EDITORIAL

Risk for colorectal cancer in ulcerative colitis: Changes, causes and management strategies

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Abstract

The risk of colorectal cancer for any patient with ulcerative colitis is known to be elevated, and is estimated to be 2% after 10 years, 8% after 20 years and 18% after 30 years of disease. Risk factors for cancer include extent and duration of ulcerative colitis, primary sclerosing cholangitis, a family history of sporadic colorectal cancer, severity of histologic bowel inflammation, and in some studies, young age at onset of colitis. In this review, the authors discuss recent epidemiological trends and causes for the observed changes. Population-based studies published within the past 5 years suggest that this risk has decreased over time, despite the low frequency of colectomies. The crude annual incidence rate of colorectal cancer in ulcerative colitis ranges from approximately 0.06% to 0.16% with a relative risk of 1.0-2.75. The exact mechanism for this change is unknown; it may partly be explained by the more widespread use of maintenance therapy and surveillance colonoscopy.

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INTRODUCTION AND EPIDEMIOLOGY

Since the first report of an inflammatory bowel disease (IBD) case associated with colorectal cancer (CRC) by Crohn and Rosenberg[1], significant efforts have been made to elucidate this presumed association. Nowadays, the association between IBD and the increased risk for CRC is widely accepted. Although CRC, complicating ulcerative colitis and Crohn's disease, accounts only for 1%-2% of all cases of CRC in the general population, it is considered a serious complication of the disease and accounts for approximately 10%-15% of all deaths in IBD patients[2]. The age at diagnosis of CRC associated with IBD is 15-20 years earlier compared to sporadic cancers. In the meta-analysis by Eaden *et al*[3], the average age at diagnosis was 43.2 years. Similarly, in a recent publication from Eastern Europe[4], it was found to be 50.9 years, 10-15 years younger compared to sporadic CRC cases from the same area (62.2 years)[5]. According to US[6] and Canadian[7] publications, almost two-thirds of the affected patients were males, yet results are conflicting[4,8]. In addition, the frequency of multiple CRCs is higher than in patients with sporadic CRC[9].

The increased risk of CRC in UC is almost a universal finding[3,10-13], yet the extent of this risk varies considerably with differences in study design and geographic area. The initial reports were published by tertiary gastroenterology centers, thus the high risk detected might have been a consequence of referral bias and over-interpretation due to the high percentage of extensive and chronically active cases in these cohorts. Results of population-based studies are more reliable; however, several geographical and ethnic differences have been noted.

The report of the meta-analysis by Eaden *et al*[3] in 2001 was one of several milestones in this subject. The incidence of UC-associated CRC was estimated based on 116 articles involving 54 478 patients in whom 1698 CRC cases were detected. This was a mixture of referral center-based, hospital-based, and population-based studies of variable methodological qualities and levels of detail. The reported incidence was higher in the US

Table 1 Risk of colorectal cancer in recent population-based studies

Study	Location	Observed period	UC cohort size	Follow-up (person- years)	CRC	Annual crude incidence (%)	Cumulative incidence at 30 years (%)
North America							
Bernstein et al[7]	Manitoba, Canada	1984-1997	2672	19655	36 CRC	0.16	NR
Bernstein et al[7]	Manitoba, Canada	1984-1997	2672	19655	13 rectum	0.06	NR
Jess et al[8]	Olmsted County, USA	1940-2004	378	5567	6	0.10	2
Europe							
Winther et al[16]	Copenhagen County, Denmark	1962-1987	1160	22290	13	0.06	2.1
Palli et al[15]	Florence, Italy	1978-1992	689	7877	10	0.12	NR
Lakatos et al[4]	Veszprem, Hungary	1974-2004	723	8564	13	0.15	7.5

NR: Not reported.

and UK than in Scandinavia. Only limited data were available from other European countries, for example Eastern Europe[14]. Based on the 41 studies, the duration of UC was 3 (2-4) cases per 1000 person-years, equaling an annual risk of 0.3% or 1 in 333 patients. However, this calculation did not take into account varying degrees of annual risk based on the duration of UC. The well known risk figures at 10 years' (1.6%), 20 years' (8.3%), and 30 years' disease (18.4%) duration were derived from 19 studies that reported CRC incidence according to UC duration at a 10-year interval. In other words, one would expect to diagnose CRC in almost one in five individuals with UC after 30 years' disease duration.

The new, independent population-based studies suggest, however, a lower incidence rate (Table 1)[4,7,8,15-17]. During the follow-up of 689 UC patients in Florence between 1978 and 1992, ten new CRC cases were reported[15], equaling a yearly incidence of 0.13%. Bernstein et al[7] reported 36 colon and 13 rectal cancers in 2672 patients, the annual risks of colon and rectal cancer being 0.16% and 0.06%, respectively, in a follow-up of 19 665 person-years. In an inception cohort from Denmark between 1962 and 1987, only 13 cases of CRC were reported among 1160 patients with UC, and followed up for 22 290 person-years, yielding an annual risk of 0.06%[16]. The 30-year cumulative CRC risk was 2.1%. The rate of surgery in Denmark is among the highest reported worldwide. A much smaller cohort of 378 patients with UC diagnosed between 1940 and 2001 in Olmsted County were followed up for 5567 person-years, leading to detection of six CRCs[8]. The crude annual incidence was 0.1%, while the cumulative risk after 30-years' disease duration was as low as 2.0%. The authors of the study concluded that, in general, the risk of CRC is not increased in UC, only in patients with extensive disease. Finally, despite one of highest incidence rates for sporadic CRC, and a much lower non-CRC related colectomy rate (3.4%), the incidence of UC-related CRC was only moderately increased in a Hungarian population-based study. The cohort consisted of 723 individuals diagnosed with UC over a 30-year period and followed up for 8564 person-years. The cumulative risk for CRC during the follow-up of these 723 UC patients was 0.6% after a disease duration of 10 years, 5.4% after 20 years, and 7.5% after 30 years, with an overall incidence

rate of 1.52/1000 person-years. Somewhat contradicotry, Terdiman et al[18] still report a significantly increased risk for both UC and CD (OR$_{CRC}$, 6.72-6.60) based on insurance database reports in 364 IBD-CRC and 1172 IBD patients. Similarly intriguing data were presented at the 2008 European Crohn's and Colitis Organization Congress. Based on the Dutch National Registry, almost 50% of all IBD-associated CRC cases developed in patients with Crohn's disease[19]. How these reports might influence current surveillance strategies is unclear.

Therefore, these population-based studies would indicate a much lower UC-related CRC incidence rate, ranging from 1/500 to 1/1600 patients annually. The causes for this change remain unclear, but possibilities include more widespread institution of surveillance colonoscopy and a higher prevalence of patients on maintenance therapy. An additional option may be that the population-based acquisition of the data, in other words, the study design per se, is at least partially responsible for the apparent decline in the incidence rates. In these studies, the proportion of severe or extensive cases was much lower compared to that reported by tertiary centers[3,17].

The risk of CRC can also be expressed in relative terms, as standardized morbidity ratio (SMR; observed cancers in a UC cohort divided by expected cancers, with expected rates derived from the general population) or an incidence rate ratio (IRR; observed incidence of cancers in a UC cohort divided by observed incidence of cancers in a control cohort of the general population). The SMR or IRR values in the new population-based studies were only moderately increased in Denmark, Canada, and Italy. Compared to the general population, the risk varied between 1.05 and 2.75. Although these studies suggest that the relative risk of CRC is considerably lower than previously described, some would argue that the low rates of CRC observed in these studies are the successful result of timely and appropriate access to good health care, including maintenance therapies, surveillance colonoscopy, and surgery[20]. This is further corroborated by the data arising from a large colonoscopic surveillance program at St. Mark's Hospital between 1970 and 2001[17]. Six hundred patients with extensive UC were followed up for 5932 person-years. The cumulative probability of CRC in UC patients undergoing surveillance was only 7.6% after

30 years. Linear regression suggested that CRC incidence declined over the course of the study, supporting a role for surveillance in decreasing the risk for CRC. In addition, although the prognosis of UC-related CRC cases has generally been considered to be worse compared to sporadic cases, the experience from the study at St. Mark's Hospital[17] is much better. In 600 patients during 5932 patient-years of follow-up, 30 patients (5%) developed CRC, with a 5-year survival rate of 73.3%. Similarly high 5-year survival rates were reported from the Mayo Clinic[21] (55%) and from Eastern Europe[4] (68.4% at 5 years and 10 years).

The incidence of colorectal dysplasia in UC is even more difficult to determine than the incidence of CRC. There is considerable interobserver variability as well as a lack of uniform definitions. In addition, underlying inflammation might influence the diagnosis of dysplasia. Two population-based studies have examined the incidence of colorectal dysplasia in UC. In Sweden[22], 52/204 patients (24%), including 66% with pancolitis developed dysplasia at some points in their disease course, during follow-up with a median of 16.5 years. Lower incidence rates were reported from the US[23], where adherence to surveillance was lower. A total of 22 dysplastic lesions were diagnosed. In concordance, relatively low incidence rates were reported from the St. Mark's Hospital[17]. During a follow-up of 5080 person-years, the cumulative probability of dysplasia at 20 years was 7.7% and 15.8% at 30 years. Low grade dysplasia developed in 7.8%, while high grade developed in 3.2% of the patients. In addition, polypoid dysplasia was revealed in 3.3% and sporadic adenoma in 5.3% of the patients.

RISK FACTORS FOR COLORECTAL CANCER IN ULCERATIVE COLITIS

The most important risk factors for UC-associated CRC are disease duration and extent. The possible mechanisms include chronic inflammation and as the duration of chronic bowel inflammation increases, so does the risk for colorectal dysplasia and CRC. In some studies, this annual risk rises exponentially with a duration beyond 30 years. This has led some guidelines to recommend surveillance colonoscopy every 1 year to 3 years between years 8 and 20 and every 1 year to 2 years thereafter[24]. In contrast, some of the recently published population-based studies could not demonstrate a clear-cut relation in UC duration[8], and cancer risk or the gradual increase of the risk was much lower[4,7].

In the landmark trial by Ekbom *et al*[12], more than 3000 UC patients were followed up and the risk for CRC increased gradually from 1.7-fold in proctitis and 2.8-fold in left-sided colitis to 14.8-fold in pancolitis, compared to the general population. Most studies including the meta-analysis by Eaden *et al*[11], have come to similar conclusions. The overall prevalence of CRC among patients with UC in all 116 studies was 3.7%, but when restricted to the 35 studies that stratified their analyses by extent of UC, the prevalence of CRC among patients with ex-
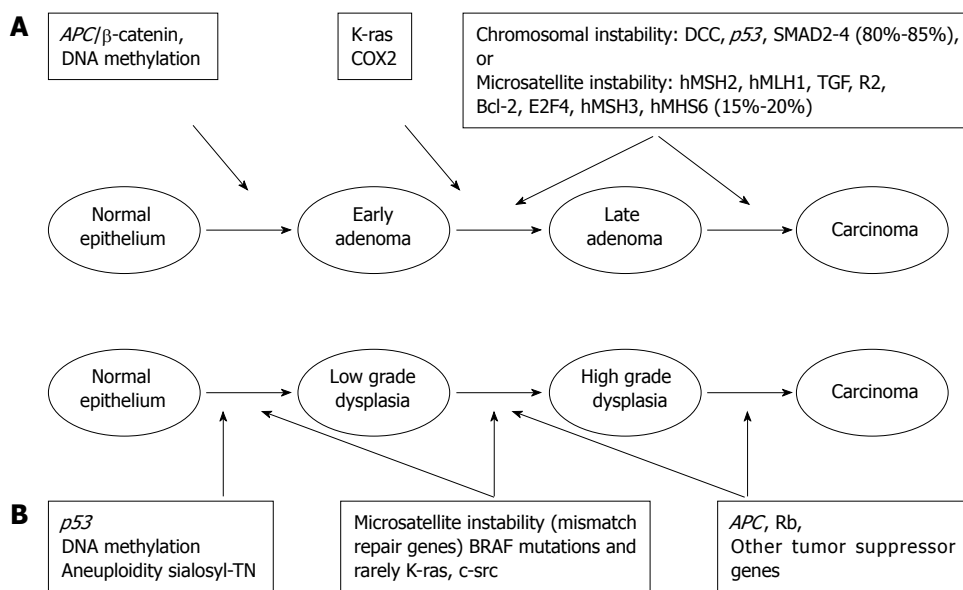
tensive involvement rose to 5.4%.

Important risk factors include primary sclerosing cholangitis (PSC)[25-27], family history of CRC[28], whereas the role of other factors, such as age at onset of UC, frequency of flare-ups, severity of inflammation[29], "backwash ileitis"[30], smoking, medical therapy used (5-aminosalicylates, azathioprine)[31], is more controversial.

There is some debate as to whether patients with an early onset of colitis have a higher risk than patients with a later onset. Ekbom *et al*[12] identified the age below 15 years at onset as an independent risk factor for CRC. The cumulative risk for CRC after a disease duration of 35 years was 40% in extensive colitis if the disease started before the age of 15 years, while it was 25% if the disease onset was between 15 years and 39 years of age. Furthermore, disease onset during childhood was also established as an independent risk factor in the meta-analysis[3]. In contrast, other studies could not confirm this finding[4,32]; for example the age at onset above 30-40 years was associated with a higher risk in an American study, compared with a group of patients with onset below 20 years of age[33]. Since disease duration may be longer, theoretically, the risk of CRC should be greater in patients whose disease begins during early childhood.

Several studies have recognized PSC as a risk factor for CRC in UC patients[4,27,34,35]; however, this was not proven in all studies[36]. In one of the first reports, Broome *et al*[37] noted in a case-control study that the prevalence of PSC was 28% in the 17 patients with UC investigated with colorectal dysplasia or DNA aneuploidy *vs* 0 in the 55 patients without precancerous abnormalities. In the study by Kornfeld *et al*[35], the cumulative CRC risk was 33% at 20 years and 40% at 30 years after UC diagnosis. In addition, the percentage of right-sided CRCs was higher in the subgroup of colitis patients with PSC[34]. In the study by Shetty *et al*, right-sided CRCs were observed in 76% of pateitns. The mechanism by which PSC induces CRC remains unclear. It has been hypothesized that alterations in the bile salt pool and a high concentration of bile acids in the colon may, at least partially, be responsible for the increased risk, but evidence also supports a strong association between PSC and quiescent to mild pancolitis. Colonic disease activity was milder in the 29 patients with PSC-IBD compared to the 58 patients with extensive UC without PSC in the study by Lundqvist *et al*[38]. Furthermore, patients with PSC were twice as likely to have never required corticosteroid treatment (52% *vs* 24%). In another study, patients with PSC-IBD were significantly less likely to require a proctocolectomy, in comparison to patients with extensive UC without PSC[27].

The role of smoking in the development of UC-associated CRC has been a focus of controversy. Nonetheless, it has been identified as a risk factor for sporadic CRC[39]. In UC, an additive protective role might be hypothesized, as it might attenuate the inflammation and prevent relapses.

Finally, until recently, no direct evidence was available to support a link between the severity of inflammation

A

| APC/β-catenin, DNA methylation | | K-ras COX2 | | Chromosomal instability: DCC, *p53*, SMAD2-4 (80%-85%), or Microsatellite instability: hMSH2, hMLH1, TGF, R2, Bcl-2, E2F4, hMSH3, hMHS6 (15%-20%) |

Normal epithelium → Early adenoma → Late adenoma → Carcinoma

B

| p53 DNA methylation Aneuploidity sialosyl-TN | | Microsatellite instability (mismatch repair genes) BRAF mutations and rarely K-ras, c-src | | APC, Rb, Other tumor suppressor genes |

Normal epithelium → Low grade dysplasia → High grade dysplasia → Carcinoma

Figure 1 Summary of geneticalterations in sporadic colorectal cancer (**A**) and colitis-associated colorectal cancer (**B**). The timing of p53 and APC mutations is different; unlike in sporadic neoplasia, mutations and LOH in p53 are early events in UC-associated CRCs. The opposite was reported for APC mutations[42].

and the risk for CRC. A number of case-control studies with negative result relied on indirect outcome measures such as hospitalization, frequency of diagnostic testing, and frequency of symptomatic exacerbations[40]. Rutter et al[29] retrospectively reviewed endoscopic and pathologic reports of 68 UC patients with CRC or dysplasia and 136 UC patients without CRC, and assigned a severity score to each segment of the colon for each colonoscopy. The endoscopic (OR, 2.5; 95% CI, 1.4-4.4) or histologic (OR, 5.1; 95% CI, 2.4-11.1) scores were associated with the risk of CRC in univariate analysis. In addition, the histologic score was identified as an independent risk factor for CRC even after adjustment for confounding variables. This association was recently confirmed in a report from the Texas University[41]. During follow-up, 15 UC patients progressed to advanced neoplasia (high-grade dysplasia or colorectal cancer), and 65 progressed to neoplasia (low-grade dysplasia, high-grade dysplasia, or colorectal cancer). Univariate and multivariate analysis demonstrated significant relationships between histologic inflammation over time and progression to advanced neoplasia (HR, 2.2-3.4).

GENETICS OF ULCERATIVE COLITIS ASSOCIATED COLORECTAL CANCERS

Both genetic and environmental factors contribute to the pathogenesis of CRC in IBD. Most sporadic CRC cases arise from a preceding adenoma (adenoma-carcinoma cascade) associated with unique genetic mutations. IBD-related cancers, however, are associated with a partially different genetic background[42]. The increased risk is thought to be an acquired event in IBD, although common inherited factors (e.g. glycosylation of mucin) have been proposed as a link between both forms of IBD and CRC[43].

Complete elucidation of the mechanism of UC-CRC carcinogenesis will require further investigations; however, chronic inflammation is thought to be the most

important driving mechanism. Although the same three molecular pathways that have been described for sporadic colon carcinogenesis [loss of heterozygosity (LOH), microsatellite instability (MSI) and CpG methylator phenotype (CIMP)] are also found in colitis-associated neoplasms, yet the timing and frequency of some of the key genetic changes are different (Figure 1), possibly due to the different main driving mechanisms.

Changes in DNA methylation and microsatellite instability are also frequently found at an early stage in UC-associated CRCs. The prevalence in dysplasia-cancer cases ranges from < 1% to 70%[44-46], for example hypermethylation of p14ARF occurs in approximately 30% of cases with dysplasia[47]. Unlike sporadic MSI-H (MSI-high) CRCs, MSI-H IBD CRCs present with heterogeneous mismatch repair defects involving MLH1, MSH2, MSH6, or PMS2, and a low frequency of MLH1 promoter methylation. They exhibit frequent BRAF but no KRAS mutations and frameshift mutations in genes containing coding repeat sequences. IBD patients exhibiting MSI-H present at younger age at diagnosis, and there is neither female predominance nor right-sided predominance[48]. In UC patients with MSI-H CRCs, MSI could already be demonstrated 2-12 years prior to the diagnosis of CRC in about 25% of the cases[49]. In contrast, hypermethylation of different target genes is a relatively rare event (MINT1, 2, 31, hMLH1, p16, p14, MGMT, HPP1, SFRP1, ERa and LINE-1)[50]. Thus MSI seems to be an important mechanism in UC-related carcinogenesis, at least in a subset of UC-CRC cases.

Loss of heterozygosity is a frequent but late event, primarily affecting SMAD4 and DCC loci (PACAP at 18p or DCC, SMAD2, SMAD4, GALNR at 18q-n)[51]. Unlike in sporadic CRCs, IBD-associated cancer mutations and LOH in p53 are early events that can already be found in macroscopically normal looking mucosa[52-54]. In contrast, mutations in k-ras are relatively infrequent. Since mutations in k-ras are believed to occur in sporadic adenoima cases[55], this may partially explain the flat growth pattern of CRCs in IBD. Mutations in k-ras are

associated with polyp formation, which might explain why neoplasias in IBD are usually flat. Mutations of APC are infrequent (0%-3%), late events in UC, often occurring only in HGD or cancers[56]. Genetic events in DALM (dysplasia-associated lesion or mass) are similar to those observed in other UC-CRC cases including changes in MSI and LOH[57].

Recently, an association was reported by the Mayo Clinic[58] between the G308A TNFα polymorphism and the risk of UC-associated CRC in 114 UC-CRC cases and matched controls, further corroborating the importance of chronic inflammation in CRC pathogenesis.

HOW CAN WE DECREASE THE RISK OF CRC IN IBD?

The positive association between UC and CRC raises several practical questions. The causes behind the changing trends in UC-related CRC epidemiology are complex. One key element may be the early diagnosis and treatment of precancerous lesions by colonoscopic surveillance or sometimes prophylactic colectomy, while the third option is primary chemoprevention. Nowadays, prophylactic colectomy is obsolete. Nonetheless, the high colectomy rate, especially in Scandinavian countries has been associated with lower CRC risks[16]. There are however, obvious changes in the patient management, also in Scandinavia. In the new population-based cohorts, a decrease in the colectomy rate can be observed[59].

ENDOSCOPIC SURVEILLANCE IN IBD

Endoscopic surveillance remains an important but often disputed cornerstone of IBD management[60]. Colonoscopic surveillance to detect dysplasia and/or cancer is routinely indicated in compliant UC patients in clinical practice. Surveillance colonoscopy may permit earlier detection of CRC, with a correspondingly improved prognosis; however, unequivocal evidence is lacking that surveillance colonoscopy prolongs survival in patients with UC. Based on previous epidemiological data, international guidelines of the Crohn's and Colitis Foundation of America (CCFA)[24] and very recently the European Crohn's and Colitis Organisation (ECCO)[61] suggest a relatively strict surveillance policy. Whether these recommendations require adjustments in light of new epidemiological data that suggest a much lower CRC incidence remains questionable. Many factors (e.g. cost effectiveness, geographical differences, access to endoscopy and pathology) need to be considered. Nonetheless, it is possibile that the lower incidence rates reported in recent population-based studies are at least partly a consequence of the vigorous surveillance programs.

As of today, the guidelines regarding the surveillance of CRC in UC patients can be summarized as follows: (1) Surveillance endoscopy should be performed in remission; (2) Initial screening colonoscopy should be performed in each patient after a 8-10 year disease duration, partly to reassess disease extent; (3) Regular surveillance should begin after 8-10 years for pancolitis and after 15-20 years for left-sided disease. There should be a decrease in the screening interval with increasing disease duration (from 2 to 1 year). No surveillance is indicated in proctitis; (4) Two to four random biopsy specimens, every 10 cm, should be taken from the entire colon, with additional samples of suspicious areas. Alternatively methylene blue or indigo carmine chromoendoscopy can be offered for appropriately trained endoscopists and is superior to random biopsies in the detection rate of neoplastic lesions; and (5) Patients with primary sclerosis cholangitis represent a subgroup at higher risk, thus surveillance should be performed annually from the time of PSC diagnosis.

The use of random biopsies is being increasingly criticized. Since the reports by Rutter *et al*[62] and Rubin *et al*[63], we know that dysplasia (71.7%-77.3%) and cancer (89.3%-100%) were macroscopically visible during colonoscopies in UC patients without PSC. Thus, the cost of additional random biopsies is difficult to justify. On the other hand, random biopsies visualize only 1% of total colonic mucosa surface area, promoting a high sampling error. In a retrospective analysis, it was demonstrated that the probability of detecting dysplasia was 90% if 33 and 95% if 56 random biopsies were taken[64], with current guidelines for dysplasia surveillance recommending a minimum of 33 biopsies. In addition, almost half of patients with dysplasia initially detected in flat mucosa were later diagnosed to have colorectal cancer in the colectomy specimen[65]. Furthermore, almost one-third of patients with low grade dysplasia progressed to high grade dysplasia or cancer during follow-up. In the most recent meta-analysis, low-grade dysplasia was found to be associated with a 9-fold increased risk of developing CRC and a 12-fold risk of developing advanced neoplasia[66]. However, because some follow-up studies of patients with low-grade dysplasia have shown a low rate of CRC development (2%-10% during a 10-year follow-up)[67], it seems there is a reasonable compromise to continue surveillance with extensive biopsy sampling at shorter intervals (e.g. 3-6 mo) in those who will adhere strictly to the surveillance program. In summary, a patient with low-grade dysplasia in flat mucosa should be offered proctocolectomy or repeat surveillance biopsies within 3-6 mo, while high-grade dysplasia in flat mucosa and adenocarcinoma are indications for proctocolectomy.

Raised lesions on a background of UC have been traditionally referred to as dysplasia-associated lesion or mass (DALM). Until recently, this finding had been considered an absolute indication for colectomy. It is increasingly recognized, however, that some of these raised lesions may resemble sporadic adenomas and that they may be treated by endoscopic resection[68], if polypectomy can be performed safely and completely, without any dysplasia present in the adjacent mucosa in patients who will adhere to strict surveillance program afterwards.

The detection of CRC by surveillance is still not very

Table 2 Summary of studies investigating the chemopreventive effect of sulfasalazine and 5-ASA therapies in ulcerative colitis

Study	Study design	n	Drug studies	Principal outcome
Pinczowski et al[31]	Case-control	298	Sulfasalazine > 3 mo	OR_{CRC}: 0.38 (95% CI, 0.2-0.69) patients administered sulfasalazine
Moody et al[101]	Case-control	175	Sulfasalazine < 6 mo	10-fold elevated risk in non-exposed patients (30% vs 3%)
Eaden et al[40]	Case-control	102	Sulfasalazine, mesalasine regular use	OR_{CRC}: 0.25 (95% CI, 0.13-0.48) in regular users
Lindberg et al[102]	Cohort study	143	Sulfasalazine > 6 mo	Non-significant decrease of risk (34% vs 44%)
Bernstein et al[87]	Case-control	373	5-ASA	Non-significant elevation of risk in patients exposed
Rutter et al[29]	Case-control	204	5-ASA	Non-significant elevation of risk of dysplasia in patients exposed
Rubin et al[90]	Case-control	124	5-ASA > 1.2 g regular use	OR_{CRC}: 0.28 (95% CI, 0.09-0.85) in regular users

encouraging. Almost half of 92 CRC cases identified in surveillance programs in 1916 UC patients were in advanced stages (Dukes' C or D)[69] and only 12% of CRC cases were identified during surveillance colonoscopies in earlier studies. In concordance, a meta-analysis by the Cochrane group in 2006[70] failed to demonstrate a benefit for surveillance programs in preventing CRC-related death in UC (OR, 0.81, 95% CI, 0.17-3.83), but authors included only two studies in their final analysis. Furthermore, in the largest and most meticulous screening programs[17] reported to date, involving 600 patients, 2627 colonoscopies, 5932 patient-year of follow-up and a caecal intubation rate of 98.7% without significant complications, 16 of 30 cancers were interval cancers.

The diagnosis of dysplasia is demanding. During a period of active disease, it is almost impossible to differentiate between inflammation and true dysplasia. Furthermore, a significant interobserver variation was reported for the detection of dysplasia, and an agreement concerning low-grade dysplasia may be as low as 43%. Therefore, because of important prognostic implications, any case of dysplasia should be confirmed by an experienced pathologist[71,72].

Targeted biopsies represent an alternative to random biopsies. All studies have confirmed an improved yield of surveillance colonoscopy by dye spraying (e.g. methylene blue or indigo carmine). When applied, random biopsies of apparently normal mucosa had no additional value compared to targeted biopsies obtained after dye staining of the mucosa. In the study by Rutter et al[73], the clinical accuracy of consecutive, random (n = 2904) and targeted (indigocarmine: 157) biopsies was compared. Nine dysplastic lesions were diagnosed at chromoendoscopy, while no dysplasia was detected in random biopsies and no additional lesions were detected. Separate prospective studies have arrived at similar conclusions[74,75], including the study by Hurlstone et al, who compared magnified chromoendoscopic surveillance in 350 UC patients and 350 disease-extent matched controls on traditional surveillance using random biopsies. Sixty-nine dysplastic lesions were identified by chromoendoscopy, compared with only 24 dysplastic lesions in the traditional surveillance group (P < 0.001). The diagnostic yield for detecting a dysplastic lesion increased in these studies by 3-4.5 folds and comparable diagnostic yields from chromoendoscopy have been obtained with both methylene blue and indigo carmine. In fact, Marion et al[76] was the first to identify a significant increase in the total number of patients (not just lesions) with dysplasia following chromoendoscopy (1.5-fold).

Currently there are only limited data available regarding the role of advanced endoscopic techniques [e.g. narrow band imaging (NBI), fluorescence endoscopy, optical coherence tomography or confocal laser endomicroscopy][77,78]. In a study by Kiesslich et al[79] endomicroscopy or colonoscopy were performed in 153 UC patients. Despite a significantly lower number of biopsies taken in the targeted group, the number of identified dysplastic lesions increased by 4.7 folds. In a very recent report by the same group[80], confocal chromoscopic endomicroscopy was superior to chromoscopy alone for the detection and characterization of intraepithelial neoplasia in chronic ulcerative colitis.

In contrast, the use of NBI[81] did not improve the diagnostic accuracy compared to conventional colonoscopy. Although more lesions were identified using NBI, an almost equal number of dysplastic foci were identified and missed by both methods. Despite the promising results, further studies are needed before the use of these advanced techniques can be suggested in clinical practice.

CHEMOPREVENTION IN IBD-IS IT POSSIBLE?

Given the theory that chronic inflammation is the driving force behind malignant transformation, the possibility exists for the use of maintenance anti-inflammatory therapy as primary chemoprevention[82]. The ideal chemopreventive agent would be safe, effective at preventing neoplastic progression, inexpensive, and able to prevent flares and control disease activity and symptoms. 5-aminosalicylic acid (5-ASA), including mesalazine and sulfasalazine, are attractive candidates; they are safe, relatively inexpensive, and effective maintenance therapy. Mesalazine is a potent anti-inflammatory drug exhibiting strong scavenger capacity, affecting in vitro NFκB activity and apoptosis at least partly by increasing peroxisome proliferator-activated receptor-γ (PPAR-γ) expression[83-85].

However, data supporting this possible chemopreventive effect are somewhat conflicting (Table 2). Promising results were produced by a case-control study by Eaden et al[40], who identified 102 cases of CRC from a population of UC patients treated at a combination of academic and community-based gastroenterology practices. Overall

the use of any 5-ASA compound was associated with a 75% decreased risk of CRC (95% CI, 0.13-0.48). Among all 5-ASA compounds, mesalamine use was associated with the greatest degree of protection, providing the most benefit at doses greater than 1.2 g/d (OR, 0.09; 95% CI, 0.03-0.28). Sulfasalazine use was associated with a smaller protective effect, which was statistically significant only at doses of 2 g/d or more (OR, 0.41; 95% CI, 0.18-0.92). Of note, however, > 2 outpatient visits/year, use of systemic steroids, and regular colonoscopic surveillance were also associated with the decreased risk. If sulfasalazine is used, folate supplementation is mandatory, since folate deficiency alone might increase the risk of CRC in IBD[86]. In contrast, other studies, including the one by Bernstein *et al*[87], failed to demonstrate a protective effect even after stratifying for dose and duration of therapy. Since controlled trials would necessitate withholding a drug used for remission maintenance by randomizing some patients into the placebo arm, these studies will never be performed due to ethical reasons. In addition, based on available data and statistical power analysis, theoretically, the follow-up of a total of 5260 patients for at least 10 years would be necessary to demonstrate a positive effect for 5-ASA *vs* placebo, if the estimated risk of cancer is approximately 0.51[88]. A much larger sample size would be required if a comparison with placebo would not be an option and the primary objective would be to assess a dose response.

A more recent meta-analysis has provided a systematic overview of the studies available with respect to 5-aminosalicylates[89]. A total of nine studies, three cohort and six case-control studies, were included. Half of the studies found significantly diminished incidence of colon cancer in aminosalicylate users, with an adjusted summary OR covering all trials of 0.51 (95% CI, 0.37-0.69). Only two studies focused on dysplasia incidence and 5-ASA use was not associated with lower risk of dysplasia (OR, 1.18). Nonetheless, the combination of both endpoints, dysplasia and cancer, again resulted in an OR of 0.51 (95% CI, 0.38-0.69). Surprisingly, the results were similar in short-term users (2-6 mo) or long-term users (2-20 years) with an OR of 0.56 and 0.50, respectively. An even lower OR was obtained in patients on a dose of 1.2 g/d or more (OR, 0.19-0.28). These conclusions were confirmed by a very large British study in regular mesalazine users with an OR of 0.31. In contrast, in the subgroup of CD patients, although numbers were small, the OR was 1.66, indicating no preventive effect for 5-ASA. Therefore, evidence in UC may not be simply extrapolated to CD. In the editorial[65] of this meta-analyis, the authors concluded that 5-ASA is a probable chemopreventive agent based on safety and current maintenance use. Reports following the meta-analysis were also contradicory. Investigating 96 cases and matched controls, Rubin *et al*[90] found that aminosalicylate use of 1.2 g/d or more was associated with a 72% reduction in the odds of dysplasia/CRC (OR, 0.28; 95% CI, 0.09-0.85). A trend for dose response was also reported (*P* = 0.056). Of note, the OR for doses between 1.2-2.4 g/d was 0.19, while for doses ≥ 2.4 g/d

it was 0.48. In contrast, no benefit for 5-ASA use was found in a study based on two large claim databases[18]. Among patients with IBD (364 CRC cases, 1172 controls), exposure to 5-ASA therapy of any dose or duration during the 12 mo preceeding CRC diagnosis was not associated with a reduced risk of CRC (OR, 0.97; 95% CI, 0.77-1.23). However, there was a trend toward a decreased risk of CRC with increasing number of mesalamine prescriptions (≥ 5 prescriptions) in the previous year, though statistical significance was not achieved (trend, *P* = 0.08). No long-term prescription data were analyzed.

The chemopreventive role for ursodeoxycholic acid (UDCA) therapy in PSC is well-supported by both experimental data and clinical studies[91,92]. In a post hoc analysis of a randomized clinical trial, three patients (10%) initially assigned to UDCA developed colorectal dysplasia or CRC compared to eight patients initially assigned to placebo (35%)[92]. The relative risk of dysplasia or CRC was 0.26 in the UDCA group.

There is only limited evidence for the role of other anti-inflammatory agents. In the study by Eaden *et al*[40], 5% of cases and 19% of controls used systemic steroids (durations unknown), which was associated with a statistically significant reduction in CRC risk among UC patients (OR, 0.26; 95% CI, 0.01-0.70). No dose response effect was demonstrated. Results are, however, conflicting as in the later study by Lashner *et al*[93], a positive effect by at least 6 mo of azathioprine or 6-mercaptopurine therapy could not be demonstrated. Similarly, no preventive effect (HR, 1.06-1.3) of azathioprine/6-mercaptopurine use could be demonstrated during an 8-year follow-up in a more recent study[94]. Of note, azathioprine was reported to be associated with a 4-fold elevated risk of lymphomas in some previous studies[95] and a recent meta-analysis[96]. Although IBD itself was not associated with an increased risk for lymphoma[97], disease severity cannot be excluded as a confounding variable. Finally, no data are available on anti-TNF agents in this context. Risk for malignancy (RR, 1.1; 95% CI, 0.71-1.63) and lymphoma (RR, 1.3; 95% CI, 0.36-5.03) was not increased in CD according to the TREAT (TREAT-Crohn's therapy, resource, evaluation, assessment and tool) registry[98] and some other studies[99]. Somewhat in contrast, a recent meta-analysis[100] on the safety of TNF inhibitors in rheumatoid arthritis patients has shown a significantly increased risk of malignancies (OR, 3.29; 95% CI, 1.09-9.08). Many of the patients however, received a combination of anti-TNF and methotrexate, and only a single patient with colorectal cancer (rectal) was reported.

CONCLUSION

The risk of colorectal cancer for any patient with ulcerative colitis is known to be elevated, and was estimated to be 2% after 10 years, 8% after 20 years and 18% after 30 years of disease. Recent population-based studies published within the past 5 years suggest that this risk has decreased over time, despite the relatively low

frequency of colectomies. The crude annual incidence rate of colorectal cancer in ulcerative colitis ranges from approximately 0.06% to 0.16% with a relative risk of 1.0-2.75. Risk factors for cancer include extent and duration of ulcerative colitis, primary sclerosing cholangitis, a family history of sporadic colorectal cancer, severity of histologic bowel inflammation, and in some studies, young age at onset of colitis. Complete elucidation of the mechanism of UC-CRC carcinogenesis will require further investigations; however, chronic inflammation is thought to be the most important driving mechanism. Although the same three molecular pathways that have been described for sporadic colon carcinogenesis [loss of heterozygosity (LOH), microsatellite instability (MSI) and CpG methylator phenotype (CIMP)] are also found in colitis-associated neoplasms, yet the timing and frequency of some of the key genetic changes are different. The exact mechanism for this change in epidemiology trends of UC-associated CRC is unknown. One key element may be the early diagnosis and treatment of precancerous lesions by colonoscopic surveillance or sometimes prophylactic colectomy, while a third option is primary chemoprevention. Nowadays, prophylactic colectomy is obsolete. Increasing amount of evidence is now available supporting an improved yield of surveillance colonoscopy by targeted biopsies. The method of choice or data regarding the role of advanced endoscopic techniques is under investigation. Another important factor contributing to the changing trends in epidemiology may be the more widespread use of maintenance therapy by aminosalicylates and UDCA in patients with PSC, making 5-ASAs a probable chemopreventive agent based on safety profile and current maintenance use. As of today, based on available literature and international guidelines, the use of surveillance edoscopy and maintenance chemopreventive therapy should be advised and discussed in patients with ulcerative colitis.

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