

# Colorectal Cancer Prevention in Inflammatory Bowel Disease and the Role of 5-Aminosalicylic Acid: a Clinical Review and Update

David T. Rubin,<sup>\*</sup> Marcia R. Cruz-Correa,<sup>†</sup> Christoph Gasche,<sup>‡</sup> Jeremy R. Jass,<sup>§</sup> Gary R. Lichtenstein,<sup>¶</sup> Elizabeth A. Montgomery,<sup>||</sup> Robert H. Riddell,<sup>\*\*</sup> Matthew D. Rutter,<sup>††</sup> Thomas A. Ullman,<sup>‡‡</sup> Fernando S. Velayos,<sup>§§</sup> and Steven Itzkowitz<sup>‡‡</sup> the 5-ASA in Colorectal Cancer Prevention Meeting Group

**Abstract:** A roundtable consensus meeting was held to consolidate current knowledge on the etiology of colorectal cancer in patients with inflammatory bowel disease and to review current strategies, both diagnostic and preventive, specifically addressing the role of 5-aminosalicylic acid. Specific topics that were addressed included: the epidemiology of colorectal cancer, including an assessment of risk factors and the impact of colonoscopy on colorectal cancer incidence and mortality; the origin and evolution of dysplasia nomenclature and the natural history of dysplasia; review of the experience of St. Mark's Hospital (London) as gleaned from its surveillance database; mechanisms by which 5-aminosalicylic acid is thought to exert a chemopreventive effect; the potential future role of 5-aminosalicylic acid in chemopreventive strategies; chemoprevention in familial adenomatous polyposis; and other future research directions. This article provides a comprehensive overview of the issues discussed and should act as a guide to shaping the design of future studies in this area.

(*Inflamm Bowel Dis* 2007;13:000–000)

**Key Words:** Inflammatory bowel disease, ulcerative colitis, Crohn's disease, 5-aminosalicylic acid, chemoprevention, dysplasia, colorectal cancer

Received for publication August 31, 2007; accepted September 4, 2007.

From the <sup>\*</sup>University of Chicago Medical Center, Chicago, Illinois; <sup>†</sup>University of Puerto Rico Comprehensive Cancer Center, San Juan, Puerto Rico; <sup>‡</sup>Medical University of Vienna, Vienna, Austria; <sup>§</sup>St. Mark's Hospital, Harrow, United Kingdom; <sup>||</sup>University of Pennsylvania, Philadelphia, Pennsylvania; <sup>¶</sup>Johns Hopkins University School of Medicine, Baltimore, Maryland; <sup>\*\*</sup>Mount Sinai Hospital, Toronto, Ontario, Canada; <sup>††</sup>University Hospital of North Tees, Stockton on Tees, United Kingdom; <sup>‡‡</sup>Mount Sinai School of Medicine, New York, New York; and <sup>§§</sup>University of California, San Francisco, California.

Supported by Shire Pharmaceuticals Inc., Wayne, Pennsylvania

Reprints: David T. Rubin, Section of Gastroenterology, Hepatology, and Nutrition, Department of Medicine, University of Chicago Medical Center, 5841 South Maryland Avenue, MC 4076, Chicago, IL 60637 (e-mail: drubin@medicine.bsd.uchicago.edu)

Copyright © 2007 Crohn's & Colitis Foundation of America, Inc.

DOI 10.1002/ibd.20297

Published online in Wiley InterScience (www.interscience.wiley.com).

A roundtable meeting was held June 24, 2006, with the aim of bringing together leading physicians and researchers in the field of prevention of colorectal cancer (CRC) in patients with inflammatory bowel disease (IBD). The goals of the meeting were to consolidate current clinical and scientific knowledge on the etiology of CRC/IBD and to review current strategies, both diagnostic and preventive, specifically focusing on the role of 5-aminosalicylic acid (5-ASA).

This report provides an overview of the presentations made and the consensus reached by the group on the current state of CRC prevention in patients with IBD using 5-ASA therapy, as well as suggestions for future research. Presentations were delivered covering the incidence and prevalence of CRC in patients with IBD, the origin and evolution of dysplasia nomenclature, the natural history of dysplasia in IBD, lessons learned from the St. Mark's Surveillance Database, the clinical evidence of 5-ASA chemoprevention, the mechanisms underlying 5-ASA chemoprevention, and lessons learned from the study of chemoprevention in familial adenomatous polyposis and sporadic CRC. Future research directions were also discussed, including prospective studies in high-risk populations and retrospective studies using large population databases.

## INCIDENCE AND PREVALENCE OF COLORECTAL CANCER IN INFLAMMATORY BOWEL DISEASE

The previously accepted increased risk of CRC in IBD has prompted medical society guidelines to endorse cancer prevention strategies.<sup>1,2</sup> In addition, it has provoked ongoing discussions regarding the effectiveness of such strategies and ways in which they might be improved. With this in mind, the opening presentation of the meeting explored the incidence of CRC in patients with IBD, focusing specifically on how it compares with that of the general population, and examined whether certain patient subtypes are at an increased risk of developing this malignancy. Dr. Steven Itzkowitz of the Mount Sinai School of Medicine (New York) presented the supporting data and also discussed the impact of colonoscopy on the incidence of CRC and its effect on CRC-related mortality.

Most studies assessing the incidence of CRC in patients with IBD have found an increase in the risk of CRC versus control subjects.<sup>3–5</sup> In a cohort of 3117 patients with ulcerative colitis (UC) (diagnosed between 1922 and 1983) from the Uppsala Healthcare Region in Sweden, the incidence of CRC relative to the expected incidence was increased, resulting in a standardized incidence ratio (SIR) of 5.7 [95% confidence interval (CI): 4.6–7.0].<sup>4</sup> Similarly, in another Swedish population-based cohort study of 1547 patients with UC from Stockholm County (diagnosed between 1955 and 1984), the SIR for CRC was reported to be 4.1 (95% CI: 2.7–5.8).<sup>5</sup> Considering both UC and Crohn's disease (CD), a Canadian matched-cohort study of 5529 patients with IBD (diagnosed between 1984 and 1997) included in the Manitoba Health database found the incidence rate ratio (IRR) for colon carcinoma to be similarly increased in patients with UC (IRR 2.75; 95% CI: 1.91–3.97) and CD (IRR 2.64; 95% CI: 1.69–4.12). For rectal cancer, the IRR of patients with UC increased (IRR 1.90; 95% CI: 1.05–3.43), but not that of patients with CD (IRR 1.08; 95% CI: 0.43–2.70).<sup>3</sup> In contrast with the results of these studies, Jess et al found no statistical increase in the incidence of CRC in 692 patients with either UC or CD from Olmsted County, Minnesota (diagnosed between 1940 and 2001).<sup>6</sup> In this retrospective study, the SIR for CRC of patients with UC and CD was 1.1 (95% CI: 0.4–2.4) and 1.9 (95% CI: 0.7–4.1), respectively. The latter finding confirms the results of a previous meta-analysis of 6 CD studies, which also reported a SIR for CRC of 1.9 (95% CI: 1.4–2.5),<sup>7</sup> which was statistically significant in this meta-analysis. Other population-based studies conducted in Italy and Denmark have reported either no or only a modestly increased risk of CRC in patients with UC or CD.<sup>8,9</sup>

Although the incidence of CRC appears to be elevated in patients with IBD, there is substantial geographic variation. A meta-analysis by Eaden et al of 116 studies published in 2001 estimated the incidence of CRC in U.S. patients with UC to be 5 cases per 1000 person-years, which equates to an annual risk of 0.5%.<sup>10</sup> Although a similar incidence was estimated for UK patients (4 cases per 1000 person-years), the incidence of CRC in Scandinavian patients and in patients in other countries was estimated to be considerably lower (2 cases per 1000 person-years). The reasons for these variations are unclear but may involve a combination of genetic factors, diet, use of medicines, and/or use of preventive strategies. Considering data from all countries, the meta-analysis estimated an overall prevalence of CRC of 3.7% among patients with UC.<sup>10</sup>

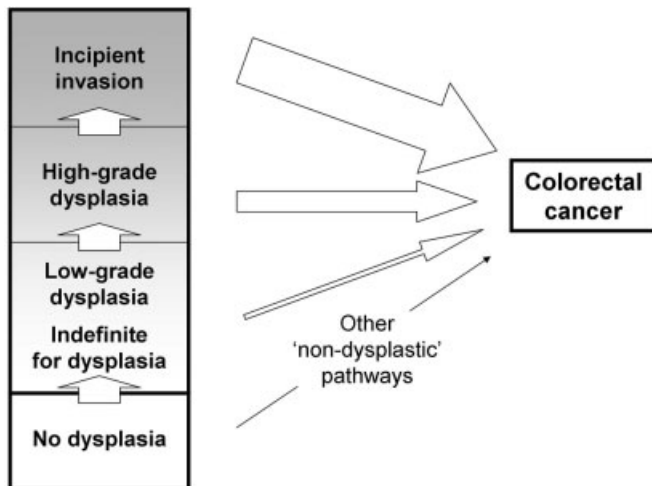
As reported above, patients with UC and patients with CD seem to have a similar risk of developing CRC.<sup>3</sup> Nonetheless, studies have shown that certain patients with IBD may have a greater risk of developing CRC than others. For example, a recent meta-analysis of 12 studies showed that patients with Crohn's colitis (but not ileitis) have an elevated

risk of CRC.<sup>11</sup> In this meta-analysis, the overall relative risk (RR) of CRC of patients with CD was 2.5 (95% CI: 1.3–4.7). When stratified by disease type, patients with colonic disease had an RR for CRC of 4.5 (95% CI: 1.3–14.9), but patients with ileal disease only had an RR of 1.1 (95% CI: 0.8–1.5). In UC, extent of disease and age at diagnosis may influence the risk of CRC. Indeed, several studies have demonstrated a higher risk of CRC in patients with more extensive disease, with the highest risk observed in patients with pancolitis.<sup>4,6,10</sup> In some studies, younger age at diagnosis also appears to increase the risk of CRC in patients with UC.<sup>3,4,10</sup>

Overall, factors that appear to increase the risk of CRC of patients with IBD include duration, severity, and extent of IBD; family history of CRC; primary sclerosing cholangitis; age at UC diagnosis; degree of histologic/endoscopic inflammatory activity; and presence of dysplasia of any grade (indefinite, low, or high).<sup>11–14</sup> However, it may be difficult to compare the exact relative risks for these various factors because of differences in the patient populations and how the analyses were performed.

The cumulative incidence of CRC has been shown to increase with increased disease duration among both patients with UC<sup>10,14</sup> and patients with CD.<sup>11</sup> In a meta-analysis by Eaden et al, the cumulative incidence of CRC in patients with UC was estimated to be 1.6%, 8.3%, and 18.4% after 10, 20, and 30 years, respectively.<sup>10</sup> However, a less pronounced increase in the cumulative CRC incidence over time has been reported in subsequent population-based studies,<sup>12</sup> as well as in a 30-year analysis of the colonoscopic surveillance program at St. Mark's Hospital (Harrow, UK) for detection of neoplasia in patients with long-standing UC (2.5%, 7.6%, and 10.8% after 20, 30, and 40 years, respectively).<sup>14</sup> In the Canavan et al meta-analysis, the cumulative incidence of CRC in patients with CD was estimated to be 2.9%, 5.6%, and 8.3% after 10, 20, and 30 years, respectively.<sup>11</sup>

Although the possibility of an increased risk of CRC is of considerable concern, particularly for those with long-standing disease, there is some evidence to suggest that performing surveillance colonoscopies can reduce the risk of CRC in patients with UC.<sup>15,16</sup> In 2 matched, case-control studies of patients with UC, having 1–2 colonoscopies over the course of the disease reduced the risk of CRC compared with having no intervention [odds ratio (OR) 0.22 (95% CI: 0.09–0.55;  $P = 0.001$ ) and 0.4 (95% CI: 0.2–0.7;  $P < 0.05$ ), respectively].<sup>15,16</sup> In 1 of the studies, additional colonoscopies (>2 over the course of the disease) reduced the risk slightly further (OR 0.3; 95% CI: 0.1–0.8;  $P < 0.05$ ),<sup>16</sup> but in the other study, further intervention was found not to be beneficial (OR 0.42; 95% CI: 0.16–1.10;  $P = 0.08$ ).<sup>15</sup> Unsurprisingly, having any number of barium enemas did not significantly reduce the risk of CRC.<sup>15</sup> Importantly, surveillance colonoscopy may also reduce the risk of mortality because of CRC.<sup>17</sup> In a nested case-control study of 142



**Figure 1.** Proposed pathway of colorectal cancer development from dysplasia in patients with ulcerative colitis. Indefinite for dysplasia has a similar risk of colorectal cancer development as low-grade dysplasia and, at least in some patients, likely represents the low end of the same category.

patients with UC, having at least 1 or 2 or more colonoscopies significantly reduced the risk of CRC-related mortality compared with having no intervention [RR: 0.29 (95% CI: 0.06–1.31) and 0.22 (95% CI: 0.03–1.74), respectively].<sup>17</sup> These data highlight the importance of surveillance colonoscopy for patients with IBD.

### ORIGIN AND EVOLUTION OF DYSPLASIA NOMENCLATURE

CRC in IBD is associated with dysplastic changes (as described in the article by Riddell and colleagues<sup>18</sup>) that act as markers of synchronous and future cancer risk and provide a noncancerous target for identifying prevention strategies. In this regard, Dr. Robert Riddell (Mount Sinai Hospital, Toronto, Ontario, Canada) provided meeting participants with an overview of the origin and evolution of IBD-related dysplasia nomenclature.

In the IBD setting, the term *dysplasia* is used to describe noninvasive epithelial changes and is graded as negative, indefinite for dysplasia (IND), low-grade dysplasia (LGD), or high-grade dysplasia (HGD). Hence, there are only 2 recognized grades of confirmed dysplasia (LGD and HGD), both of which describe an unequivocal neoplastic change. It should be noted that there is not necessarily a chronological progression from IND to LGD, then to HGD, then to invasive carcinoma. CRC can occur in association with any grade of dysplasia and even in the absence of dysplasia, but the risk of synchronous and metachronous adenocarcinoma is higher in patients with higher grades of dysplasia (Fig. 1).

More recently, Schlemper and coworkers developed the Vienna classification system to describe gastrointestinal epi-

thelial neoplasia.<sup>19</sup> This classification system splits neoplasia into 5 categories: (1) negative for neoplasia/dysplasia; (2) indefinite for neoplasia/dysplasia; (3) noninvasive low-grade neoplasia (low-grade adenoma/dysplasia); (4) noninvasive high-grade neoplasia [(i) high-grade adenoma/dysplasia; (ii) noninvasive carcinoma (carcinoma in situ); (iii) suspicion of invasive carcinoma]; and (5) invasive neoplasia [(i) intramucosal carcinoma; (ii) submucosal carcinoma or beyond]. Although this system may improve the reliability of diagnoses, it has not yet been accepted as an appropriate classification scheme, and there are still ongoing issues with the classification of dysplasia in IBD.

The first issue with the classification of dysplasia in IBD is how best to define IND. IND is usually diagnosed by exclusion if the epithelial changes are shown *not* to be benign, reactive, neoplastic, or adenomatous. In this regard, surface maturation has been proposed as an exclusion marker for IND, as it may be regarded as a feature of regeneration and therefore excludes all reactive changes.<sup>20</sup> The term *maturation* refers to cellular maturation as viewed by histological examination in surface epithelial cells and epithelial crypt cells. In nondysplastic colonic mucosa, basal cells appear less mature than those at the surface, which exhibit mitotic activity and have a high nucleus-to-cytoplasm ratio. Although maturation can be a useful exclusion marker, it cannot be relied on solely, as some dysplasias also show signs of maturation (e.g., bottom-up dysplasia, which is seen classically in most sessile/villous and serrated dysplasias). Furthermore, invasive carcinomas mature as they invade surrounding tissues, producing mucin, goblet cells, signet ring cells, and keratinization (in squamous carcinomas).

The second issue with the classification of dysplasia concerns the difficulty of detecting small areas of dysplasia by histological examination. If a dysplastic area is relatively small, it is unlikely to be sampled in randomly obtained biopsies and therefore will remain undetected. In this respect, new endoscopic techniques (e.g., chromoendoscopy) are likely to improve the efficiency of detection of intraepithelial neoplasias in patients with IBD. In a randomized trial of 165 patients with long-standing UC, a significantly higher number of intraepithelial neoplasias were detected using methylene-blue-aided chromoendoscopy than with conventional colonoscopy (32 versus 10;  $P = 0.0032$ ).<sup>21</sup> Moreover, chromoendoscopy had a sensitivity and specificity of 93% for differentiating between neoplastic and nonneoplastic lesions. These results highlight the great potential of new endoscopic techniques. However, this strategy assumes that dysplasia always precedes invasion; it may not do so in endocrine carcinomas and carcinomas that are analogous to diffuse gastric cancer, thus detecting “early” lesions may be the best that can be hoped for. Some detected carcinomas may have destroyed any evidence of dysplasia or the dysplasia may simply not have been sampled.

**TABLE 1.** Colorectal Cancer Rates in Ulcerative Colitis Patients with High-, Low-, Indefinite-, or Negative-Grade Dysplasia Undergoing Colectomy

Dysplasia grade	Number of patients (%) with colorectal cancer for whom	
	Colectomy performed immediately	Colectomy performed after follow-up
<b>High</b>		
Bernstein et al (1994) <sup>22</sup>	10/24 (42%)	15/47 (32%)
Connell et al (1994) <sup>23</sup>	8/12 (67%)	—
Rutter et al (2006) <sup>14</sup>	5/11 (45%)	—
<b>Low</b>		
Bernstein et al (1994) <sup>22</sup>	3/16 (19%)	17/204 (8%)
Ullman et al (2003) <sup>24</sup>	2/11 (19%)*	—
Rutter et al (2006) <sup>14</sup>	2/10 (20%)	—
<b>Indefinite</b>		
Bernstein et al (1994) <sup>22</sup>	—	9/95 (9%)
<b>Negative</b>		
Bernstein et al (1994) <sup>22</sup>	—	11/595 (2%)

\*Includes 1 patient who had a colectomy 2 months after diagnosis of low-grade dysplasia because of a subsequent finding of high-grade dysplasia.

### NATURAL HISTORY OF DYSPLASIA IN INFLAMMATORY BOWEL DISEASE

CRC prevention strategies that rely on a diagnosis of dysplasia require the natural history of dysplasia to be well understood. An overview of the natural history of dysplasia in IBD was provided by Thomas Ullman, MD, of the Mount Sinai School of Medicine (New York). In his introduction, Dr. Ullman pointed out that the progression from normal mucosa to carcinoma differs for sporadic CRC and colitis-associated CRC. Sporadic CRC proceeds through an adenomatous polyp phase prior to becoming carcinoma, whereas colitis-associated CRC proceeds via a dysplastic phase that may not be polypoid. Dr. Ullman also reiterated Dr. Riddell's comment that progression through the dysplastic phase may not be sequential in colitis-associated CRC.

Several colonoscopic surveillance studies have shown that the probability of finding CRC following HGD is high in patients with UC.<sup>14,22,23</sup> In these studies, if colectomy was performed at the time of diagnosis of HGD, CRC was detected in 42% to 67% of cases (Table 1).<sup>14,22–24</sup> These data clearly illustrate that patients with HGD have a very high risk of progressing to a malignancy.

In comparison, the probability of finding CRC following LGD is lower than for HGD, but still appears to be of significance.<sup>14,22–25</sup> The results of colonoscopic surveillance studies showed that if colectomy was performed at the time of diagnosis of LGD, CRC was already present in 19% to 20%

of cases (Table 1).<sup>14,22</sup> Overall progression from LGD to HGD or cancer over 5 years has been estimated to occur in 33% to 54% of patients.<sup>23,24,26</sup> Moreover, the results of a recent meta-analysis of 20 surveillance studies indicate that the risk of developing cancer is 9 times higher (OR: 9.0; 95% CI: 4.0–20.5) and the risk of developing any advanced lesion is 12 times higher (HGD, CRC, or dysplasia-associated lesion or mass; OR: 11.9; 95% CI: 5.2–27) once LGD is diagnosed, compared with patients who have UC without dysplasia.<sup>25</sup> Importantly, it has been shown that patients may progress from LGD to CRC without an intervening HGD or early-stage CRC, despite continued surveillance.<sup>24</sup>

There is also evidence that patients with IND are at higher risk of developing CRC than those without dysplasia. In a combined analysis of 10 prospective surveillance colonoscopy UC studies, the probability of finding CRC was 9% (9 of 95) in patients with IND and 2% (11 of 595) in patients who were negative for dysplasia, when colectomy was carried out after follow-up surveillance (Table 1).<sup>22</sup> Although this analysis reported a rate of CRC in patients with IND similar to that in patients with LGD (8%), current opinion is that the risk in IND patients is intermediate between that of patients without dysplasia and those with LGD.

### THE ST. MARK'S SURVEILLANCE DATABASE: LESSONS LEARNED

Our understanding of the natural history of CRC in IBD has been gained largely from retrospective studies, which are often confounded by small sample sizes or an inability to account for key variables. In contrast, the St. Mark's Hospital (Harrow, UK) surveillance database is the largest prospective database of IBD and cancer outcomes. In his presentation, Dr. Matthew Rutter of the University Hospital of North Tees (Stockton-on-Tees, UK) reviewed the lessons learned from the creation and follow-up of this database.

The St. Mark's surveillance database, which was originally established in the 1960s, serves a dual clinical and research role by providing a prospective method of extensive data collection and ensuring adherence to the surveillance protocol. All patients with extensive UC presenting at St. Mark's Hospital for outpatient appointments or endoscopy are included in the database. For each patient, detailed records are kept on patient demographics, key dates (onset of symptoms, diagnosis, first seen at clinic, index colonoscopy, surgery/death/leaving surveillance, etc.), and all clinic visits, including any treatment or tests received.

A recent interrogation of St. Mark's database uncovered some important findings regarding the relationship between CRC and UC. The first finding is that severe colonic inflammation in patients with UC is associated with an increased risk of CRC compared with 2 matched controls, 1 of them matched for sex and extent of UC, the other for age at onset of colitic symptoms and duration of UC (to within 5

years).<sup>13</sup> Univariate analysis of data obtained from 204 patients revealed a highly significant correlation between the degree of colonoscopic (OR 2.54; 95% CI: 1.45–4.44;  $P = 0.001$ ) and histologic (OR 5.13; 95% CI: 2.36–11.14;  $P < 0.001$ ) inflammation and the risk of colorectal neoplasia. On multivariate analysis, the histologic inflammation score (OR 4.69; 95% CI: 2.10–10.48;  $P < 0.001$ ), but not the colonoscopic inflammation score, remained significant. The discovery that inflammation severity is a key risk factor for CRC is important, as it is possible to influence this parameter using pharmacologic therapy. It should be noted that previous case-control UC studies failed to show an association between CRC and surrogate markers of inflammation severity (e.g., frequency of symptomatic exacerbations).<sup>15,27</sup> An earlier study by Gomes et al also failed to show a clear correlation between clinical indices of disease activity and tissue inflammation (histology and endoscopic macroscopic scores) in 50 patients with IBD undergoing routine colonoscopy.<sup>28</sup>

In the same analysis of the St. Mark's database, 5-ASA use was found to have no significant effect on the incidence of CRC.<sup>13</sup> In fact, using sulfasalazine for at least 10 years was actually associated with a nonsignificant increase in CRC risk compared with no prior use or use for less than 3 months (OR 1.58; 95% CI: 0.71–3.51). In contrast, use of mesalamine for at least 10 years was associated with a modest decrease in CRC risk (OR 0.65; 95% CI: 0.26–1.62), but again, this effect was not significant. These findings suggest that mesalamine may protect against the development of CRC and that sulfasalazine should be avoided unless alternative treatments are contraindicated or inappropriate.

A more recent analysis of 600 patients included in the St. Mark's database showed that the cumulative incidence of CRC increases linearly over time.<sup>14</sup> The cumulative incidence of CRC in patients with UC was 0% after 10 years of disease, 2.5% after 20 years, 7.6% after 30 years, 10.8% after 40 years, and 13.5% after 45 years. This result would appear to contradict the findings of the Eaden et al meta-analysis, in which the rate of increase in CRC was shown to increase exponentially after the first 10 years following diagnosis.<sup>10</sup> The St. Mark's analysis also reported a gradual statistically significant decline in CRC incidence (particularly for proximal cancers) over the last 30 years (linear regression  $r = -0.40$ ;  $P = 0.04$ ).<sup>14</sup> This observation is supported by a previous study of Swedish patients with pancolitis that reported a decrease in the incidence of CRC over the 5 decades prior to 1998.<sup>29</sup> Conversely, 2 other studies reported a rise in the incidence of CRC in patients with UC,<sup>10,30</sup> although in only 1 of the studies did this increase reach statistical significance.<sup>30</sup> Why the incidence of CRC varied between studies is unclear but is likely to be multifactorial and related to study selection bias, use of disease-modifying or chemopreventive drugs, the effect of surveillance, geographic variation (e.g., differing colectomy rates), and other unknown external influences. The

attendees of this meeting believed that the use of anti-inflammatory therapies is the most likely explanation for the reduced CRC incidence at St. Mark's Hospital.

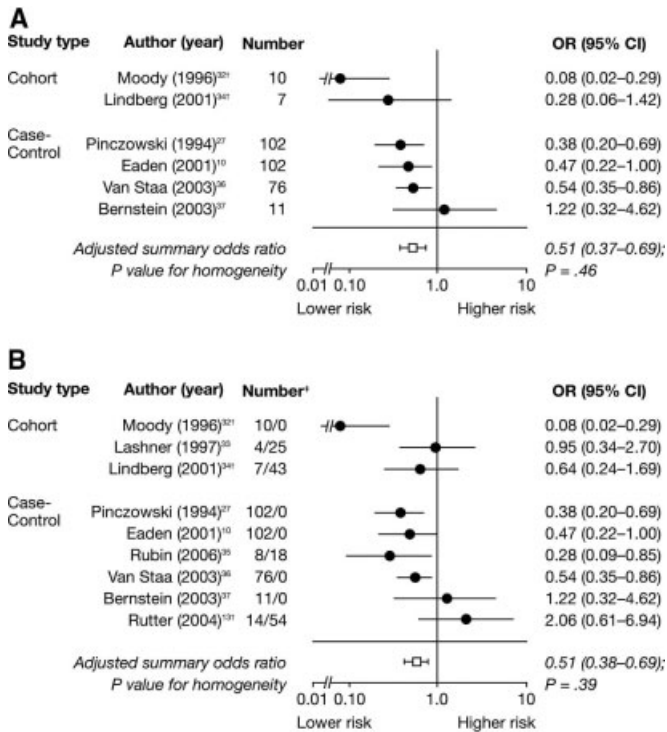
### CLINICAL EVIDENCE OF 5-AMINOSALICYLIC ACID CHEMOPREVENTION

5-ASA therapy is the treatment of choice in active mild to moderate UC. In addition to its efficacy and safety as an anti-inflammatory therapy, 5-ASA is also believed to have unique chemopreventive properties. During his presentation, Dr. Fernando Velayos of the University of California (San Francisco, Calif.) reviewed the clinical evidence demonstrating the chemopreventive properties of 5-ASA and highlighted the questions that still need to be answered about the future role of 5-ASA in CRC prevention in patients with IBD.

Multiple studies have assessed the utility of 5-ASA in preventing dysplasia and cancer in patients with UC, whereas fewer studies have assessed this endpoint in patients with CD. Looking across the UC studies, a recent meta-analysis of 9 observational studies involving a total of 1932 patients reported a protective association between 5-ASA use and CRC (OR 0.51; 95% CI: 0.37–0.69) or a combined endpoint of CRC and dysplasia (OR 0.51; 95% CI: 0.38–0.69; Fig. 2),<sup>10,13,27,31–37</sup> which equates to a 49% reduction in the risk of CRC or CRC/dysplasia with regular 5-ASA use. The derivative studies generally reported similar findings, even though they were subject to their own unique limitations and strengths in how they were performed.

Given the apparent protective effect of 5-ASA use on CRC development, it is perhaps unsurprising that compliance with prescribed 5-ASA therapy can influence the risk of CRC. In a UK community-based cohort study of 175 patients with UC (diagnosed between 1972 and 1981), compliance with sulfasalazine resulted in a significant reduction in the risk of CRC.<sup>32</sup> The crude proportion of patients who developed CRC was 3% (5 of 152) in the compliant group and 31% (5 of 16) in the noncompliant group (those not compliant with or advised to stop taking sulfasalazine),  $P < 0.001$ . Another UK case-control study of 102 patients with UC and CRC plus matched controls showed that CRC could be substantially reduced by taking 5-ASA on a regular basis compared with no 5-ASA use (OR 0.47; 95% CI: 0.22–1.00).<sup>15</sup> Likewise, a nested case-control study involving 18,969 patients with IBD in the UK General Practice Research Database (1987–2001) showed that regular 5-ASA users (defined as  $\geq 6$  prescriptions in the previous 12 months) had a significantly reduced risk of CRC compared with irregular 5-ASA users (adjusted OR 0.60; 95% CI: 0.38–0.96).<sup>38</sup> In the latter 2 studies, regular mesalamine users achieved a reduction in CRC risk that was numerically greater than that achieved by regular sulfasalazine users. Neither study reported any analysis of the impact of infliximab on the development of CRC.<sup>15,38</sup>

Even with these supporting data, several questions still



**Figure 2.** Odds ratios for the effect of 5-aminosalicylic acid on the development of (A) colorectal cancer/dysplasia or (B) colorectal cancer alone.\*Reproduced with permission from Blackwell Publishing (2005).<sup>31</sup> †All cancer patients in the study by Rutter et al had taken 5-ASA for at least 3 months and therefore there was no reference group; ‡only unadjusted odds ratio reported; †number of cancer cases/number of dysplasia cases; OR, odds ratio; CI, confidence interval.

need to be addressed. First, should all UC patients be taking 5-ASA to reduce the risk of cancer? At present, less information is available regarding chemopreventive action of other IBD therapies compared with that of 5-ASA, and it is currently unclear whether a patient receiving another treatment (e.g., azathioprine) would benefit from additional 5-ASA in terms of chemoprevention.

Second, is one 5-ASA therapy better than another? As already stated, some studies have shown a difference between sulfasalazine and mesalamine in CRC risk reduction.<sup>13,15,38</sup> It is possible, however, that sociodemographic factors may have had a bearing on this effect. For example, sulfasalazine is cheaper than most mesalamine formulations. Hence, cost may influence prescribing decisions. Also, sulfasalazine has been available for more than 60 years, whereas the newer mesalamine formulations were only introduced in the early 1990s. Sulfasalazine users may therefore be older than mesalamine users and have other factors that may make them at higher risk of developing CRC. Because sulfasalazine inhibits the absorption of folate<sup>39</sup> and folate deficiency may be associated with a higher risk of sporadic colon cancer,<sup>40</sup> it

is also possible that the lack of a chemopreventive effect with sulfasalazine may be a result of reduced folate.

Third, what is the optimal 5-ASA dose for chemoprevention? Two studies have found a dose–response in which the odds of CRC or dysplasia/CRC decreased as the total dose of 5-ASA increased.<sup>15,35</sup> In both studies, 5-ASA doses equivalent to mesalamine of at least 1.2 g/day provided the greatest risk reduction (72%–81%). However, these studies assessed dose–response in different ways, making it difficult to interpret the data as whole.

Finally, how important is prevention of dysplasia relative to prevention of cancer? Some studies have assessed both parameters as a combined endpoint,<sup>31</sup> which makes it difficult to determine the relative importance of preventing dysplasia compared with CRC. Nevertheless, the vast majority of IBD patients who develop CRC will first develop dysplasia, and because dysplasia can be monitored and a colectomy can be performed prior to CRC development, dysplasia may be the more relevant endpoint.

## 5-ASA CHEMOPREVENTION: INSIGHT INTO MECHANISMS

Although multiple clinical studies have suggested a role for 5-ASA in prevention of CRC in patients with IBD, less is known about how 5-ASA exerts a chemopreventive effect. In this regard, the mechanisms by which 5-ASA is thought to exert a chemopreventive effect were reviewed by Dr. Christoph Gasche of the Medical University of Vienna (Vienna, Austria).

The clinical efficacy of 5-ASA in IBD is presumably mediated via an anti-inflammatory action in the colon. However, the mechanisms by which 5-ASA exerts this anti-inflammatory effect have not been fully elucidated. Proposed mechanisms include modulation of inflammatory cytokine production,<sup>41</sup> inhibition of cyclooxygenase (COX; a regulator of inflammation and cell proliferation via formation of prostaglandins),<sup>42</sup> inhibition of inducible nitric oxide synthase (an important final effector of mucosal injury in IBD),<sup>43,44</sup> inhibition of nuclear factor  $\kappa$ B (a transcription factor responsible for the expression of multiple genes involved in inflammatory responses and promotion of carcinogenesis via blockade of apoptosis),<sup>42,45,46</sup> activation of the peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ; a nuclear receptor, highly expressed in the colon, which plays a key role in bacterial-induced inflammation),<sup>47</sup> and an antimicrobial action.<sup>48</sup> Although these mechanisms underlie the anti-inflammatory effect of 5-ASA, some may also contribute to a chemopreventive effect. For example, PPAR- $\gamma$  activation, which was first demonstrated by Rousseaux et al,<sup>47</sup> may be relevant to CRC prevention,<sup>47</sup> as PPAR- $\gamma$  is involved in many important cellular processes, including cell-cycle control and apoptosis.<sup>49</sup> Furthermore, the PPAR- $\gamma$  ligand rosiglitazone

has demonstrated efficacy for the treatment of active mild to moderate UC, supporting the role of PPAR- $\gamma$  as an important therapeutic target in UC.<sup>50</sup>

New studies have shown that 5-ASA (mesalamine) may also have direct chemopreventive effects in addition to anti-inflammatory properties. In addition to acting as an oxygen free-radical scavenger,<sup>42</sup> mesalamine has been shown to reduce the activity of the Wnt/ $\beta$ -catenin pathway in CRC cell lines via inhibition of protein phosphatase 2A.<sup>51</sup> Constitutive activation of this pathway, mainly because of mutation of a specific gene (*Apc*), is observed in most CRCs, and it is accepted that dysregulation of the Wnt/ $\beta$ -catenin pathway is essential for early colorectal tumorigenesis. Thus, any reduction in Wnt/ $\beta$ -catenin pathway activity is likely to be protective against the development of CRC. In addition to interfering with the Wnt/ $\beta$ -catenin pathway, 5-ASA has also been shown to disrupt epidermal growth factor receptor (EGFR) signaling (a pathway that activates mitogenic signaling in CRC cells) by enhancing the activity of SH-PTP2, a phosphatase that targets phosphorylated EGFR and thereby inactivates the receptor.<sup>52</sup>

As shown in cultured colorectal cells, mesalamine may also exert chemopreventive effects by improving the fidelity of cellular replication.<sup>53</sup> Inefficiency in any of the processes that govern replication fidelity (DNA polymerase accuracy, its proofreading activity, and the proficiency of the postreplication mismatch repair pathway) can lead to cancer. By improving replication fidelity (via prevention of frameshift mutations independent of mismatch repair proficiency),<sup>53</sup> mesalamine would be expected to reduce the speed and frequency of cancer development.

Additional in vitro studies have shown that mesalamine may also exert an effect on cell-cycle progression by slowing replication speed (without affecting microtubule polymerization or spindle orientation)<sup>54</sup> and activating intra-S-phase cell-cycle checkpoints, which block chromosome replication.<sup>55</sup> In addition, preliminary data from CRC cell lines suggest that mesalamine may counteract inflammation-driven carcinogenesis through demethylation of transcriptionally silenced tumor-suppressor genes.<sup>56</sup> CpG island methylation (which acts to silence tumor-suppressor genes) has been identified as a mechanism of colon carcinogenesis and is present not only in UC but also in sporadic CRC.<sup>57,58</sup>

Clearly, further research is needed to establish the extent to which these different effects play a role in any chemopreventive action associated with 5-ASA. Such research will undoubtedly affect the future role of 5-ASA for chemoprevention in patients with IBD and possibly also in patients with other conditions associated with an increased risk of CRC, such as Lynch syndrome (hereditary non-polyposis colorectal cancer) or multiple colonic polyps.

## CHEMOPREVENTION IN FAMILIAL ADENOMATOUS POLYPOSIS AND SPORADIC COLORECTAL CANCER: LESSONS FROM STUDYING A RARE DISEASE

Familial adenomatous polyposis (FAP) is a rare autosomal-dominant disease widely characterized by the development of hundreds of colorectal adenomas (though adenomas may also develop at other sites); patients with FAP are at a dramatically increased risk of developing CRC. In the final presentation of the meeting, Dr. Marcia Cruz-Correa of the University of Puerto Rico Cancer Center (San Juan, Puerto Rico) discussed studies of chemoprevention in FAP as a comparative model for discussion of future studies of chemoprevention in IBD.

With regard to chemoprevention, nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to provide secondary chemoprevention in patients with FAP. This has been shown in randomized, double-blind, placebo-controlled trials using sulindac and also using the COX-2-selective NSAID celecoxib. Sulindac 150 mg twice daily significantly reduced the mean number [to 44% of baseline after 9 months ( $P = 0.014$  versus placebo)] and diameter [to 35% of baseline versus placebo ( $P < 0.001$ )] of colorectal adenomas in patients with FAP.<sup>59</sup> Similarly, celecoxib 400 mg twice daily led to reductions of 28% ( $P = 0.003$ ) and 31% ( $P = 0.001$ ) in the mean number and diameter, respectively, of colorectal adenomas versus baseline.<sup>60</sup>

Even though the use of NSAIDs appears to be only partially effective, there is some evidence that the beneficial effects of NSAIDs on polyp number and size can be maintained over the long term.<sup>61</sup> NSAIDs are believed to exert their chemopreventive effect via reduction of prostaglandin synthesis, which occurs through inhibition of COX-1 and COX-2 enzymes.<sup>62</sup> NSAIDs evidently provide modestly effective treatment but not primary protection from the development of polyps in FAP. In a randomized, double-blind trial of 41 patients with FAP, there were no differences between patients treated with sulindac 75/150 mg twice daily and those treated with the placebo in mean number, size, or speed of development of adenomas over a 4-year period.<sup>63</sup>

Bioflavonoids may also offer secondary chemoprevention for patients with FAP. In a small uncontrolled study of 5 patients with FAP with prior colectomy, combination treatment with oral curcumin 480 mg and quercetin 20 mg 3 times a day reduced the mean number (60% decrease from baseline) and size (51% decrease from baseline) of ileal and rectal adenomas after a mean of 6 months, with minimal side effects.<sup>64</sup> The chemopreventive effects of bioflavonoids are believed to be a result of their antioxidant and anti-inflammatory properties. Various in vitro studies have shown that these agents act at the colonic mucosal level to inhibit tumor cell proliferation.<sup>65–67</sup>

The information gained from chemoprevention studies in FAP provides valuable insights into the future possibilities

**TABLE 2.** Preferred Components of Future Trials of 5-ASA Chemoprevention in Patients With Inflammatory Bowel Disease

Type of study	Comments
Large, prospective, placebo-controlled studies in the general IBD population	<ul style="list-style-type: none"> <li>● Gold standard</li> <li>● Very expensive and logistically difficult because of the large number of patients required</li> </ul>
Prospective studies in high-risk populations	<ul style="list-style-type: none"> <li>● Fewer patients needed</li> <li>● Could include patients with FAP and hereditary nonpolyposis CRC, and/or selected IBD patient groups</li> <li>● Need to record concurrent medication use and consider in statistical analyses</li> <li>● Generalizing results to other disease states and general IBD population may be an issue</li> </ul>
Retrospective studies using large population databases	<ul style="list-style-type: none"> <li>● Databases kept by medical insurance companies and/or national health services</li> <li>● Need to include data from more than one source</li> <li>● Information to be collected on: <ul style="list-style-type: none"> <li>— Patients undergoing colonoscopy</li> <li>— Family history</li> <li>— Concurrent medication use</li> <li>— Probiotic use</li> <li>— Cumulative dose of 5-ASA</li> <li>— Compliance</li> <li>— Degree and severity of inflammation</li> </ul> </li> </ul>

5-ASA, 5-aminosalicylic acid; IBD, inflammatory bowel disease; FAP, familial adenomatous polyposis; CRC, colorectal cancer.

of 5-ASA in IBD patients. In patients with FAP, the development of polyps is recognized as a risk factor for developing CRC, and as such the development of polyps is used as a surrogate marker in chemoprevention in FAP. Similarly, as patients with IBD develop dysplasia as a precursor to CRC, it may be possible to use dysplasia as a surrogate marker in CRC chemoprevention in IBD.

## DISCUSSION AND FUTURE RESEARCH DIRECTIONS

The presentations at this meeting demonstrate the status of our current knowledge regarding the chemopreventive role of 5-ASA in IBD-related CRC. The open discussion that followed focused on the remaining unanswered questions and how future studies should seek to address them.

There was general agreement on the limitations of existing retrospective studies. Because of the design of retrospective studies, key areas that have not been sufficiently addressed include concurrent use of other medications, accurate data on dosing, and collection of data on the number of patients who undergo colectomy. The attendees agreed that the ideal study would be a prospective, placebo-controlled study examining the incidence of CRC in the general IBD population (Table 2). However, given the incidence of CRC in this population, the attendees estimated such a study would need to include in excess of 50,000 subjects.<sup>68</sup> Because such a study is likely to be prohibitively expensive and logistically difficult, there are 2 options for future studies: (1) prospective

studies in high-risk populations and (2) retrospective studies using large population databases (Table 2). An additional option would be to identify other surrogate markers of neoplasia that occur early in the pathogenesis of IBD-related CRC and ascertain a sensitive and specific manner in which they could be used for clinical study.

## PROSPECTIVE STUDIES IN HIGH-RISK POPULATIONS

The first approach discussed was to assess whether 5-ASA is chemopreventive in patients with or without IBD at increased risk for developing CRC. Higher-risk patients discussed included those with FAP, those with hereditary nonpolyposis CRC, and/or those with selected types of IBD. As these patients have a higher risk of CRC than does the general population, fewer patients would need to be recruited for the study to be adequately powered. However, there may be problems in how to generalize results from such a study to other populations. Specifically, it is not clear to what extent the mechanism of developing CRC will be similar between any of these disease states and the general population. It is also unclear whether any chemopreventive action of 5-ASA will work similarly in the progression to CRC in these higher-risk disease states or in the general population. The situation becomes more complicated if studies assess progression to dysplasia or if only patients with dysplasia or IND are recruited, as dysplasia with the same appearance but arising

from different disease states may be different at the molecular level and may differ in the potential to develop into CRC. Furthermore, any studies assessing 5-ASA in high-risk populations will need to adequately address potential confounding variables (such as the degree of inflammation) and, importantly, to monitor the concurrent use of medications and account for these medications in any statistical analysis. The concurrent use of medications given as part of the standard of care will be particularly prevalent in patients with a very high risk of CRC (e.g., those with FAP). Also, an effect may be masked if the mechanism of chemoprevention for 5-ASA overlaps with these other medications being received concurrently.

### RETROSPECTIVE STUDIES USING LARGE POPULATION DATABASES

The second approach that was discussed was to use data from large population databases. Suitable databases include those maintained by medical insurance companies (e.g., U.S. Healthcare and Kaiser) and/or national health services (e.g., the UK General Practice Research Database and the Icelandic Cancer Registry). The attendees stressed the need to incorporate data from more than 1 source, as individual databases may not contain all the required information on, for example, clinical history and patient demographics, concurrent medication use, and compliance with prescribed medications.

One factor that must be addressed in any retrospective study assessing CRC risk is how to include data on patients undergoing colonoscopy. These may be the patients with the highest risk of CRC, and in many cases, colonoscopy is performed because of the presence or progression of dysplasia. Overall, the key factors the attendees thought should be examined in any study assessing CRC risk were family history, concurrent medication use, probiotic use (there is experimental evidence these microorganisms may play a protective role against the development of cancer in animal models),<sup>48</sup> cumulative dose of 5-ASA, and degree and severity of inflammation.

In the past 10 years, our knowledge of the role of 5-ASA as a chemopreventive agent in UC-related CRC has increased dramatically. However, there remains insufficient information about its true effects and who is most likely to benefit. Additional questions will need to be addressed once this initial ambitious work is completed. (1) Are systemic 5-ASA therapies more effective than topical formulations? (2) How important is the timing of exposure? (3) Should 5-ASA therapy be continued when patients require other treatments for disease control (e.g., immunomodulators or biologics in patients with IBD or colectomy in patients with FAP)? It was the hope of the attendees that this meeting report will act as a road map for how to perform future studies in this area. The results of these studies and of preclinical

studies examining the mode of action of 5-ASA should provide the basis for answering these questions.

### ACKNOWLEDGMENTS

The authors thank Noel Curtis (GeoMed) for professional medical writing support and Karen Middleton (GeoMed) for editorial assistance.

### REFERENCES

1. Carter MJ, Lobo AJ, Travis SP. Guidelines for the management of inflammatory bowel disease in adults. *Gut*. 2004;53:V1–16.
2. Kornbluth A, Sachar DB. Ulcerative Colitis Practice Guidelines in Adults (Update): American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol*. 2004;99:1371–1385.
3. Bernstein CN, Blanchard JF, Kliever E, et al. Cancer risk in patients with inflammatory bowel disease: a population-based study. *Cancer*. 2001;91:854–862.
4. Ekbom A, Helmick C, Zack M, et al. Ulcerative colitis and colorectal cancer. A population-based study. *N Engl J Med*. 1990;323:1228–1233.
5. Karlen P, Lofberg R, Brostrom O, et al. Increased risk of cancer in ulcerative colitis: a population-based cohort study. *Am J Gastroenterol*. 1999;94:1047–1052.
6. Jess T, Loftus EV, Jr., Velayos FS, et al. Risk of intestinal cancer in inflammatory bowel disease: a population-based study from olmsted county, Minnesota. *Gastroenterology*. 2006;130:1039–1046.
7. Jess T, Gomborg M, Matzen P, et al. Increased risk of intestinal cancer in Crohn's disease: a meta-analysis of population-based cohort studies. *Am J Gastroenterol*. 2005;100:2724–2729.
8. Palli D, Trallori G, Bagnoli S, et al. Hodgkin's disease risk is increased in patients with ulcerative colitis. *Gastroenterology*. 2000;119:647–653.
9. Winther KV, Jess T, Langholz E, et al. Long-term risk of cancer in ulcerative colitis: a population-based cohort study from Copenhagen County. *Clin Gastroenterol Hepatol*. 2004;2:1088–1095.
10. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut*. 2001;48:526–535.
11. 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.
12. Loftus EV, Jr. Epidemiology and risk factors for colorectal dysplasia and cancer in ulcerative colitis. *Gastroenterol Clin North Am*. 2006;35:517–531.
13. Rutter M, Saunders B, Wilkinson K, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. *Gastroenterology*. 2004;126:451–459.
14. Rutter MD, Saunders BP, Wilkinson KH, et al. Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. *Gastroenterology*. 2006;130:1030–1038.
15. Eaden J, Abrams K, Ekbom A, et al. Colorectal cancer prevention in ulcerative colitis: a case-control study. *Aliment Pharmacol Ther*. 2000;14:145–153.
16. Velayos FS, Loftus EV, Jr., Jess T, et al. Predictive and protective factors associated with colorectal cancer in ulcerative colitis: A case-control study. *Gastroenterology*. 2006;130:1941–1949.
17. Karlen P, Kornfeld D, Brostrom O, et al. Is colonoscopic surveillance reducing colorectal cancer mortality in ulcerative colitis? A population based case control study. *Gut*. 1998;42:711–714.
18. Riddell RH, Goldman H, Ransohoff DF, et al. Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. *Hum Pathol*. 1983;14:931–968.
19. Schlemper RJ, Riddell RH, Kato Y, et al. The Vienna classification of gastrointestinal epithelial neoplasia. *Gut*. 2000;47:251–255.
20. Montgomery E, Bronner MP, Goldblum JR, et al. Reproducibility of the diagnosis of dysplasia in Barrett esophagus: a reaffirmation. *Hum Pathol*. 2001;32:368–378.
21. Kiesslich R, Fritsch J, Holtmann M, et al. Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. *Gastroenterology*. 2003;124:880–888.
22. Bernstein CN, Shanahan F, Weinstein WM. Are we telling patients the

- truth about surveillance colonoscopy in ulcerative colitis? *Lancet*. 1994; 343:71–74.
23. Connell WR, Lennard-Jones JE, Williams CB, et al. Factors affecting the outcome of endoscopic surveillance for cancer in ulcerative colitis. *Gastroenterology*. 1994;107:934–944.
  24. Ullman T, Croog V, Harpaz N, et al. Progression of flat low-grade dysplasia to advanced neoplasia in patients with ulcerative colitis. *Gastroenterology*. 2003;125:1311–1319.
  25. Thomas T, Abrams KA, Robinson RJ, et al. Meta-analysis: cancer risk of low-grade dysplasia in chronic ulcerative colitis. *Aliment Pharmacol Ther*. 2007;25:657–668.
  26. Ullman TA, Loftus EV, Jr., Kakar S, et al. The fate of low grade dysplasia in ulcerative colitis. *Am J Gastroenterol*. 2002;97:922–927.
  27. Pinczowski D, Ekblom A, Baron J, et al. Risk factors for colorectal cancer in patients with ulcerative colitis: a case-control study. *Gastroenterology*. 1994;107:117–120.
  28. Gomes P, du BC, Smith CL, et al. Relationship between disease activity indices and colonoscopic findings in patients with colonic inflammatory bowel disease. *Gut*. 1986;27:92–95.
  29. Rubio CA, Befrits R, Ljung T, et al. Colorectal carcinoma in ulcerative colitis is decreasing in Scandinavian countries. *Anticancer Res*. 2001; 21:2921–2924.
  30. Lashner BA, Provencher KS, Bozdech JM, et al. Worsening risk for the development of dysplasia or cancer in patients with chronic ulcerative colitis. *Am J Gastroenterol*. 1995;90:377–380.
  31. 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.
  32. Moody GA, Jayanthi V, Probert CS, et al. Long-term therapy with sulphasalazine protects against colorectal cancer in ulcerative colitis: a retrospective study of colorectal cancer risk and compliance with treatment in Leicestershire. *Eur J Gastroenterol Hepatol*. 1996;8:1179–1183.
  33. Lashner BA, Provencher KS, Seidner DL, et al. The effect of folic acid supplementation on the risk for cancer or dysplasia in ulcerative colitis. *Gastroenterology*. 1997;112:29–32.
  34. Lindberg BU, Broome U, Persson B. Proximal colorectal dysplasia or cancer in ulcerative colitis. The impact of primary sclerosing cholangitis and sulfasalazine: results from a 20-year surveillance study. *Dis Colon Rectum*. 2001;44:77–85.
  35. Rubin DT, Losavio A, Yadron N, et al. Aminosalicylate Therapy in the Prevention of Dysplasia and Colorectal Cancer in Ulcerative Colitis. *Clin Gastroenterol Hepatol*. 2006;4:1346–1350.
  36. van Staa TP, Card T, Leufkens HG, et al. Prior aminosalicylate use and the development of colorectal cancer in inflammatory bowel disease (IBD): A large British epidemiological study. *Am J Gastroenterol*. 2003;98:S244.
  37. Bernstein CN, Blanchard JF, Metge C, et al. Does the use of 5-aminosalicylates in inflammatory bowel disease prevent the development of colorectal cancer? *Am J Gastroenterol*. 2003;98:2784–2788.
  38. van Staa TP, Card T, Logan RF, et al. 5-Aminosalicylate use and colorectal cancer risk in inflammatory bowel disease: a large epidemiological study. *Gut*. 2005;54:1573–1578.
  39. Swinson CM, Perry J, Lumb M, et al. Role of sulphasalazine in the aetiology of folate deficiency in ulcerative colitis. *Gut*. 1981;22:456–461.
  40. Prinz-Langenohl R, Fohr I, Pietrzik K. Beneficial role for folate in the prevention of colorectal and breast cancer. *Eur J Nutr*. 2001;40:98–105.
  41. Zimmerman MJ, Jewell DP. Cytokines and mechanisms of action of glucocorticoids and aminosalicylates in the treatment of ulcerative colitis and Crohn's disease. *Aliment Pharmacol Ther*. 1996;10 Suppl 2:93–98.
  42. Allgayer H. Review article: mechanisms of action of mesalazine in preventing colorectal carcinoma in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2003;18 Suppl 2:10–14.
  43. Hasko G, Szabo C, Nemeth ZH, et al. Sulphasalazine inhibits macrophage activation: inhibitory effects on inducible nitric oxide synthase expression, interleukin-12 production and major histocompatibility complex II expression. *Immunology*. 2001;103:473–478.
  44. Kennedy M, Wilson L, Szabo C, et al. 5-aminosalicylic acid inhibits iNOS transcription in human intestinal epithelial cells. *Int J Mol Med*. 1999;4:437–443.
  45. Greten FR, Eckmann L, Greten TF, et al. IKKbeta links inflammation and tumorigenesis in a mouse model of colitis-associated cancer. *Cell*. 2004;118:285–296.
  46. Wahl C, Liptay S, Adler G, et al. Sulfasalazine: a potent and specific inhibitor of nuclear factor kappa B. *J Clin Invest*. 1998;101:1163–1174.
  47. Rousseaux C, Lefebvre B, Dubuquoy L, et al. Intestinal antiinflammatory effect of 5-aminosalicylic acid is dependent on peroxisome proliferator-activated receptor-gamma. *J Exp Med*. 2005;201:1205–1215.
  48. Swidsinski A, Weber J, Loening-Baucke V, et al. Spatial organization and composition of the mucosal flora in patients with inflammatory bowel disease. *J Clin Microbiol*. 2005;43:3380–3389.
  49. Jalving M, Koornstra JJ, De JS, et al. Review article: the potential of combinational regimen with non-steroidal anti-inflammatory drugs in the chemoprevention of colorectal cancer. *Aliment Pharmacol Ther*. 2005;21:321–339.
  50. Lewis JD, Lichtenstein GR, Deren JJ, et al. A randomized, placebo-controlled trial of the PPAR-gamma ligand rosiglitazone for active ulcerative colitis. *Gastroenterology*. 2007;132(Suppl. 1):Abstract 639a.
  51. Bos CL, Diks SH, Hardwick JC, et al. Protein phosphatase 2A is required for mesalazine-dependent inhibition of Wnt/β-catenin pathway activity. *Carcinogenesis*. 2006;27:2371–2382.
  52. Monteleone G, Franchi L, Fina D, et al. Silencing of SH-PTP2 defines a crucial role in the inactivation of epidermal growth factor receptor by 5-aminosalicylic acid in colon cancer cells. *Cell Death Differ*. 2006;13: 202–211.
  53. Gasche C, Goel A, Natarajan L, et al. Mesalazine improves replication fidelity in cultured colorectal cells. *Cancer Res*. 2005;65:3993–3997.
  54. Reinacher-Schick A, Schoeneck A, Graeven U, et al. Mesalazine causes a mitotic arrest and induces caspase-dependent apoptosis in colon carcinoma cells. *Carcinogenesis*. 2003;24:443–451.
  55. Luciani MG, Campregher C, Fortune JM. Mesalazine affects cell cycle progression in colorectal cells by reversibly activating a replication checkpoint. *Gastroenterology*. 2007;132:221–235.
  56. Goel A, Nagasaka T, Gasche C, et al. Mesalazine inhibits DNA methyltransferases and reactivates methylation-silenced genes in human colon cancer cells. *Gut*. 2006;55(Nov. Suppl.):A75 (Abstract OP-G-327).
  57. Ahuja N, Li Q, Mohan AL, et al. Aging and DNA methylation in colorectal mucosa and cancer. *Cancer Res*. 1998;58:5489–5494.
  58. Issa JP, Ahuja N, Toyota M, et al. Accelerated age-related CpG island methylation in ulcerative colitis. *Cancer Res*. 2001;61:3573–3577.
  59. Giardiello FM, Hamilton SR, Krush AJ, et al. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. *N Engl J Med*. 1993;328:1313–1316.
  60. Steinbach G, Lynch PM, Phillips RK, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med*. 2000;342:1946–1952.
  61. Cruz-Correa M, Hyland LM, Romans KE, et al. Long-term treatment with sulindac in familial adenomatous polyposis: a prospective cohort study. *Gastroenterology*. 2002;122:641–645.
  62. Raju R, Cruz-Correa M. Chemoprevention of colorectal cancer. *Dis Colon Rectum*. 2006;49:113–124.
  63. Giardiello FM, Yang VW, Hyland LM, et al. Primary chemoprevention of familial adenomatous polyposis with sulindac. *N Engl J Med*. 2002; 346:1054–1059.
  64. Cruz-Correa M, Shoskes DA, Sanchez P, et al. Combination treatment with curcumin and quercetin of adenomas in familial adenomatous polyposis. *Clin Gastroenterol Hepatol*. 2006;4:1035–1038.
  65. Hosokawa N, Hosokawa Y, Sakai T, et al. Inhibitory effect of quercetin on the synthesis of a possibly cell-cycle-related 17-kDa protein, in human colon cancer cells. *Int J Cancer*. 1990;45:1119–1124.
  66. Ranelletti FO, Ricci R, Laroocca LM, et al. Growth-inhibitory effect of quercetin and presence of type-II estrogen-binding sites in human colon-cancer cell lines and primary colorectal tumors. *Int J Cancer*. 1992;50: 486–492.
  67. Sharma RA, Ireson CR, Verschoyle RD, et al. Effects of dietary curcumin on glutathione S-transferase and malondialdehyde-DNA adducts in rat liver and colon mucosa: relationship with drug levels. *Clin Cancer Res*. 2001;7:1452–1458.
  68. Rubin DT, Lashner BA. Will a 5-ASA a day keep the cancer (and dysplasia) away? *Am J Gastroenterol*. 2005;100:1354–1356.