although the mechanisms make these medications attractive options, there have been no prospective studies done to study their efficacy in the context of IBD-CRC. A systematic review and meta-analysis by Burr *et al*[83] reported on the effect of aspirin and NSAIDs on IBD-CRC. They found only 9 retrospective studies in IBD which included the use of either or both these drugs with CRC as one of the outcomes. The authors concluded that the studies presented several limitations including selection bias as well as confounding. Also, the number of patients included was a small and overall large variation in studies that led to no strong conclusions[83].

At present, the use of aspirin or NSAIDs as chemopreventive agents is not part of any guidelines. This is unlikely to change as large prospective studies that study IBD-CRC are unlikely to be carried out.

**Folic acid:** IBD leads to impaired folate absorption. Folate is involved in DNA methylation and may produce epigenetic changes that affect the gut microbial and host immune interactions[84]. Folic acid has been investigated in the past as a chemopreventive agent. The effect of folate supplementation on dysplasia and cancer in IBD was first reported by Lashner *et al*[85] in a case-control study. In this study, all patients with pancolitis of > 7-year duration (except those with known HGD and invasive cancer) in the surveillance program exposed to folate supplements were compared to the control group (patients in the surveillance program, no dysplasia and not exposed to folate). Although folate supplementation was associated with a 62% lower incidence of dysplasia or cancer, the duration, and dose of folate intake were unclear, and results did not reach statistical significance probably because it was underpowered. Another retrospective study by the same group reported that the relative risk of neoplasia was lower (0.54) with folate supplementation (after at least 6-mo of exposure). The authors concluded that daily

folate supplementation may protect against the development of neoplasia in UC, although the results did not reach statistical significance.

The effects of folate supplementation were best summarised by a systematic review and meta-analysis by Burr *et al*[86] in which they included ten studies with low to moderate heterogeneity and a total of 4517 patients. The authors concluded that the results showed a pooled hazard ratio of 0.58 (95%CI: 0.37-0.80) suggesting an overall protective effect for folate supplementation on the development of IBD-CRC[86].

While there is weak evidence from retrospective studies in favour of folate supplementation, in the absence of prospective randomised data to support this, it is unlikely that folic acid will be used routinely for chemoprevention. At present, it is not part of guidelines by most national and international societies despite it being a cheap, safe, and well-tolerated supplement.

### Surgery

Surgery in the form of colectomy remains an important and effective strategy in preventing IBD-CRC, particularly in patients who have HGD or 'indefinite' dysplasia or invisible dysplasia detected on biopsies. Among visible lesions seen during endoscopy, polypoid lesions and some non-polypoid lesions with LGD in selective cases can generally be managed with endoscopic resection if full resection can be achieved, and further surveillance may be a reasonable option as per current guidelines[61].

However, non-polypoid lesions that cannot be managed endoscopically or the presence of invisible dysplasia regardless of degree are considered high-risk for progression to cancer and therefore recommended to undergo surgery[61].

The presence of visible dysplasia perhaps is relatively straightforward with the grade of dysplasia determining the intensity of future surveillance or need for surgery, but invisible dysplasia poses a challenge. Although the proportion of invisible dysplastic lesions is low due to the use of advanced endoscopic techniques[87], the detection of such lesions can present a dilemma in management, particularly because patients do not readily accept colectomy despite physician recommendations[88].

The risk of cancer with visible LGD has been known to be low with a larger body of evidence. In a retrospective study by Ten Hove *et al*[89], the incidence rate of advanced cancer was low at 1.34 per 100 years in patients with LGD after a follow-up of nearly 5 years, with no significant difference between chromoendoscopy and WLE and a systematic review by Kabir *et al*[90] reported a pooled estimated rate of cancer in visible LGD at 2.7%. However, there is very little data available on invisible dysplasia. In their systematic review, Kabir *et al*[90] reported that pooled estimates of cancer due to invisible HGD and invisible LGD were 11.4% and 2.4% respectively, based on two cohort studies and one case series. With such a high risk of progression to cancer, surgery should be considered as a serious and realistic option in reducing the risk of IBD-CRC.

### Diet therapy and gut microbiota modulation

Our better understanding of the human gut microbiome has opened up a new possibility of treatment for IBD and IBD-CRC[91]. Recent molecular level research on the gut microbiota using whole-genome sequencing technology has proved that some factors can alter the microbiome and the pathogenesis of IBD[92].

It has been hypothesized that diet plays a key role in the modulation of the gut microbiota composition. Gut microbiota in turn plays a major role in maintaining gut homeostasis and is associated with the modulation of host inflammatory and immune responses[93]. Studies have shown that nutritional components (added sugars, trans-fats, omega-6 fatty acids, red processed meat *etc*.) contribute to a chronic inflammatory condition by regulating various immune and inflammatory pathways[94,95]. Diet has been identified as one of the vital factors associated with CRC etiology[94,96].

Dietary therapy is also considered to be helpful, especially in children with CD who receive exclusive enteral nutrition[95,97]. Therefore, microbiome-modulating interventions like the application of probiotics[98,99], prebiotics[97,100,101], antibiotics, faecal microbiota transplantation (FMT)[102,103], and gene manipulation is being widely explored as new treatment options for a large number of chronic inflammatory diseases including UC, CD, and CRC. Genetic studies involving IBD patients reported 163 IBD susceptibility gene loci. These loci were found to be involved in regulating the host and gut microbes' interactions[104,105]. Mechanistically, it is plausible that by correcting the gut microbiota composition, the innate immune system can be modulated, leading to lesser inflammatory damage to the gut epithelium. This could enhance gut barrier function, prevent pathogen colonization and exert selective cytotoxicity against tumour cells[92]. These actions could break the vicious cycle of inflammation-mediated dysplasia.

### Future directions

**Advanced endoscopic technologies:** There have been several recent advances made with novel endoscopic technologies such as endocytoscopy, confocal laser endomicroscopy (CLE), both of which allow examination of the bowel mucosa with histology-like images at 500-fold to 1000-fold magnification, allowing *in vivo* evaluation in real-time.

Endocytoscopy has been reported to be effective in recognising low-grade adenoma in the colon [106]. Its utility in IBD surveillance has not been evaluated thoroughly yet and is a subject of research. There is evidence that CLE is a useful tool in assessing dysplasia, with a stronger evidence base in the evaluation of Barrett's oesophagus. It has been studied in the context of IBD and shown to increase the rate of detection of neoplastic lesions. In a consensus-based report on the applications of CLE, although there was wide agreement that CLE can detect dysplasia effectively in IBD[107], its adoption is limited by cost and lack of expertise. This is likely to change in the future as endoscopists become more familiar with the technology and wider use may drive down costs.

Full-spectrum endoscopy (FUSE) is an emerging technique that employs two lateral additional cameras to a standard colonoscope, allowing operators to view behind folds and blind spots. Leong and Koo[1] investigated its ability to detect dysplastic lesions in a robust study design involving patients undergoing surveillance. They prospectively randomised 52 patients to either standard colonoscopy or FUSE and then crossed over to the other group for a repeat procedure. FUSE missed significantly fewer dysplastic lesions compared to standard (25% *vs* 71.4%) with a slightly longer withdrawal time. Kudo *et al*[108] reported similar findings in their tandem colonoscopy trial. The advantages of this technique are apparent but are currently not part of guidelines and recommendations by relevant societies. Further research and familiarity with the technique are likely to encourage more clinicians to use this for surveillance.

**Artificial intelligence:** The next generation of advancement comes in the form of using artificial intelligence (AI) in endoscopy. AI is currently being used widely in innumerable areas and its applications are seemingly unlimited. AI in IBD has been evaluated by Stidham *et al*[109] where they found that performance of deep learning models was similar to experienced human reviewers when grading endoscopic severity in UC. AI built into endoscopic systems to aid detection of dysplastic lesions is currently a subject of research globally, with few early reports available in literature[110].

**Microbiota modulation:** The discovery of microbiota-regulated mucosal and systemic immune response pathways have opened up avenues to explore the impact of this response on the development of cancer immunotherapies. However, it should also be considered that an individual's commensal gut microbiota keeps evolving and changing throughout the lifetime based on various environmental factors[23]. This phenomenon plays a pivotal role in phenotypic variation in disease development, progression, and therapeutic success among individuals. Therefore, it will not be wrong to hypothesize that future gut microbiota modulating therapies need to be personalized according to an individual's microbiota.

## CONCLUSION

IBD-related CRC is a serious complication that deserves attention. The evolution of strategies in reducing this risk over decades is interesting. Although surveillance is now the cornerstone of early detection of neoplasia, the key to reducing this risk is keeping patients in remission. It is encouraging that there are some signals of lowered risk of IBD-CRC recently but with increasing disease burden, we have to remain vigilant. Further research into exploring pathways involved in CRC will provide a better understanding and potential new targets to exploit, be it for new or repurposed drugs. The expansion in the use of advanced endoscopic techniques is likely to improve neoplasia detection and help patients. AI carries the potential to bring about a paradigm shift in endoscopy and surveillance but needs rigorous evaluation before it is deployed for routine clinical use. Lastly, modulation of microbiota may well be something to watch out for in the future as a reliable intervention in this cohort.

## FOOTNOTES

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## REFERENCES

1 **Leong RW**, Koo JH. Colorectal cancer in inflammatory bowel disease. *J Gastroenterol Hepatol* 2009; **24**: 503-505 [PMID: 19368629 DOI: 10.1111/j.1440-1746.2009.05790.x]
2 **Eaden JA**, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut* 2001; **48**: 526-535 [PMID: 11247898 DOI: 10.1136/gut.48.4.526]
3 **Canavan C**, Abrams KR, Mayberry J. Meta-analysis: colorectal and small bowel cancer risk in patients with Crohn's disease. *Aliment Pharmacol Ther* 2006; **23**: 1097-1104 [PMID: 16611269 DOI: 10.1111/j.1365-2036.2006.02854.x]
4 **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**: G7-17 [PMID: 15194558 DOI: 10.1152/ajpgi.00079.2004]
5 **Kim ER**, Chang DK. Colorectal cancer in inflammatory bowel disease: the risk, pathogenesis, prevention and diagnosis. *World J Gastroenterol* 2014; **20**: 9872-9881 [PMID: 25110418 DOI: 10.3748/wjg.v20.i29.9872]
6 **Beaugerie L**, Itzkowitz SH. Cancers Complicating Inflammatory Bowel Disease. *N Engl J Med* 2015; **373**: 195 [PMID: 26154801 DOI: 10.1056/NEJMc1505689]
7 **Choi CH**, Rutter MD, Askari A, Lee GH, Warusavitarne J, Moorghen M, Thomas-Gibson S, Saunders BP, Graham TA, Hart AL. Forty-Year Analysis of Colonoscopic Surveillance Program for Neoplasia in Ulcerative Colitis: An Updated Overview. *Am J Gastroenterol* 2015; **110**: 1022-1034 [PMID: 25823771 DOI: 10.1038/ajg.2015.65]
8 **Averboukh F**, Ziv Y, Kariv Y, Zmora O, Dotan I, Klausner JM, Rabau M, Tulchinsky H. Colorectal carcinoma in inflammatory bowel disease: a comparison between Crohn's and ulcerative colitis. *Colorectal Dis* 2011; **13**: 1230-1235 [PMID: 21689324 DOI: 10.1111/j.1463-1318.2011.02639.x]
9 **Kiran RP**, Khoury W, Church JM, Lavery IC, Fazio VW, Remzi FH. Colorectal cancer complicating inflammatory bowel disease: similarities and differences between Crohn's and ulcerative colitis based on three decades of experience. *Ann Surg* 2010; **252**: 330-335 [PMID: 20622662 DOI: 10.1097/SLA.0b013e3181e61e69]
10 **Zhou Q**, Shen ZF, Wu BS, Xu CB, He ZQ, Chen T, Shang HT, Xie CF, Huang SY, Chen YG, Chen HB, Han ST. Risk of Colorectal Cancer in Ulcerative Colitis Patients: A Systematic Review and Meta-Analysis. *Gastroenterol Res Pract* 2019; **2019**: 5363261 [PMID: 31781191 DOI: 10.1155/2019/5363261]
11 **Söderlund S**, Granath F, Broström O, Karlén P, Löfberg R, Ekbom A, Askling J. Inflammatory bowel disease confers a lower risk of colorectal cancer to females than to males. *Gastroenterology* 2010; **138**: 1697-1703 [PMID: 20167217 DOI: 10.1053/j.gastro.2010.02.007]
12 **Jess T**, Rungoe C, Peyrin-Biroulet L. Risk of colorectal cancer in patients with ulcerative colitis: a meta-analysis of population-based cohort studies. *Clin Gastroenterol Hepatol* 2012; **10**: 639-645 [PMID: 22289873 DOI: 10.1016/j.cgh.2012.01.010]
13 **Gillen CD**, Walmsley RS, Prior P, Andrews HA, Allan RN. Ulcerative colitis and Crohn's disease: a comparison of the colorectal cancer risk in extensive colitis. *Gut* 1994; **35**: 1590-1592 [PMID: 7828978 DOI: 10.1136/gut.35.11.1590]
14 **Stiehl A**, Benz C, Sauer P. Primary sclerosing cholangitis. *Can J Gastroenterol* 2000; **14**: 311-315 [PMID: 10799084 DOI: 10.1155/2000/983681]
15 **Ricciuto A**, Kamath BM, Griffiths AM. The IBD and PSC Phenotypes of PSC-IBD. *Curr Gastroenterol Rep* 2018; **20**: 16 [PMID: 29594739 DOI: 10.1007/s11894-018-0620-2]
16 **Guerra I**, Bujanda L, Castro J, Merino O, Tosca J, Camps B, Gutiérrez A, Gordillo Ábalos J, de Castro L, Iborra M, Carbajo AY, Taxonera C, Rodríguez-Lago I, Mesonero F, de Francisco R, Gómez-Gómez GJ, Chaparro M, Tardillo CA, Rivero M, Algaba A, Martín Arranz E, Cañete F, Vicente R, Sicilia B, Antolín B, Prieto V, Márquez L, Benítez JM, Camo P, Piqueras M, Gargallo CJ, Hinojosa E, Huguet JM, Pérez Calle JL, Van Domselaar M, Rodriguez C, Calvet X, Muñoz-Villafranca C, García-Sepulcre MF, Munoz-Garrido P, Fernández-Clotet A, Gómez Irwin L, Hernández S, Guardiola J, Sempere L, González Muñoza C, Hernández V, Beltrán B, Barrio J, Alba C, Moraleja I, López-Sanromán A, Riestra S, Martínez Montiel P, Garre A, Arranz L, García MJ, Martín Arranz MD, Corsino P, Arias L, Fernández-Salazar L, Fernández-Pordomingo A, Andreu M, Iglesias E, Ber Y, Mena R, Arroyo Villarino MT, Mora M, Ruiz L, López-Serrano P, Blazquez I, Villoria A, Fernández M, Bermejo F, Banales JM, Domènech E, Gisbert JP; Spanish GETECCU group (ENEIDA Project). Clinical Characteristics, Associated Malignancies and Management of Primary Sclerosing Cholangitis in Inflammatory Bowel Disease Patients: A Multicentre Retrospective Cohort Study. *J Crohns Colitis* 2019; **13**: 1492-1500 [PMID: 31063540 DOI: 10.1093/ecco-jcc/jjz094]
17 **Mertz A**, Nguyen NA, Katsanos KH, Kwok RM. Primary sclerosing cholangitis and inflammatory bowel disease comorbidity: an update of the evidence. *Ann Gastroenterol* 2019; **32**: 124-133 [PMID: 30837784 DOI: 10.20524/aog.2019.0344]
18 **Lynch SV**, Pedersen O. The Human Intestinal Microbiome in Health and Disease. *N Engl J Med* 2016; **375**: 2369-2379 [PMID: 27974040 DOI: 10.1056/NEJMra1600266]

19 **Ni J**, Shen TD, Chen EZ, Bittinger K, Bailey A, Roggiani M, Sirota-Madi A, Friedman ES, Chau L, Lin A, Nissim I, Scott J, Lauder A, Hoffmann C, Rivas G, Albenberg L, Baldassano RN, Braun J, Xavier RJ, Clish CB, Yudkoff M, Li H, Goulian M, Bushman FD, Lewis JD, Wu GD. A role for bacterial urease in gut dysbiosis and Crohn's disease. *Sci Transl Med* 2017; **9** [PMID: 29141885 DOI: 10.1126/scitranslmed.aah6888]

20 **Balzan S**, de Almeida Quadros C, de Cleva R, Zilberstein B, Cecconello I. Bacterial translocation: overview of mechanisms and clinical impact. *J Gastroenterol Hepatol* 2007; **22**: 464-471 [PMID: 17376034 DOI: 10.1111/j.1440-1746.2007.04933.x]

21 **Yu LC**. Microbiota dysbiosis and barrier dysfunction in inflammatory bowel disease and colorectal cancers: exploring a common ground hypothesis. *J Biomed Sci* 2018; **25**: 79 [PMID: 30413188 DOI: 10.1186/s12929-018-0483-8]

22 **Rogala AR**, Oka A, Sartor RB. Strategies to Dissect Host-Microbial Immune Interactions That Determine Mucosal Homeostasis vs. Intestinal Inflammation in Gnotobiotic Mice. *Front Immunol* 2020; **11**: 214 [PMID: 32133003 DOI: 10.3389/fimmu.2020.00214]

23 **Matson V**, Chervin CS, Gajewski TF. Cancer and the Microbiome-Influence of the Commensal Microbiota on Cancer, Immune Responses, and Immunotherapy. *Gastroenterology* 2021; **160**: 600-613 [PMID: 33253684 DOI: 10.1053/j.gastro.2020.11.041]

24 **Kåhrström CT**. Host response: Phagocytosis runs like clockwork. *Nat Rev Microbiol* 2012; **10**: 162 [PMID: 22330881 DOI: 10.1038/nrmicro2751]

25 **Swidsinski A**, Göktas O, Bessler C, Loening-Baucke V, Hale LP, Andree H, Weizenegger M, Hölzl M, Scherer H, Lochs H. Spatial organisation of microbiota in quiescent adenoiditis and tonsillitis. *J Clin Pathol* 2007; **60**: 253-260 [PMID: 16698947 DOI: 10.1136/jcp.2006.037309]

26 **Motta JP**, Flannigan KL, Agbor TA, Beatty JK, Blackler RW, Workentine ML, Da Silva GJ, Wang R, Buret AG, Wallace JL. Hydrogen sulfide protects from colitis and restores intestinal microbiota biofilm and mucus production. *Inflamm Bowel Dis* 2015; **21**: 1006-1017 [PMID: 25738373 DOI: 10.1097/MIB.0000000000000345]

27 **Díaz P**, Valenzuela Valderrama M, Bravo J, Quest AFG. *Helicobacter pylori* and Gastric Cancer: Adaptive Cellular Mechanisms Involved in Disease Progression. *Front Microbiol* 2018; **9**: 5 [PMID: 29403459 DOI: 10.3389/fmicb.2018.00005]

28 **Flanagan L**, Schmid J, Ebert M, Soucek P, Kunicka T, Liska V, Bruha J, Neary P, Dezeeuw N, Tommasino M, Jenab M, Prehn JH, Hughes DJ. Fusobacterium nucleatum associates with stages of colorectal neoplasia development, colorectal cancer and disease outcome. *Eur J Clin Microbiol Infect Dis* 2014; **33**: 1381-1390 [PMID: 24599709 DOI: 10.1007/s10096-014-2081-3]

29 **Wu S**, Rhee KJ, Albesiano E, Rabizadeh S, Wu X, Yen HR, Huso DL, Brancati FL, Wick E, McAllister F, Housseau F, Pardoll DM, Sears CL. A human colonic commensal promotes colon tumorigenesis *via* activation of T helper type 17 T cell responses. *Nat Med* 2009; **15**: 1016-1022 [PMID: 19701202 DOI: 10.1038/nm.2015]

30 **Wu N**, Yang X, Zhang R, Li J, Xiao X, Hu Y, Chen Y, Yang F, Lu N, Wang Z, Luan C, Liu Y, Wang B, Xiang C, Wang Y, Zhao F, Gao GF, Wang S, Li L, Zhang H, Zhu B. Dysbiosis signature of fecal microbiota in colorectal cancer patients. *Microb Ecol* 2013; **66**: 462-470 [PMID: 23733170 DOI: 10.1007/s00248-013-0245-9]

31 **Gevers D**, Kugathasan S, Denson LA, Vázquez-Baeza Y, Van Treuren W, Ren B, Schwager E, Knights D, Song SJ, Yassour M, Morgan XC, Kostic AD, Luo C, González A, McDonald D, Haberman Y, Walters T, Baker S, Rosh J, Stephens M, Heyman M, Markowitz J, Baldassano R, Griffiths A, Sylvester F, Mack D, Kim S, Crandall W, Hyams J, Huttenhower C, Knight R, Xavier RJ. The treatment-naive microbiome in new-onset Crohn's disease. *Cell Host Microbe* 2014; **15**: 382-392 [PMID: 24629344 DOI: 10.1016/j.chom.2014.02.005]

32 **Claessen MM**, Schipper ME, Oldenburg B, Siersema PD, Offerhaus GJ, Vleggaar FP. WNT-pathway activation in IBD-associated colorectal carcinogenesis: potential biomarkers for colonic surveillance. *Cell Oncol* 2010; **32**: 303-310 [PMID: 20208143 DOI: 10.3233/CLO-2009-0503]

33 **Ma XT**, Wang S, Ye YJ, Du RY, Cui ZR, Somsouk M. Constitutive activation of Stat3 signaling pathway in human colorectal carcinoma. *World J Gastroenterol* 2004; **10**: 1569-1573 [PMID: 15162527 DOI: 10.3748/wjg.v10.i11.1569]

34 **Lin L**, Hron JD, Peng SL. Regulation of NF-kappaB, Th activation, and autoinflammation by the forkhead transcription factor Foxo3a. *Immunity* 2004; **21**: 203-213 [PMID: 15308101 DOI: 10.1016/j.immuni.2004.06.016]

35 **Romano M**, DE Francesco F, Zarantonello L, Ruffolo C, Ferraro GA, Zanus G, Giordano A, Bassi N, Cillo U. From Inflammation to Cancer in Inflammatory Bowel Disease: Molecular Perspectives. *Anticancer Res* 2016; **36**: 1447-1460 [PMID: 27069120]

36 **Laurent C**, Svrcek M, Flejou JF, Chenard MP, Duclos B, Freund JN, Reimund JM. Immunohistochemical expression of CDX2, β-catenin, and TP53 in inflammatory bowel disease-associated colorectal cancer. *Inflamm Bowel Dis* 2011; **17**: 232-240 [PMID: 20815042 DOI: 10.1002/ibd.21451]

37 **Kanaan Z**, Rai SN, Eichenberger MR, Barnes C, Dworkin AM, Weller C, Cohen E, Roberts H, Keskey B, Petras RE, Crawford NP, Galandiuk S. Differential microRNA expression tracks neoplastic progression in inflammatory bowel disease-associated colorectal cancer. *Hum Mutat* 2012; **33**: 551-560 [PMID: 22241525 DOI: 10.1002/humu.22021]

38 **Alpert L**, Yassan L, Poon R, Kadri S, Niu N, Patil SA, Mujacic I, Montes D, Galbo F, Wurst MN, Zhen CJ, Cohen RD, Rubin DT, Pekow JR, Weber CR, Xiao SY, Hart J, Segal J, Setia N. Targeted mutational analysis of inflammatory bowel disease-associated colorectal cancers. *Hum Pathol* 2019; **89**: 44-50 [PMID: 31054900 DOI: 10.1016/j.humpath.2019.04.013]

39 **Watanabe S**, Tsuchiya K, Nishimura R, Shirasaki T, Katsukura N, Hibiya S, Okamoto R, Nakamura T, Watanabe M. *TP53* Mutation by CRISPR System Enhances the Malignant Potential of Colon Cancer. *Mol Cancer Res* 2019; **17**: 1459-1467 [PMID: 30988165 DOI: 10.1158/1541-7786.MCR-18-1195]

40 **Lin L**, Liu A, Peng Z, Lin HJ, Li PK, Li C, Lin J. STAT3 is necessary for proliferation and survival in colon cancer-initiating cells. *Cancer Res* 2011; **71**: 7226-7237 [PMID: 21900397 DOI: 10.1158/0008-5472.CAN-10-4660]

41 **Corvinus FM**, Orth C, Moriggl R, Tsareva SA, Wagner S, Pfitzner EB, Baus D, Kaufmann R, Huber LA, Zatloukal K, Beug H, Ohlschläger P, Schütz A, Halbhuber KJ, Friedrich K. Persistent STAT3 activation in colon cancer is associated with enhanced cell proliferation and tumor growth. *Neoplasia* 2005; **7**: 545-555 [PMID: 16036105 DOI:

10.1593/neo.04571]
42 **Lin Q**, Lai R, Chirieac LR, Li C, Thomazy VA, Grammatikakis I, Rassidakis GZ, Zhang W, Fujio Y, Kunisada K, Hamilton SR, Amin HM. Constitutive activation of JAK3/STAT3 in colon carcinoma tumors and cell lines: inhibition of JAK3/STAT3 signaling induces apoptosis and cell cycle arrest of colon carcinoma cells. *Am J Pathol* 2005; **167**: 969-980 [PMID: 16192633 DOI: 10.1016/s0002-9440(10)61187-x]
43 **Gui X**, Iacucci M, Ghosh S. Dysregulation of IL6/IL6R-STAT3-SOCS3 signaling pathway in IBD-associated colorectal dysplastic lesions as compared to sporadic colorectal adenomas in non-IBD patients. *Pathol Res Pract* 2020; **216**: 153211 [PMID: 32979687 DOI: 10.1016/j.prp.2020.153211]
44 **de Lau W**, Barker N, Clevers H. WNT signaling in the normal intestine and colorectal cancer. *Front Biosci* 2007; **12**: 471-491 [PMID: 17127311 DOI: 10.2741/2076]
45 **Pinto D**, Clevers H. Wnt control of stem cells and differentiation in the intestinal epithelium. *Exp Cell Res* 2005; **306**: 357-363 [PMID: 15925592 DOI: 10.1016/j.yexcr.2005.02.022]
46 **Aust DE**, Terdiman JP, Willenbucher RF, Chang CG, Molinaro-Clark A, Baretton GB, Loehrs U, Waldman FM. The APC/beta-catenin pathway in ulcerative colitis-related colorectal carcinomas: a mutational analysis. *Cancer* 2002; **94**: 1421-1427 [PMID: 11920497 DOI: 10.1002/cncr.10334]
47 **Nazemalhosseini Mojarad E**, Kashfi SM, Mirtalebi H, Almasi S, Chaleshi V, Kishani Farahani R, Tarban P, Molaei M, Zali MR, J K Kuppen P. Prognostic Significance of Nuclear β-Catenin Expression in Patients with Colorectal Cancer from Iran. *Iran Red Crescent Med J* 2015; **17**: e22324 [PMID: 26421170 DOI: 10.5812/ircmj.22324v2]
48 **Mårtensson A**, Oberg A, Jung A, Cederquist K, Stenling R, Palmqvist R. Beta-catenin expression in relation to genetic instability and prognosis in colorectal cancer. *Oncol Rep* 2007; **17**: 447-452 [PMID: 17203186]
49 **Warren S**, Sommers SC. Pathogenesis of ulcerative colitis. *Am J Pathol* 1949; **25**: 657-679 [PMID: 18152861]
50 **Chiu K**, Riddell RH, Schaeffer DF. DALM, rest in peace: a pathologist's perspective on dysplasia in inflammatory bowel disease in the post-DALM era. *Mod Pathol* 2018; **31**: 1180-1190 [PMID: 29789648 DOI: 10.1038/s41379-018-0068-9]
51 **Mark-Christensen A**, Laurberg S, Haboubi N. Dysplasia in Inflammatory Bowel Disease: Historical Review, Critical Histopathological Analysis, and Clinical Implications. *Inflamm Bowel Dis* 2018; **24**: 1895-1903 [PMID: 29668897 DOI: 10.1093/ibd/izy075]
52 **Iacucci M**, Uraoka T, Fort Gasia M, Yahagi N. Novel diagnostic and therapeutic techniques for surveillance of dysplasia in patients with inflammatory bowel disease. *Can J Gastroenterol Hepatol* 2014; **28**: 361-370 [PMID: 25157526 DOI: 10.1155/2014/825947]
53 **Laine L**, Kaltenbach T, Barkun A, McQuaid KR, Subramanian V, Soetikno R; SCENIC Guideline Development Panel. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. *Gastroenterology* 2015; **148**: 639-651.e28 [PMID: 25702852 DOI: 10.1053/j.gastro.2015.01.031]
54 **Wu XR**, Zheng XB, Huang Y, Cao Q, Zhang HJ, Miao YL, Zou KF, Chen M, Zhang FM, Mei Q, Gonzalo D, Allende D, Hu PJ, Shen B, Liu XL, Lan P. Risk factors for colorectal neoplasia in patients with underlying inflammatory bowel disease: a multicenter study. *Gastroenterol Rep (Oxf)* 2019; **7**: 67-73 [PMID: 30792868 DOI: 10.1093/gastro/goy039]
55 **de Jong ME**, Kanne H, Nissen LHC, Drenth JPH, Derikx LAAP, Hoentjen F. Increased risk of high-grade dysplasia and colorectal cancer in inflammatory bowel disease patients with recurrent low-grade dysplasia. *Gastrointest Endosc* 2020; **91**: 1334-1342.e1 [PMID: 31923409 DOI: 10.1016/j.gie.2019.12.041]
56 **Sonnenberg A**, Genta RM. Epithelial Dysplasia and Cancer in IBD Strictures. *J Crohns Colitis* 2015; **9**: 769-775 [PMID: 26079724 DOI: 10.1093/ecco-jcc/jjv108]
57 **Rutter MD**, Saunders BP, Wilkinson KH, Rumbles S, Schofield G, Kamm MA, Williams CB, Price AB, Talbot IC, Forbes A. Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. *Gastroenterology* 2006; **130**: 1030-1038 [PMID: 16618396 DOI: 10.1053/j.gastro.2005.12.035]
58 **Cairns SR**, Scholefield JH, Steele RJ, Dunlop MG, Thomas HJ, Evans GD, Eaden JA, Rutter MD, Atkin WP, Saunders BP, Lucassen A, Jenkins P, Fairclough PD, Woodhouse CR; British Society of Gastroenterology; Association of Coloproctology for Great Britain and Ireland. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). *Gut* 2010; **59**: 666-689 [PMID: 20427401 DOI: 10.1136/gut.2009.179804]
59 **Lutgens MW**, Oldenburg B, Siersema PD, van Bodegraven AA, Dijkstra G, Hommes DW, de Jong DJ, Stokkers PC, van der Woude CJ, Vleggaar FP. Colonoscopic surveillance improves survival after colorectal cancer diagnosis in inflammatory bowel disease. *Br J Cancer* 2009; **101**: 1671-1675 [PMID: 19826420 DOI: 10.1038/sj.bjc.6605359]
60 **Lamb CA**, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, Hayee B, Lomer MCE, Parkes GC, Selinger C, Barrett KJ, Davies RJ, Bennett C, Gittens S, Dunlop MG, Faiz O, Fraser A, Garrick V, Johnston PD, Parkes M, Sanderson J, Terry H; IBD guidelines eDelphi consensus group, Gaya DR, Iqbal TH, Taylor SA, Smith M, Brookes M, Hansen R, Hawthorne AB. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut* 2019; **68**: s1-s106 [PMID: 31562236 DOI: 10.1136/gutjnl-2019-318484]
61 **Magro F**, Gionchetti P, Eliakim R, Ardizzone S, Armuzzi A, Barreiro-de Acosta M, Burisch J, Gecse KB, Hart AL, Hindryckx P, Langner C, Limdi JK, Pellino G, Zagórowicz E, Raine T, Harbord M, Rieder F; European Crohn's and Colitis Organisation [ECCO]. 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 [PMID: 28158501 DOI: 10.1093/ecco-jcc/jjx008]
62 **Iacucci M**, McQuaid K, Gui XS, Iwao Y, Lethebe BC, Lowerison M, Matsumoto T, Shivaji UN, Smith SCL, Subramanian V, Uraoka T, Sanduleanu S, Ghosh S, Kiesslich R. A multimodal (FACILE) classification for optical diagnosis of inflammatory bowel disease associated neoplasia. *Endoscopy* 2019; **51**: 133-141 [PMID: 30541154 DOI: 10.1055/a-0757-7759]
63 **Watanabe K**, Nishishita M, Shimamoto F, Fukuchi T, Esaki M, Okamoto Y, Maehata Y, Oka S, Nishiyama S, Fujii S, Hirai F, Matsui T, Kakimoto K, Okada T, Inoue T, Hida N, Goto H, Nozaki R, Sakurai T, Kashida H, Takeuchi K, Ohmiya N, Saruta M, Saito S, Saito Y, Tanaka S, Fujiwara Y, Arakawa T, Suzuki Y, Ajioka Y, Tajiri H. 722 Comparison Between Newly-Developed Narrow Band Imaging and Panchromoendoscopy for Surveillance Colonoscopy in Patients With Longstanding Ulcerative Colitis: A Prospective Multicenter Randomized Controlled Trial, Navigator Study.

*Gastrointestinal Endoscopy* 2016; **83**: AB172 [DOI: 10.1016/j.gie.2016.03.147]

64 **Bisschops R**, Bessissow T, Dekker E, East JE, Para-Blanco A, Ragunath K, Bhandari P, Rutter M, Schoon E, Wilson A, John JM, Van Steen K, Baert F, Ferrante M. Pit pattern analysis with high-definition chromoendoscopy and narrow-band imaging for optical diagnosis of dysplasia in patients with ulcerative colitis. *Gastrointest Endosc* 2017; **86**: 1100-1106.e1 [PMID: 28986266 DOI: 10.1016/j.gie.2017.09.024]

65 **Collins PD**, Mpofu C, Watson AJ, Rhodes JM. Strategies for detecting colon cancer and/or dysplasia in patients with inflammatory bowel disease. *Cochrane Database Syst Rev* 2006; CD000279 [PMID: 16625534 DOI: 10.1002/14651858.CD000279.pub3]

66 **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 [PMID: 30353058 DOI: 10.1038/s41395-018-0354-7]

67 **Watanabe T**, Ajioka Y, Mitsuyama K, Watanabe K, Hanai H, Nakase H, Kunisaki R, Matsuda K, Iwakiri R, Hida N, Tanaka S, Takeuchi Y, Ohtsuka K, Murakami K, Kobayashi K, Iwao Y, Nagahori M, Iizuka B, Hata K, Igarashi M, Hirata I, Kudo SE, Matsumoto T, Ueno F, Watanabe G, Ikegami M, Ito Y, Oba K, Inoue E, Tomotsugu N, Takebayashi T, Sugihara K, Suzuki Y, Watanabe M, Hibi T. Comparison of Targeted *vs* Random Biopsies for Surveillance of Ulcerative Colitis-Associated Colorectal Cancer. *Gastroenterology* 2016; **151**: 1122-1130 [PMID: 27523980 DOI: 10.1053/j.gastro.2016.08.002]

68 **Bisschops R**, East JE, Hassan C, Hazewinkel Y, Kamiński MF, Neumann H, Pellisé M, Antonelli G, Bustamante Balen M, Coron E, Cortas G, Iacucci M, Yuichi M, Longcroft-Wheaton G, Mouzyka S, Pilonis N, Puig I, van Hooft JE, Dekker E. Advanced imaging for detection and differentiation of colorectal neoplasia: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2019. *Endoscopy* 2019; **51**: 1155-1179 [PMID: 31711241 DOI: 10.1055/a-1031-7657]

69 **Marion JF**, Waye JD, Present DH, Israel Y, Bodian C, Harpaz N, Chapman M, Itzkowitz S, Steinlauf AF, Abreu MT, Ullman TA, Aisenberg J, Mayer L; Chromoendoscopy Study Group at Mount Sinai School of Medicine. Chromoendoscopy-targeted biopsies are superior to standard colonoscopic surveillance for detecting dysplasia in inflammatory bowel disease patients: a prospective endoscopic trial. *Am J Gastroenterol* 2008; **103**: 2342-2349 [PMID: 18844620 DOI: 10.1111/j.1572-0241.2008.01934.x]

70 **Imperatore N**, Castiglione F, Testa A, De Palma GD, Caporaso N, Cassese G, Rispo A. Augmented Endoscopy for Surveillance of Colonic Inflammatory Bowel Disease: Systematic Review With Network Meta-analysis. *J Crohns Colitis* 2019; **13**: 714-724 [PMID: 30597029 DOI: 10.1093/ecco-jcc/jjy218]

71 **Gasia MF**, Ghosh S, Panaccione R, Ferraz JG, Kaplan GG, Leung Y, Novak KL, Seow CH, Iacucci M. Targeted Biopsies Identify Larger Proportions of Patients With Colonic Neoplasia Undergoing High-Definition Colonoscopy, Dye Chromoendoscopy, or Electronic Virtual Chromoendoscopy. *Clin Gastroenterol Hepatol* 2016; **14**: 704-12.e4 [PMID: 26804384 DOI: 10.1016/j.cgh.2015.12.047]

72 **Iacucci M**, Kaplan GG, Panaccione R, Akinola O, Lethebe BC, Lowerison M, Leung Y, Novak KL, Seow CH, Urbanski S, Minoo P, Gui X, Ghosh S. A Randomized Trial Comparing High Definition Colonoscopy Alone With High Definition Dye Spraying and Electronic Virtual Chromoendoscopy for Detection of Colonic Neoplastic Lesions During IBD Surveillance Colonoscopy. *Am J Gastroenterol* 2018; **113**: 225-234 [PMID: 29134964 DOI: 10.1038/ajg.2017.417]

73 **Lippman SM**, Benner SE, Hong WK. Cancer chemoprevention. *J Clin Oncol* 1994; **12**: 851-873 [PMID: 8151328 DOI: 10.1200/jco.1994.12.4.851]

74 **Lyakhovich A**, Gasche C. Systematic review: molecular chemoprevention of colorectal malignancy by mesalazine. *Aliment Pharmacol Ther* 2010; **31**: 202-209 [PMID: 19891667 DOI: 10.1111/j.1365-2036.2009.04195.x]

75 **Andrews JM**, Travis SP, Gibson PR, Gasche C. Systematic review: does concurrent therapy with 5-ASA and immunomodulators in inflammatory bowel disease improve outcomes? *Aliment Pharmacol Ther* 2009; **29**: 459-469 [PMID: 19077129 DOI: 10.1111/j.1365-2036.2008.03915.x]

76 **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 [PMID: 27906680 DOI: 10.18632/oncotarget.13715]

77 **Velayos FS**, Terdiman JP, Walsh JM. Effect of 5-aminosalicylate use on colorectal cancer and dysplasia risk: a systematic review and metaanalysis of observational studies. *Am J Gastroenterol* 2005; **100**: 1345-1353 [PMID: 15929768 DOI: 10.1111/j.1572-0241.2005.41442.x]

78 **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 [PMID: 28261835 DOI: 10.1111/apt.14023]

79 **Jess T**, Lopez A, Andersson M, Beaugerie L, Peyrin-Biroulet L. Thiopurines and risk of colorectal neoplasia in patients with inflammatory bowel disease: a meta-analysis. *Clin Gastroenterol Hepatol* 2014; **12**: 1793-1800.e1 [PMID: 24907505 DOI: 10.1016/j.cgh.2014.05.019]

80 **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 [PMID: 29205426 DOI: 10.1111/apt.14436]

81 **Wang D**, Dubois RN. The role of COX-2 in intestinal inflammation and colorectal cancer. *Oncogene* 2010; **29**: 781-788 [PMID: 19946329 DOI: 10.1038/onc.2009.421]

82 **Rothwell PM**, Wilson M, Price JF, Belch JF, Meade TW, Mehta Z. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. *Lancet* 2012; **379**: 1591-1601 [PMID: 22440947 DOI: 10.1016/S0140-6736(12)60209-8]

83 **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 [PMID: 27053860 DOI: 10.3748/wjg.v22.i13.3679]

84 **Leddin D**, Tamim H, Levy AR. Is folate involved in the pathogenesis of inflammatory bowel disease? *Med Hypotheses*

2013; **81**: 940-941 [PMID: 24045091 DOI: 10.1016/j.mehy.2013.08.025]

85 **Lashner BA**, Heidenreich PA, Su GL, Kane SV, Hanauer SB. Effect of folate supplementation on the incidence of dysplasia and cancer in chronic ulcerative colitis. A case-control study. *Gastroenterology* 1989; **97**: 255-259 [PMID: 2568304 DOI: 10.1016/0016-5085(89)90058-9]

86 **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 [PMID: 26905603 DOI: 10.1097/MCG.0000000000000498]

87 **Rutter MD**. Importance of nonpolypoid (flat and depressed) colorectal neoplasms in screening for CRC in patients with IBD. *Gastrointest Endosc Clin N Am* 2014; **24**: 327-335 [PMID: 24975524 DOI: 10.1016/j.giec.2014.03.002]

88 **Siegel CA**, Schwartz LM, Woloshin S, Cole EB, Rubin DT, Vay T, Baars J, Sands BE. When should ulcerative colitis patients undergo colectomy for dysplasia? *Inflamm Bowel Dis* 2010; **16**: 1658-1662 [PMID: 20186940 DOI: 10.1002/ibd.21233]

89 **Ten Hove JR**, Mooiweer E, van der Meulen de Jong AE, Dekker E, Ponsioen CY, Siersema PD, Oldenburg B. Clinical implications of low grade dysplasia found during inflammatory bowel disease surveillance: a retrospective study comparing chromoendoscopy and white-light endoscopy. *Endoscopy* 2017; **49**: 161-168 [PMID: 27951611 DOI: 10.1055/s-0042-119394]

90 **Kabir M**, Fofaria R, Arebi N, Bassett P, Tozer PJ, Hart AL, Thomas-Gibson S, Humphries A, Suzuki N, Saunders B, Warusavitarne J, Faiz O, Wilson A. Systematic review with meta-analysis: IBD-associated colonic dysplasia prognosis in the videoendoscopic era (1990 to present). *Aliment Pharmacol Ther* 2020; **52**: 5-19 [PMID: 32432797 DOI: 10.1111/apt.15778]

91 **Fong W**, Li Q, Yu J. Gut microbiota modulation: a novel strategy for prevention and treatment of colorectal cancer. *Oncogene* 2020; **39**: 4925-4943 [PMID: 32514151 DOI: 10.1038/s41388-020-1341-1]

92 **Zheng L**, Wen XL. Gut microbiota and inflammatory bowel disease: The current status and perspectives. *World J Clin Cases* 2021; **9**: 321-333 [PMID: 33521100 DOI: 10.12998/wjcc.v9.i2.321]

93 **Shaoul R**, Day AS. Nutritional regulators of intestinal inflammation. *Curr Opin Gastroenterol* 2019; **35**: 486-490 [PMID: 31464809 DOI: 10.1097/MOG.0000000000000585]

94 **López-Alarcón M**, Perichart-Perera O, Flores-Huerta S, Inda-Icaza P, Rodríguez-Cruz M, Armenta-Álvarez A, Bram-Falcón MT, Mayorga-Ochoa M. Excessive refined carbohydrates and scarce micronutrients intakes increase inflammatory mediators and insulin resistance in prepubertal and pubertal obese children independently of obesity. *Mediators Inflamm* 2014; **2014**: 849031 [PMID: 25477716 DOI: 10.1155/2014/849031]

95 **De Almeida CV**, de Camargo MR, Russo E, Amedei A. Role of diet and gut microbiota on colorectal cancer immunomodulation. *World J Gastroenterol* 2019; **25**: 151-162 [PMID: 30670906 DOI: 10.3748/wjg.v25.i2.151]

96 **Demeyer D**, Honikel K, De Smet S. The World Cancer Research Fund report 2007: A challenge for the meat processing industry. *Meat Sci* 2008; **80**: 953-959 [PMID: 22063824 DOI: 10.1016/j.meatsci.2008.06.003]

97 **Limketkai BN**, Wolf A, Parian AM. Nutritional Interventions in the Patient with Inflammatory Bowel Disease. *Gastroenterol Clin North Am* 2018; **47**: 155-177 [PMID: 29413010 DOI: 10.1016/j.gtc.2017.09.007]

98 **Batista D**, Raffals L. Role of intestinal bacteria in the pathogenesis of pouchitis. *Inflamm Bowel Dis* 2014; **20**: 1481-1486 [PMID: 25046009 DOI: 10.1097/MIB.0000000000000055]

99 **Konstantinov SR**, Kuipers EJ, Peppelenbosch MP. Functional genomic analyses of the gut microbiota for CRC screening. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 741-745 [PMID: 24042452 DOI: 10.1038/nrgastro.2013.178]

100 **Tong LC**, Wang Y, Wang ZB, Liu WY, Sun S, Li L, Su DF, Zhang LC. Propionate Ameliorates Dextran Sodium Sulfate-Induced Colitis by Improving Intestinal Barrier Function and Reducing Inflammation and Oxidative Stress. *Front Pharmacol* 2016; **7**: 253 [PMID: 27574508 DOI: 10.3389/fphar.2016.00253]

101 **Fukuda S**, Toh H, Hase K, Oshima K, Nakanishi Y, Yoshimura K, Tobe T, Clarke JM, Topping DL, Suzuki T, Taylor TD, Itoh K, Kikuchi J, Morita H, Hattori M, Ohno H. Bifidobacteria can protect from enteropathogenic infection through production of acetate. *Nature* 2011; **469**: 543-547 [PMID: 21270894 DOI: 10.1038/nature09646]

102 **Costello SP**, Hughes PA, Waters O, Bryant RV, Vincent AD, Blatchford P, Katsikeros R, Makanyanga J, Campaniello MA, Mavrangelos C, Rosewarne CP, Bickley C, Peters C, Schoeman MN, Conlon MA, Roberts-Thomson IC, Andrews JM. Effect of Fecal Microbiota Transplantation on 8-Week Remission in Patients With Ulcerative Colitis: A Randomized Clinical Trial. *JAMA* 2019; **321**: 156-164 [PMID: 30644982 DOI: 10.1001/jama.2018.20046]

103 **Paramsothy S**, Kamm MA, Kaakoush NO, Walsh AJ, van den Bogaerde J, Samuel D, Leong RWL, Connor S, Ng W, Paramsothy R, Xuan W, Lin E, Mitchell HM, Borody TJ. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. *Lancet* 2017; **389**: 1218-1228 [PMID: 28214091 DOI: 10.1016/S0140-6736(17)30182-4]

104 **Lavoie S**, Conway KL, Lassen KG, Jijon HB, Pan H, Chun E, Michaud M, Lang JK, Gallini Comeau CA, Dreyfuss JM, Glickman JN, Vlamakis H, Ananthakrishnan A, Kostic A, Garrett WS, Xavier RJ. The Crohn's disease polymorphism, *ATG16L1* T300A, alters the gut microbiota and enhances the local Th1/Th17 response. *Elife* 2019; **8** [PMID: 30666959 DOI: 10.7554/eLife.39982]

105 **Liu JZ**, van Sommeren S, Huang H, Ng SC, Alberts R, Takahashi A, Ripke S, Lee JC, Jostins L, Shah T, Abedian S, Cheon JH, Cho J, Dayani NE, Franke L, Fuyuno Y, Hart A, Juyal RC, Juyal G, Kim WH, Morris AP, Poustchi H, Newman WG, Midha V, Orchard TR, Vahedi H, Sood A, Sung JY, Malekzadeh R, Westra HJ, Yamazaki K, Yang SK; International Multiple Sclerosis Genetics Consortium; International IBD Genetics Consortium, Barrett JC, Alizadeh BZ, Parkes M, Bk T, Daly MJ, Kubo M, Anderson CA, Weersma RK. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. *Nat Genet* 2015; **47**: 979-986 [PMID: 26192919 DOI: 10.1038/ng.3359]

106 **Kudo T**, Suzuki K, Mori Y, Misawa M, Ichimasa K, Takeda K, Nakamura H, Maeda Y, Ogawa Y, Hayashi T, Wakamura K, Ishida F, Inoue H, Kudo SE. Endocytoscopy for the differential diagnosis of colorectal low-grade adenoma: a novel possibility for the "resect and discard" strategy. *Gastrointest Endosc* 2020; **91**: 676-683 [PMID: 31785276 DOI: 10.1016/j.gie.2019.11.029]

107 **Wang KK**, Carr-Locke DL, Singh SK, Neumann H, Bertani H, Galmiche JP, Arsenescu RI, Caillol F, Chang KJ, Chaussade S, Coron E, Costamagna G, Dlugosz A, Ian Gan S, Giovannini M, Gress FG, Haluszka O, Ho KY, Kahaleh M, Konda VJ, Prat F, Shah RJ, Sharma P, Slivka A, Wolfsen HC, Zfass A. Use of probe-based confocal laser endomicroscopy (pCLE) in gastrointestinal applications. A consensus report based on clinical evidence. *United European Gastroenterol J* 2015; **3**: 230-254 [PMID: 26137298 DOI: 10.1177/2050640614566066]

108 **Kudo T**, Saito Y, Ikematsu H, Hotta K, Takeuchi Y, Shimatani M, Kawakami K, Tamai N, Mori Y, Maeda Y, Yamada M, Sakamoto T, Matsuda T, Imai K, Ito S, Hamada K, Fukata N, Inoue T, Tajiri H, Yoshimura K, Ishikawa H, Kudo SE. New-generation full-spectrum endoscopy *vs* standard forward-viewing colonoscopy: a multicenter, randomized, tandem colonoscopy trial (J-FUSE Study). *Gastrointest Endosc* 2018; **88**: 854-864 [PMID: 29908178 DOI: 10.1016/j.gie.2018.06.011]

109 **Stidham RW**, Liu W, Bishu S, Rice MD, Higgins PDR, Zhu J, Nallamothu BK, Waljee AK. Performance of a Deep Learning Model *vs* Human Reviewers in Grading Endoscopic Disease Severity of Patients With Ulcerative Colitis. *JAMA Netw Open* 2019; **2**: e193963 [PMID: 31099869 DOI: 10.1001/jamanetworkopen.2019.3963]

110 **Maeda Y**, Kudo SE, Ogata N, Misawa M, Mori Y, Mori K, Ohtsuka K. Can artificial intelligence help to detect dysplasia in patients with ulcerative colitis? *Endoscopy* 2021; **53**: E273-E274 [PMID: 33003217 DOI: 10.1055/a-1261-2944]

111 **Stewénius J**, Adnerhill I, Anderson H, Ekelund GR, Florén CH, Fork FT, Janzon L, Lindström C, Ogren M. Incidence of colorectal cancer and all cause mortality in non-selected patients with ulcerative colitis and indeterminate colitis in Malmö, Sweden. *Int J Colorectal Dis* 1995; **10**: 117-122 [PMID: 7636371 DOI: 10.1007/bf00341210]

112 **Castaño-Milla C**, Chaparro M, Gisbert JP. Systematic review with meta-analysis: the declining risk of colorectal cancer in ulcerative colitis. *Aliment Pharmacol Ther* 2014; **39**: 645-659 [PMID: 24612141 DOI: 10.1111/apt.12651]

113 **Olén O**, Erichsen R, Sachs MC, Pedersen L, Halfvarson J, Askling J, Ekbom A, Sørensen HT, Ludvigsson JF. Colorectal cancer in Crohn's disease: a Scandinavian population-based cohort study. *Lancet Gastroenterol Hepatol* 2020; **5**: 475-484 [PMID: 32066530 DOI: 10.1016/S2468-1253(20)30005-4]

114 Laukoetter MG, Mennigen R, Hannig CM, Osada N, Rijcken E, Vowinkel T, Krieglstein CF, Senninger N, Anthoni C, Bruewer M. Intestinal cancer risk in Crohn's disease: a meta-analysis. *J Gastrointest Surg* 2011; **15**: 576-583 [PMID: 21152994 DOI: 10.1007/s11605-010-1402-9]

115 **Fumery M**, Dulai PS, Gupta S, Prokop LJ, Ramamoorthy S, Sandborn WJ, Singh S. Incidence, Risk Factors, and Outcomes of Colorectal Cancer in Patients With Ulcerative Colitis With Low-Grade Dysplasia: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2017; **15**: 665-674.e5 [PMID: 27916678 DOI: 10.1016/j.cgh.2016.11.025]

116 **Friedman S**, Rubin PH, Bodian C, Harpaz N, Present DH. Screening and surveillance colonoscopy in chronic Crohn's colitis: results of a surveillance program spanning 25 years. *Clin Gastroenterol Hepatol* 2008; **6**: 993-8; quiz 953 [PMID: 18585966 DOI: 10.1016/j.cgh.2008.03.019]

117 **Basseri RJ**, Basseri B, Vassilaki ME, Melmed GY, Ippoliti A, Vasiliauskas EA, Fleshner PR, Lechago J, Hu B, Berel D, Targan SR, Papadakis KA. Colorectal cancer screening and surveillance in Crohn's colitis. *J Crohns Colitis* 2012; **6**: 824-829 [PMID: 22398087 DOI: 10.1016/j.crohns.2012.01.005]

118 **Keller DS**, Windsor A, Cohen R, Chand M. Colorectal cancer in inflammatory bowel disease: review of the evidence. *Tech Coloproctol* 2019; **23**: 3-13 [PMID: 30701345 DOI: 10.1007/s10151-019-1926-2]

119 **Pache I**, Rogler G, Felley C. TNF-alpha blockers in inflammatory bowel diseases: practical consensus recommendations and a user's guide. *Swiss Med Wkly* 2009; **139**: 278-287 [PMID: 19452290]

120 **Kobelt D**, Dahlmann M, Dumbani M, Güllü N, Kortüm B, Vílchez MEA, Stein U, Walther W. Small Ones to Fight a Big Problem-Intervention of Cancer Metastasis by Small Molecules. *Cancers (Basel)* 2020; **12** [PMID: 32503267 DOI: 10.3390/cancers12061454]

121 **Atreya R**, Neurath MF. Involvement of IL-6 in the pathogenesis of inflammatory bowel disease and colon cancer. *Clin Rev Allergy Immunol* 2005; **28**: 187-196 [PMID: 16129903 DOI: 10.1385/criai:28:3:187]

122 **Allocca M**, Jovani M, Fiorino G, Schreiber S, Danese S. Anti-IL-6 treatment for inflammatory bowel diseases: next cytokine, next target. *Curr Drug Targets* 2013; **14**: 1508-1521 [PMID: 24102406 DOI: 10.2174/13894501113146660224]

123 **Coskun M**, Vermeire S, Nielsen OH. Novel Targeted Therapies for Inflammatory Bowel Disease. *Trends Pharmacol Sci* 2017; **38**: 127-142 [PMID: 27916280 DOI: 10.1016/j.tips.2016.10.014]

124 **Danese S**, Vermeire S, Hellstern P, Panaccione R, Rogler G, Fraser G, Kohn A, Desreumaux P, Leong RW, Comer GM, Cataldi F, Banerjee A, Maguire MK, Li C, Rath N, Beebe J, Schreiber S. Randomised trial and open-label extension study of an anti-interleukin-6 antibody in Crohn's disease (ANDANTE I and II). *Gut* 2019; **68**: 40-48 [PMID: 29247068 DOI: 10.1136/gutjnl-2017-314562]

125 **Murakami M**, Kamimura D, Hirano T. Pleiotropy and Specificity: Insights from the Interleukin 6 Family of Cytokines. *Immunity* 2019; **50**: 812-831 [PMID: 30995501 DOI: 10.1016/j.immuni.2019.03.027]

126 **Johnstone CN**, Chand A, Putoczki TL, Ernst M. Emerging roles for IL-11 signaling in cancer development and progression: Focus on breast cancer. *Cytokine Growth Factor Rev* 2015; **26**: 489-498 [PMID: 26209885 DOI: 10.1016/j.cytogfr.2015.07.015]

127 **Ren C**, Chen Y, Han C, Fu D, Chen H. Plasma interleukin-11 (IL-11) levels have diagnostic and prognostic roles in patients with pancreatic cancer. *Tumour Biol* 2014; **35**: 11467-11472 [PMID: 25123265 DOI: 10.1007/s13277-014-2459-y]

128 **Unver N**, McAllister F. IL-6 family cytokines: Key inflammatory mediators as biomarkers and potential therapeutic targets. *Cytokine Growth Factor Rev* 2018; **41**: 10-17 [PMID: 29699936 DOI: 10.1016/j.cytogfr.2018.04.004]

129 **Pastor MD**, Nogal A, Molina-Pinelo S, Quintanal-Villalonga Á, Meléndez R, Ferrer I, Romero-Romero B, De Miguel MJ, López-Campos JL, Corral J, García-Carboner R, Carnero A, Paz-Ares L. IL-11 and CCL-1: Novel Protein Diagnostic Biomarkers of Lung Adenocarcinoma in Bronchoalveolar Lavage Fluid (BALF). *J Thorac Oncol* 2016; **11**: 2183-2192 [PMID: 27524264 DOI: 10.1016/j.jtho.2016.07.026]

130 **Putoczki TL**, Thiem S, Loving A, Busuttil RA, Wilson NJ, Ziegler PK, Nguyen PM, Preaudet A, Farid R, Edwards KM, Boglev Y, Luwor RB, Jarnicki A, Horst D, Boussioutas A, Heath JK, Sieber OM, Pleines I, Kile BT, Nash A, Greten FR, McKenzie BS, Ernst M. Interleukin-11 is the dominant IL-6 family cytokine during gastrointestinal tumorigenesis and can

be targeted therapeutically. *Cancer Cell* 2013; **24**: 257-271 [PMID: 23948300 DOI: 10.1016/j.ccr.2013.06.017]

131 **Hohenberger M**, Cardwell LA, Oussedik E, Feldman SR. Interleukin-17 inhibition: role in psoriasis and inflammatory bowel disease. *J Dermatolog Treat* 2018; **29**: 13-18 [PMID: 28521565 DOI: 10.1080/09546634.2017.1329511]

132 **Moschen AR**, Tilg H, Raine T. IL-12, IL-23 and IL-17 in IBD: immunobiology and therapeutic targeting. *Nat Rev Gastroenterol Hepatol* 2019; **16**: 185-196 [PMID: 30478416 DOI: 10.1038/s41575-018-0084-8]

133 **Di Fusco D**, Izzo R, Figliuzzi MM, Pallone F, Monteleone G. IL-21 as a therapeutic target in inflammatory disorders. *Expert Opin Ther Targets* 2014; **18**: 1329-1338 [PMID: 25162763 DOI: 10.1517/14728222.2014.945426]

134 **Salzer E**, Kansu A, Sic H, Májek P, Ikincioğullari A, Dogu FE, Prengemann NK, Santos-Valente E, Pickl WF, Bilic I, Ban SA, Kuloğlu Z, Demir AM, Ensari A, Colinge J, Rizzi M, Eibel H, Boztug K. Early-onset inflammatory bowel disease and common variable immunodeficiency-like disease caused by IL-21 deficiency. *J Allergy Clin Immunol* 2014; **133**: 1651-9.e12 [PMID: 24746753 DOI: 10.1016/j.jaci.2014.02.034]

135 **Neurath MF**. IL-23 in inflammatory bowel diseases and colon cancer. *Cytokine Growth Factor Rev* 2019; **45**: 1-8 [PMID: 30563755 DOI: 10.1016/j.cytogfr.2018.12.002]

136 **Rosenstock E**, Farmer RG, Petras R, Sivak MV Jr, Rankin GB, Sullivan BH. Surveillance for colonic carcinoma in ulcerative colitis. *Gastroenterology* 1985; **89**: 1342-1346 [PMID: 4054527 DOI: 10.1016/0016-5085(85)90653-5]

137 **Lashner BA**, Kane SV, Hanauer SB. Colon cancer surveillance in chronic ulcerative colitis: historical cohort study. *Am J Gastroenterol* 1990; **85**: 1083-1087 [PMID: 2389720]

138 **Löfberg R**, Broström O, Karlén P, Tribukait B, Ost A. Colonoscopic surveillance in long-standing total ulcerative colitis--a 15-year follow-up study. *Gastroenterology* 1990; **99**: 1021-1031 [PMID: 2394325 DOI: 10.1016/0016-5085(90)90622-8]

139 **Nugent FW**, Haggitt RC, Gilpin PA. Cancer surveillance in ulcerative colitis. *Gastroenterology* 1991; **100**: 1241-1248 [PMID: 2013371]

140 **Lynch DA**, Lobo AJ, Sobala GM, Dixon MF, Axon AT. Failure of colonoscopic surveillance in ulcerative colitis. *Gut* 1993; **34**: 1075-1080 [PMID: 8174957 DOI: 10.1136/gut.34.8.1075]

141 **Jonsson B**, Ahsgren L, Andersson LO, Stenling R, Rutegård J. Colorectal cancer surveillance in patients with ulcerative colitis. *Br J Surg* 1994; **81**: 689-691 [PMID: 8044548 DOI: 10.1002/bjs.1800810520]

142 **Karlén P**, Kornfeld D, Broström O, Löfberg R, Persson PG, Ekbom A. Is colonoscopic surveillance reducing colorectal cancer mortality in ulcerative colitis? *Gut* 1998; **42**: 711-714 [PMID: 9659169 DOI: 10.1136/gut.42.5.711]

143 **Friedman S**, Rubin PH, Bodian C, Goldstein E, Harpaz N, Present DH. Screening and surveillance colonoscopy in chronic Crohn's colitis. *Gastroenterology* 2001; **120**: 820-826 [PMID: 11231935 DOI: 10.1053/gast.2001.22449]

144 **Biasco G**, Rossini FP, Hakim R, Brandi G, Di Battista M, Di Febo G, Calabrese C, Santucci R, Miglioli M. Cancer surveillance in ulcerative colitis: critical analysis of long-term prospective programme. *Dig Liver Dis* 2002; **34**: 339-342 [PMID: 12118951 DOI: 10.1016/s1590-8658(02)80127-x]

145 **Hata K**, Watanabe T, Kazama S, Suzuki K, Shinozaki M, Yokoyama T, Matsuda K, Muto T, Nagawa H. Earlier surveillance colonoscopy programme improves survival in patients with ulcerative colitis associated colorectal cancer: results of a 23-year surveillance programme in the Japanese population. *Br J Cancer* 2003; **89**: 1232-1236 [PMID: 14520452 DOI: 10.1038/sj.bjc.6601247]

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