

Colorectal Cancer and Dysplasia in Inflammatory Bowel Disease: A Review of Disease Epidemiology, Pathophysiology, and Management

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Abstract

Crohn disease and ulcerative colitis are chronic inflammatory bowel diseases (IBD) characterized by recurrent episodes of mucosal inflammation. This chronic mucosal inflammation has several potential consequences, one of which is the occurrence of colitis-associated colorectal cancer. Over the past decade, our

understanding of the epidemiology, pathophysiology, and overall approach to diagnosing and managing colitis-associated colorectal cancer has grown considerably. In the current review article, we outline these advancements and highlight areas in need of further research. *Cancer Prev Res*; 9(12); 887–94. ©2016 AACR.

Epidemiology

The increased risk for colorectal cancer among patients with inflammatory bowel disease (IBD) with colitis is well-established (1, 2). Earlier studies had suggested a substantial excess risk, with an estimated incidence of nearly 1% per year (3). More recently, an updated meta-analysis of population-based cohort studies has quantified the incidence of colorectal cancer among patients with IBD to be 1%, 2%, and 5% after 10, 20, and > 20 years of disease duration (4). Although this would suggest that the burden of this disease is declining, population-based data have been conflicting. A Danish study observed that the overall risk for colorectal cancer in ulcerative colitis was now similar to that of the general Danish population [relative risk (RR), 1.07; 95% confidence interval (CI), 0.95 – 1.21], and although the risk of colorectal cancer among patients with Crohn disease had remained stable over time, the risk of colorectal cancer among patients with ulcerative colitis had declined considerably (1979–1988: RR, 1.34, 95% CI, 1.13–1.58; 1999–2008: RR, 0.57, 95% CI, 0.41–0.80; ref. 5).

In contrast, a US-based study from the Kaiser Permanente Healthcare System observed that the incidence of colorectal cancer among patients with both ulcerative colitis and Crohn disease was 60% higher than the general population, even after accounting for the growth of colorectal cancer screening programs. Furthermore, observed incidence remained stable over time for both ulcerative colitis and Crohn disease (6). These variations in observations help highlight several key issues with prior studies. Dissimilarities in estimates are likely, in large part, due to different study designs,

outcome classification and ascertainment, an inability to accurately classify disease onset, insufficient study size, and differences in the threshold for performing colectomy (7). Furthermore, the presence of active inflammation has a substantial impact on the ability to diagnose dysplasia. With advancements in biologic therapies and treatment strategies over time and improvements in disease control and quality of life, a lead time bias from early dysplasia detection in patients with well-controlled IBD without active inflammation may be partially responsible for varying incidence of colorectal cancer overtime and across populations, particularly when considering the advancements being made in endoscopic imaging technology. Taken together, colitis-associated colorectal cancer remains an important consequence of long-standing IBD with an estimated incidence of approximately 5% after 20 years of disease duration, but large-scale high-quality population-based studies are still needed to quantify its true burden.

Clinical risk factors

Although uncertainty remains as to the true estimate of disease burden, high-risk subpopulations and risk factors have consistently been identified, including age of colitis onset, disease extent, duration, and severity, inflammatory complications, primary sclerosing cholangitis (PSC), and family history of colorectal cancer (Table 1; refs. 1–30). For age of disease onset, risk is highest among those diagnosed at a younger age (≤ 15 years), which is perhaps attributable to longer overall disease duration or a more aggressive phenotype among these individuals. An important marker of disease severity and persistence of inflammation may be the development of colonic strictures. Earlier studies suggested that up to 40% of colonic strictures harbored colorectal cancer (8), but more recent studies note much lower, but still substantial, risk, reporting that 2% to 3.5% of colonic strictures harbor dysplasia or colorectal cancer (9, 10). Furthermore, one of these studies suggested that the only factor associated with an increased risk for dysplasia or colorectal cancer within colonic strictures was the absence of disease activity at the time of surgery (OR, 4.86; 95% CI, 1.11 – 21.27; ref. 9). This is a direct contrast to the majority of other risk factors, which are clearly linked to disease activity and inflammation, and highlights the potential gaps in

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Table 1. Clinical risk factors for colitis-associated colorectal cancer

Age of Onset
Increased risk among those diagnosed with IBD at a younger age (≤ 15 years)
Disease Extent
Crohn's disease: Increased risk when more than 30%-50% of colonic mucosa involved
Ulcerative colitis: 10- to 15-fold increased risk with pancolitis throughout disease duration, followed by 2-fold increased risk with left-sided colitis (distal to splenic flexure) until the fourth decade of disease when estimates mirror those of pancolitis, and no risk with proctitis (rectum)
Disease Duration and Severity
Risk increases with increasing disease severity (endoscopic and histology) and becomes most apparent after 7-10 y with a linear increase thereafter
Inflammatory Complications
Foreshortened colon, strictures, inflammatory pseudopolyps
PSC
Predominately right-sided lesions and increased risk present at time of diagnosis as compared with non-PSC IBD patients where risk is apparent after 7-10 y of disease duration. Increased CRC risk remains even after liver transplant and proctocolectomy (i.e., cancer of the pouch).
Personal and Family History
Additional risk of CRC in IBD patients with a family history of CRC similar to general population. Personal history of dysplasia confers increased risk of synchronous or metachronous CRC

Abbreviation: CRC, colorectal cancer.

our knowledge and understanding of the pathogenesis of colitis-associated colorectal cancer. While risk factors have been identified, comparison of the magnitude and significance of risk is a challenge due to variation in study designs, and, in some cases, small sample size. In addition, the true prevalence of risk factors is difficult to ascertain. A recent population-based cohort study demonstrated that the true prevalence of PSC may be much higher than previously estimated (31). This might suggest that PSC as a risk factor for colorectal cancer is only of significance in clinically active PSC. More research on risk factors for colitis-associated cancer utilizing population-based data is needed.

Pathogenesis

Given the microenvironment within which colitis-associated dysplasia and colorectal cancer are arising, it is not unexpected that host immune and inflammatory responses play a key role in the pathogenesis. The mechanism through which chronic inflammation results in colorectal cancer is felt to be through the induction of cytokines and chemokines, with ensuing alterations in epithelial cell proliferation, survival, and migration (32-42; Fig. 1). In contrast to sporadic colorectal cancer, which is postulated to develop from 1 or 2 foci of dysplasia, colitis-associated colorectal cancer is hypothesized to develop

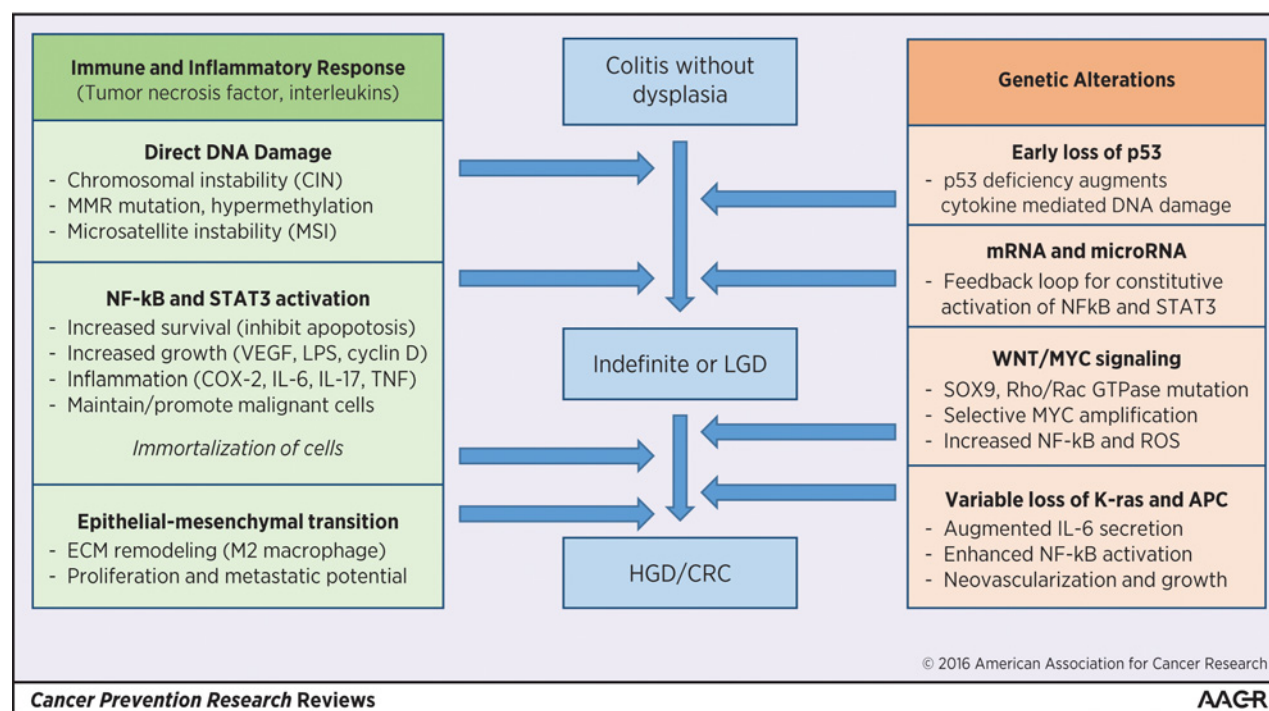


Figure 1. Key alterations within the colitis-associated colorectal cancer dysplasia-carcinoma sequence. COX-2, cyclooxygenase-2; ECM, extra-cellular matrix; LPS, lipopolysaccharide; MMR, mismatch repair mutation; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

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from multifocal dysplasia where the inflamed colonic mucosa undergoes a field change of cancer-associated molecular alterations before there is any histologic evidence of dysplasia (2, 24, 43–45). Broadly, 2 of the most common somatic genetic abnormalities identified in colorectal cancer are chromosomal instability (CIN) and microsatellite instability (MSI). These occur with the same frequency in colitis-associated colorectal cancer as they do with sporadic colorectal cancer, but there are differences with respect to the timing and frequency of some alterations in the colitis associated dysplasia–carcinoma sequence (2, 24, 46–52). For example, p53 mutations (common to both sporadic and colitis-associated colorectal cancer) appear to occur earlier in carcinogenesis in colitis-associated colorectal cancer, as these mutations are more commonly observed in colitis-associated dysplasia than among sporadic polyps (47, 51). Mutations in APC and K-ras, which are known to occur much earlier within the adenoma–carcinoma sequence of sporadic colorectal cancer, are seen less frequently in colitis-associated colorectal cancer and are thought to arise much later in the dysplasia–carcinoma sequence where they promote NF- κ B-mediated cytokine secretion, neovascularization, and maintenance of tumor growth (24, 51, 53).

Recently, whole-exome analyses of tumor specimens from patients with colitis-associated colorectal cancer were compared with exome analyses from tumor specimens from patients with sporadic colorectal cancer included in The Cancer Genome Atlas (TCGA). The comparisons suggested that colitis-associated colorectal cancers have a distinct profile and are enriched with mutations associated with cell communication, cell-to-cell signaling, and cell adhesion, all of which may be linked with the dysregulated cytokines and inflammatory mediators associated with IBD (51, 54). Limitations of this prior work include a paucity of clinical data on the patients who contributed colorectal cancer samples and small sample size ($n < 30$). Nonetheless, recognition that colitis-associated colorectal cancer may have a unique genetic profile could offer novel opportunities for chemoprevention and for the development of biomarkers for colitis surveillance. Extension of genetic profiling work to include precancerous dysplasia and expansion to include additional assessments such as DNA methylation and mucosal microbiome profiles has great potential to expand our understanding of colitis-associated colorectal cancer pathogenesis and opportunities for surveillance, intervention, and prevention.

Chemoprevention

No primary randomized controlled trials of chemoprevention for colitis-associated colorectal cancer have been conducted. In observational studies, the 2 most widely studied anti-inflammatory drugs are 5-aminosalicylic acid (5-ASA) and immunomodulators (methotrexate, azathioprine, and 6-mercaptopurine). Although both of these drug categories inhibit NF- κ B activation, and to some extent, reduce the overall burden of cytokine production (55–59), clinical data supporting their use as chemoprevention agents have been conflicting. Indeed, the majority of population-based studies suggesting no therapeutic benefit exists for this indication (60–65). Similarly, pooled meta-analyses of observational studies for other nonspecific anti-inflammatory agents, such as aspirin and non-aspirin nonsteroid anti-inflammatory drugs, have also suggested no chemoprevention benefit exists for these agents, despite their demonstrated efficacy as chemoprevention agents

for sporadic colorectal cancer (66). Among a high-risk population of patients suffering from PSC, early data suggested a substantial chemoprevention benefit with ursodeoxycholic acid (67). However, more recent meta-analyses of population-based studies have suggested that a chemoprevention benefit may not exist for all patients, particularly when considering the dose of UCDA used (68, 69). This lack of benefit with prior chemoprevention studies may be, in part, due to variability in disease activity, extent, and presence of established risk factors, or the nonspecific mechanism through which these agents inhibit inflammation and modulate cancer risk.

Given the known importance of TNF and interleukins within the pathogenesis of colitis-associated colorectal cancer, more targeted inhibition of these pathways may offer an opportunity to prevent colitis-associated colorectal cancer, particularly among high-risk individuals who have developed early dysplastic lesions where these cytokines serve to stabilize the cancer microenvironment. In non-colorectal cancer malignancy, such as ovarian and renal cell cancers, the use of TNF antagonists in early-phase clinical trials has been shown to stabilize disease and prevent further progression among those with advanced cancer (70). Within colitis-associated colorectal cancer, although animal models have suggested that TNF antagonists may prevent the development or progression of dysplasia and cancer (71), and some population-based data within IBD have demonstrated a lower frequency of colorectal cancer among those treated with infliximab (72, 73), non-IBD data have suggested a potential increased frequency of colorectal cancer with infliximab treatment (74). This has created uncertainty as to whether TNF antagonist and biologics are effective chemoprevention agents for colitis-associated colorectal cancer (75).

Overall, chemoprevention against colitis-associated colorectal cancer is understudied. Well-designed randomized controlled trials for candidate agents are needed, and large population-based registries or healthcare databases may help guide the identification of these candidate agents. An example of this can be seen within the Boston healthcare network where statin use was observed to be inversely associated with colorectal cancer risk and thus may be a potential candidate chemoprevention agent worthy of future research (76). As alluded to above, expanding understandings of the genetic and molecular profiles of colitis-associated dysplasia and colorectal cancer offers potential to engage in a new era of chemoprevention research in IBD. For example, mutations in Rac GTP may be more common in IBD-associated neoplasia, and Rac1 inhibition has been shown in animals to prevent colorectal cancer carcinogenesis (51). The potential impact of such genetic observations is highlighted by a recent successful pilot trial against adenomas in patients with familial adenomatous polypos (FAP), where observations of EGFR upregulation in FAP-associated polyps led to a successful placebo controlled proof-of-concept human trial of erlotinib that markedly reduced adenoma burden and progression (77).

Screening and surveillance

Although a great deal of research has been conducted to understand the pathogenesis of colitis-associated colorectal cancer, and attempts have been made to off-set the natural course of this disease through chemoprevention, the timing of these dysplastic transitions can vary, and tumor progression can skip one or more of these steps (78). This creates a great deal of uncertainty

Table 2. Surveillance intervals and strategies

	High risk (annually)	Intermediate risk (every 3 y)	Low risk (every 5 y)
Risk-stratified intervals			
NICE, ECCO, and BSG (85–87)	Pancolitis with moderate to severe inflammation; strictures or dysplasia within past 5 y (\pm surgery), PSC, or family history of CRC in first-degree relative > 50 y	Pancolitis with active inflammation (endoscopic or histologic); presence of pseudopolyps or family history of CRC in first-degree relative > 50 y	Pancolitis without inflammation (endoscopic or histology); left-sided UC or CD of similar extent (i.e., <50% mucosa involved) ^a
Nonstratified intervals			
ASGE, ACG, and AGA (78, 88, 89)	Active inflammation (any severity), anatomic abnormalities (foreshortened colons, strictures or pseudopolyps), history of dysplasia, PSC, or family history of CRC in first-degree relative (irrespective of age)	Extension to 1 to 3 years considered after 2 consecutive negative surveillance colonoscopies and no inflammation (no specification on how to lengthen interval)	No recommendation to extend to 5-y intervals

Abbreviations: ACG, American College of Gastroenterology; AGA: American Gastroenterology Association; ASGE, American Society of Gastrointestinal Endoscopy; BSG, British Society of Gastroenterology; CD, Crohn disease; CRC, colorectal cancer; ECCO, European Crohn's and Colitis Organization; NICE, National Institute of Health and Clinical Excellence; UC, ulcerative colitis.

^aECCO guidelines do not have specific low-risk criteria. Low risk is those without high or intermediate risk.

with regards to screening and surveillance. Efforts have therefore now focused on the early detection of dysplastic changes through endoscopic surveillance with the intent of reducing the risk of progression through early colectomy when colitis-associated dysplasia is found. This approach has been associated with a reduction in colorectal cancer-related mortality (79–84) and is now considered standard of care by several gastrointestinal societies. The optimal approach and timing to surveillance, however, continues to be debated.

Surveillance intervals

When considering endoscopic surveillance intervals, societies vary in the manner in which they stratify patients and the intervals they recommend. Broadly, surveillance can be classified as risk-stratified or nonstratified intervals (Table 2; refs. 78, 85–89). European societies have suggested a more stratified approach to surveillance, after taking into account the number of risk factors and strength of each risk factor, whereas U.S. societies have suggested a more aggressive and nonstratified approach to surveillance, assuming an equal degree of risk across subpopulations. A recent cost-effectiveness analysis suggested that the European-based risk profiling approach may be more cost-effective as compared with the nonstratified U.S. approach, but this cost-effectiveness was largely driven by the cost of colonoscopy, and it is unclear whether the different strategies are equal in their ability to improve colorectal cancer-related morbidity and mortality (90). Furthermore, the overall utilization of surveillance colonoscopy programs at the population level has been demonstrated to be low, with only a quarter of patients undergoing surveillance at recommended intervals (91, 92). Even among high-risk individuals (PSC), adherence to guidelines is reported to be less than 40% (91–94). Thus, irrespective of the interval or strategy followed, adherence to any surveillance program would be considered an optimization of current practices.

Surveillance techniques and management of dysplasia

Uncertainty and variability surround surveillance techniques and the optimal management of dysplastic lesions. Providers have traditionally failed to comply with biopsy protocols, with some reports documenting adherence to be less than 5% (92, 93, 95, 96). It is unclear whether this variation in practice and adherence to surveillance techniques is due to patient preferences, provider practice preferences, or technical challenges (i.e., time required to

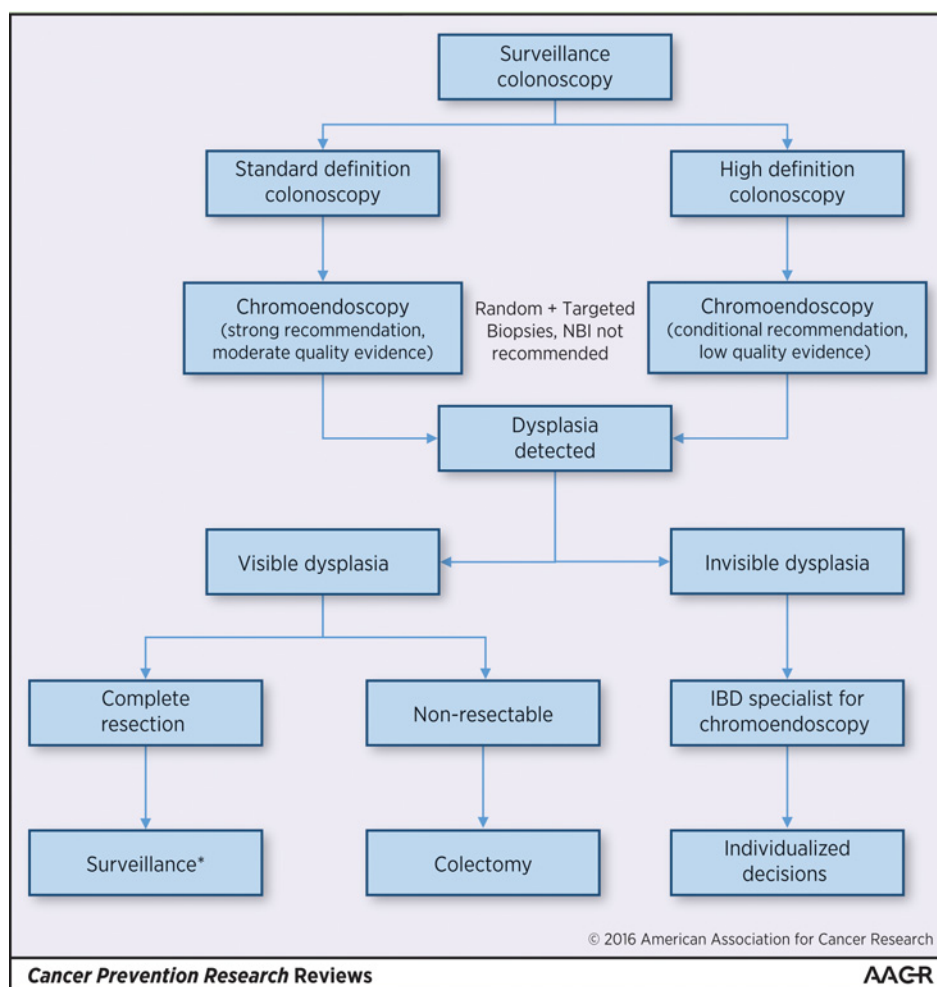
submit multiple biopsies in multiple sample jars; ref. 97), but it may help explain why the rate of early/missed colorectal cancer after colonoscopy is reported to be nearly 15% among patients with IBD as compared with only 5% in non-IBD patients (98). In an effort to address this gap, a group of experts recently came together and prepared the Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients Internal Consensus Recommendations (SCENIC Recommendations; ref. 99; Fig. 2). Within these recommendations, a key point to note is that not all dysplastic lesions require colectomy, and certain patients with focal low-grade dysplasia (LGD) or visible lesions can be monitored endoscopically or undergo focal endoscopic resection.

When performing surveillance, the SCENIC recommendations place a great deal of emphasis on the use of chromoendoscopy to optimize surveillance techniques. However, it should be noted that this recommendation is a conditional recommendation when using newer high definition colonoscopy equipment, as it is based largely upon on a single observational study and no randomized trials currently exist in this arena. Given the increased effort and time required to perform chromoendoscopy, with an unclear added benefit, several authors have brought into question the optimal use of chromoendoscopy and whether it is truly required in all patients (100, 101). Furthermore, if chromoendoscopy is to be used, it is unclear whether random biopsies are still needed beyond targeted biopsies. Nonetheless, although several of the recommendations are conditional and/or have low quality of evidence supporting them, this consensus recommendation statement helps highlight the need for a unified approach to diagnosing, characterizing, and treating these lesions in routine practice and represents a step toward a more integrated approach to dealing with colitis-associated dysplasia and colorectal cancer (102).

Emerging surveillance techniques

Recently, the use of stool-based surveillance has been considered and the detection of CpG island methylation in human DNA isolated from stool has been proposed for noninvasive screening (103). Kisiel and colleagues (104) demonstrated that methylated gene markers BMP3, vimentin, EYA4, and NDRG4 showed a high discrimination between neoplastic and non-neoplastic tissue (ROC curve of 0.91, 0.91, 0.85, and 0.84 for total IBD neoplasia and 0.97, 0.97, 0.95, and 0.85 for cancer). Azuara and colleagues (105) found that SLIT2 gene

Figure 2. Clinical approach to endoscopic dysplasia surveillance and management based on the SCENIC consensus, ref. 99.



methylation was more frequently seen in patients at high risk of dysplasia or cancer as compared with those at low risk (25% vs. 0%, $P < 0.01$), suggesting this may also be a potential stool-based surveillance biomarker. Several other studies have since been conducted to evaluate the potential of stool-based testing for colitis-associated colorectal cancer surveillance, but to date, no well-validated panels are available for routine clinical use in IBD, and further studies are needed to understand the optimized use of these stool-based biomarkers, and the com-

parative effectiveness of this approach as compared with currently accepted standards—high-definition colonoscopy with chromoendoscopy (103).

Summary

Significant advances have been made in our understanding and approach to managing colitis-associated colorectal cancer. Despite this, several important gaps remain which will need to be addressed (Table 3). Quantifying the true

Table 3. Unanswered questions and future research

Epidemiology and Risk Factors

- Population level incidence, prevalence, and trends using accurate classification and selection
- Incidence and risk for dysplasia and colitis-associated CRC with strictures and identifying strictures associated with an increased risk for harboring dysplasia or colitis-associated CRC
- Incremental impact of having multiple risk factors present at baseline or over time

Molecular Basis and Targets of Carcinogenesis

- Whole-exome sequencing of early dysplasia to understand sequence of genetic alterations
- Predictive and prognostic importance of genetic alterations for progression to CRC
- Targeted chemoprevention and personalized treatment of early dysplastic lesions with a particular emphasis on NF- κ B inhibition, anti-interleukin, and anti-cytokine biologics

Surveillance and Endoscopic Management

- Risk-stratified surveillance techniques and impact on disease outcomes
- Noninvasive surveillance techniques (stool- or blood-based DNA testing)
- Comparative effectiveness of enhanced visualization techniques

burden of disease, impact of changing treatment paradigms on disease risk, and identifying subpopulations at greatest risk is of utmost importance as we transition to personalized risk profiling and surveillance. New insights into the pathogenesis of colitis-associated colorectal cancer, and rigorous, comprehensive analyses of genetic and molecular profiles associated with colitis-associated dysplasia and colorectal cancer, could pave the way for targeted chemoprevention and surveillance strategies. Although a great deal of work has been done to optimize the surveillance and management of dysplasia and colorectal cancer, questions remain regarding the optimal integration of novel optical

technology, endoscopic therapeutics, and changing risk profiles over time. Well-designed population-level comparative effectiveness studies are needed to optimize the value and utility of colorectal cancer surveillance and screening in IBD.

Disclosure of Potential Conflicts of Interest

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