Patients with chronic colitis (ulcerative colitis or colonic Crohn’s disease) have an increased risk of colorectal cancer (CRC). Although most of the molecular alterations reported in sporadic CRC have also been observed in colitis-associated CRC, they do not occur at the same timing and frequency, indicating a different pathophysiology. In particular, recent work highlighted the importance of chronic mucosal inflammation as a key factor favouring colorectal carcinogenesis in these patients. This may also be one of the reasons explaining the role of 5-aminosalicylates as chemopreventive agents for CRC in inflammatory bowel disease (IBD) patients with colonic involvement. Beside chemoprevention, colonoscopic screening and surveillance have been shown to be the cornerstone for CRC prevention and early detection in this particular patients’ population. Periodic surveillance colonoscopy to detect dysplasia has been shown to decrease the mortality attributed to CRC. More recently, progress in imaging techniques increased our ability to identify dysplasia, and should probably now be considered to be an integral part of surveillance colonoscopy. In the future, further improvement of our knowledge of CRC biology, refinement of imaging techniques, as well as molecular discovery (e.g. identification of specific mutations in stool DNA extracts), might lead to develop more accurate diagnostic strategies to reduce the morbidity and mortality related to CRC in patients with ulcerative colitis or colonic Crohn’s disease.

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Colon cancer in inflammatory bowel disease: recent trends, questions and answers

Cancer colique au cours des maladies inflammatoires chroniques intestinales : actualité et perspectives

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Résumé
Le cancer colorectal (CCR) est plus fréquent en cas de rectocolite hémorragique et de maladie de Crohn colique. Si la plupart des altérations moléculaires identifiées dans le CCR sporadique ont également été trouvées dans les CCRs compliquant une maladie inflammatoire chronique intestinale (MICI) de localisation colique, il est bien démontré que leur fréquence diffère significativement dans ces deux situations et qu’elles surviennent à des moments distincts de la carcinogénèse colique, indiquant des mécanismes physiopathologiques différents. Des travaux récents ont en particulier souligné le rôle de l’inflammation muqueuse comme facteur clé dans la carcinogénèse au cours des MICI. Celle-ci explique aussi, au moins partiellement, les effets protecteurs des dérivés 5-aminosalicylés. À côté de la chimiothérapie par les 5-aminosalicylés, le dépistage et la surveillance endoscopiques demeurent la pierre angulaire de la prévention du CCR compliquant une MICI. Réalisée suivant des recommandations précises, cette surveillance permet de diminuer la mortalité par CCR au cours des MICI. Plus récemment, l’amélioration des techniques endoscopiques (avec en particulier le développement des colorations à l’indigo carmin ou au bleu de méthylène) a accru notre capacité à identifier les lésions dysplasiques. Ces techniques sont donc désormais partie intégrante de la stratégie de surveillance. La meilleure compréhension de la physiopathologie du CCR compliquant les MICI, l’amélioration des techniques endoscopiques, et le développement de nouveaux outils moléculaires, conduiront certainement au cours des prochaines années, à optimiser nos capacités diagnostiques, et ainsi, à réduire la morbi-mortalité liée au CCR compliquant les MICI.

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Patients presenting with inflammatory bowel disease [IBDs: ulcerative colitis (UC) and Crohn’s disease (CD)] have an increased risk of developing colorectal cancer (CRC), estimated to be globally 2 to 5 times higher than in the general population of the same age group. Several studies are endeavouring to improve knowledge on pathophysiology, risk factors, screening and prevention of CRC.

Colorectal cancer risk

Epidemiology
Schematically, 1 to 2% of CRCs observed in the general population are a complication of IBD. Nevertheless, the real magnitude of the risk of dysplasia and CRC remains difficult to estimate in UC and CD patients, due to the important variation of the data reported in the literature. These discrepant results are a consequence of several factors such as heterogeneous study design, differences in case definition, and referral centre bias. In UC patients, based on a meta-analysis published in 2001, the mean prevalence of CRC risk has been estimated at 3.7% independently of disease extent, rising to 5.4% in the case of pancolitis [1]. By pooling the results of the studies reporting data on disease duration by decade, the authors calculate a cumulative probability of CRC of 2% after 10 years of disease, 8% after 20 years, and 18% after 30 years of disease [1]. However, studies published more recently, especially those reporting general population data, suggest that this risk may probably be lower or decreased over time. For example, in a large population-based study performed by Bernstein et al. in Manitoba (Canada), the incidence rate ratio for developing CRC in UC patients compared to the general population, was found to be of 2.75 [95% confidence interval (95% CI): 1.91-3.97] [2]. A lower risk has also been reported in a small population study from Olmsted County in the United States (378 patients with UC diagnosed between 1940 and 2001): only 6 CRCs were diagnosed, yielding a 30-year cumulative probability of CRC of 2% in this cohort, not statistically different from CRC risk in the non-IBD population [3]. Surprisingly, no case of CRC was found in UC patients whose disease was diagnosed after 1980 [3]. This result was reinforced by a larger study from Denmark (22,290 person-years compared to 5,567 person-years in Winther et al. study [4]) reporting a 30-year cumulative probability of CRC in UC patients of 2.1%, a risk not different than in the general population [4]. Finally, in a study performed in a reference centre (St. Mark’s Hospital, United Kingdom), Rutter et al. reporting their 30 years experience on colonoscopic surveillance in UC, found a cumulative incidence of CRC of 2.5% at 20 years, 7.6% at 30 years, and 10.8% after 40 years of disease [5]. This change in risk magnitude has been principally attributed to a more widespread use of surveillance colonoscopy, a more frequent use of chemoprevention, and the fact that surgery was more often used in UC treatment strategy. Nevertheless, the influence of other factors (i.e. environmental factors) cannot be excluded. At the last United European Gastroenterology Week (UEGW) held in October 2008, Lutgens et al. [6] reported results of a meta-analysis they performed, including 48 publications critically appraised for type of study population, person years at risk, disease localisation in CD patients, and censoring for colectomy. Cumulative risk in all IBD patients in population-based studies were 1%, 2%, and 5% after 10, 20, and more than 30 years of disease respectively, with a pooled standardised morbidity ratio (SMR) of 3.6 (95% CI: 3.1-4.1), compared to 1%, 11%, and 43%, and a pooled SMR of 8.8 (95% CI: 7.3-11) in referral centre studies [6]. For UC patients, referral centre
studies showed also higher pooled SMR [9.0 (95% IC: 7.4-11.1)] compared to 3.7 (95% CI: 3.2-4.3) in population-based studies [6]. Patients with extensive colitis had a pooled SMR of 11.9 (9.8-14.5), whereas the pooled SMR of those with proctitis was 1.3 (0.8-2.0) [6].

In patients with CD the relative risk (RR) is globally of 2.5%, rising to 5.6% when CD is localised only in the colon, with a RR of 3.2 in patients with ileocolitis, and no increase in CRC risk (RR = 1) in patients with small bowel involvement only [7]. A meta-analysis of twelve hospital based and population-based studies confirmed this increased risk with an overall RR of 2.5 (95% CI: 1.3-4.7), a RR of 4.5 (95% CI: 1.3-14.9) in patients with colonic disease, whereas the risk in patients with ileal disease only was not different from the risk in the general population [8]. Regardless of disease distribution, the cumulative risk of CRC was 2.9% after 10 years of disease, 5.6% after 20 years, and 8.3% after 30 years [8]. A second meta-analysis, only including six population-based studies, estimated the RR for all CD patients with colonic location regardless of disease extent, of 1.9 (95% CI: 1.4-2.5) [9]. However, in patients with extensive colonic CD, this risk increased to a RR of 10.5 [9]. In the meta-analysis presented by Lutgens et al., CD patients with (ileo)colonic disease had a pooled SMR of 2.7 (95% CI: 1.7-4.4) in population-based studies compared to 6.9 (95% CI: 2.8-14.3) in studies performed in referral centres [6]. Those having CD restricted to the ileum had a pooled SMR of 1.3 (95% CI: 0.8-2.0), not statistically different from the general population.

Pathophysiology

As for sporadic CRC, CRC as a complication of IBD results from dysplastic epithelial lesions, unanimously considered as precancerous, even if their potential to develop towards CRC can prove difficult to predict, particularly in the case of low grade dysplasia (LGD). However, in contrast to sporadic CRC that almost invariably outgrows the mucosa as polyps, morphological changes linked to IBD-associated CRC are highly heterogeneous with flat lesions (representing the majority of cases of dysplasia), or less frequently raised lesions (generally referred to as dysplasia-associated lesions or masses: DALMs). Dysplasia diagnosis relies on the identification, on an optic microscope following hematoxylin-eosin staining, of architectural changes and particular cytological abnormalities [10]. Depending on their characteristics, their association and their intensity, a distinction can be made between LGD and high grade dysplasia (HGD), in flat or in raised mucosa, the repercussions of which in terms of prognosis and, consequently, of treatment and/or surveillance, are markedly different. Early identification of dysplastic lesions is therefore at the heart of CRC screening in IBD. Due to the extensive and chronic inflammation observed in colitis, the risk of detecting these lesions in association with synchronous CRC is higher than in the general population.

Sporadic CRC and IBD-associated CRC present with different molecular pathogenesis [11]. Sporadic CRC is the result of genomic instability, the two main types being chromosomal instability (85%) and microsatellite instability (15%). These two mechanisms of colonic carcinogenesis are observed in similar proportions for IBD-associated CRC, however, at different times and frequencies (Figure 1) [12]. For example, whereas in sporadic CRC, loss of APC function is typically an early event — giving the APC gene the role of “gatekeeper” of the colon —, in IBD-associated CRC, the dysfunction of APC is relatively infrequent and occurs very late in most cases [13-15]. This relatively late involvement of APC alterations in IBD-associated CRC has been suggested to explain the flat morphology of most of the dysplastic lesions compared to the polyp-like lesions found in sporadic CRC. By contrast, p53 chromosomal loss or mutations are usually observed in early stages of IBD-associated CRC but considered as a late event of the adenoma-carcinoma sequence in sporadic CRC. Microsatellite instability has also been reported in IBD-associated CRC. By contrast to sporadic CRC where methylation of the hMLH1 promoter resulting in transcriptional silencing of hMLH1 is the most frequent abnormality, recent work by Svrcek et al. [16] found that hMLH1 promoter methylation is rare in IBD-associated CRC, but reported heterogeneous abnormalities in hMLH1, hMSH2, hMSH6, and hPMS2 mismatch repair genes [16].

Figure 1 Molecular alterations in sporadic colorectal cancer (CRC) compared to IBD-related CRC. 
Altérations moléculaires au cours du cancer colorectal (CRC) sporadique ou compliquant une MICI.
Finally, epigenetic alterations by hypermethylation of promoter CpG islands, resulting in additional alteration of gene expression, have also been described in IBD-associated CRC [17]. Interestingly, high methylation in normal-appearing mucosa of UC patients with HGD or CRC was also found elsewhere in the colon, suggesting that hypermethylation is an early event in colon carcinogenesis in IBD patients, presumably as a result of chronic inflammation [17].

Increasing evidence suggests that chronic inflammation probably greatly contributes to colon carcinogenesis, in particular by producing a favourable microenvironment for cancer development and progression. Increased mucosal production of pro-inflammatory cytokines secreted by infiltrating inflammatory and immune cells, prostaglandins resulting from induction of cyclooxygenase (COX)-2 in epithelial cells and in fibroblasts of the lamina propria, as well as enhanced reactive oxygen and nitrogen species result in alterations of a large number of molecules such as DNA, RNA, proteins or lipids. In particular, they induce the formation of adducts to DNA, generating point mutations in genes like p53 and in CpG islands involved in DNA methylation. In addition, the increase in local cytokines and prostaglandins inhibits apoptosis and favours cell proliferation, thereby facilitating carcinogenesis. First clinical data highly suggesting a link between chronic inflammation and colon carcinogenesis were published in 2004 by Rutter et al. [18]. The authors found that the severity of inflammation, assessed both by endoscopy and histological analysis, significantly increased the risk of CRC (2.5 and 5.1 respectively) [18]. More recently, a cohort study among patients with UC revealed a significant relationship between the level of inflammation and progression towards HGD or CRC, with a RR of 2 [19]. Experimental data provide some information on the underlying cellular or molecular mechanisms. For example, excessive cytokine production may activate arachidonic acid metabolism by increasing the expression and/or the activity of cyclooxygenase (COX)-2 in epithelial cells or molecular mechanisms. For example, excessive cytokine production may activate arachidonic acid metabolism by increasing the expression and/or the activity of cyclooxygenase (COX)-2 in epithelial cells [20]. The result would lead to a decrease in the non-esterified arachidonic acid pool responsible for diminishing apoptosis, which in turn facilitates tumorigenesis [21]. Inflammatory mediators may also influence tumor suppressor gene activity; this has been demonstrated for macrophage migration inhibitory factor (MIF) which suppresses p53 transcriptional activity in vitro [22]. Moreover, recently, experimental data clearly established the role of tumour necrosis factor-alpha (TNF-α) as a key mediator in inflammation-driven tumour progression [23]. The authors showed that invalidating the TNF-α receptor p55 reduced drastically colon tumour formation in mice treated with azoxymethane (AOM) which accelerates and increases the incidence of colon carcinogenesis in dextran sulphate sodium (DSS)-induced experimental colitis in mice [23]. In addition, wild type mice transplanted with bone marrow from TNF-Rp55-deficient mice were less susceptible to develop colon tumours, whereas transplantation of bone marrow from wild type animals to TNF-Rp55-deficient mice resulted in an increase of tumour formation not significantly different from that seen in wild type mice [23]. Finally, administration of etanercept (a monoclonal antibody directed against the p75 TNF-α receptor) also reduced both tumour number and size in wild type mice treated with AOM and DSS [23].

Taken together, these results provide a strong rationale for chemoprevention, and also suggest that mucosal healing might be of interest for limiting colon carcinogenesis in patients with UC or colonic CD.

CRC risk factors in IBD

Different studies have demonstrated that several inherent factors of the disease and/or possibly genetic factors (Table 1) may influence the risk of developing CRC in IBD. Identifying these factors will allow us to better define a target population more likely to require colonoscopic surveillance and/or chemoprevention.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colitis extension</td>
<td>14.8</td>
</tr>
<tr>
<td>Disease duration</td>
<td>5 to 19</td>
</tr>
<tr>
<td>Association to PSC1</td>
<td>9 to 18</td>
</tr>
<tr>
<td>Age at disease onset</td>
<td>20 (&lt; 30 years)</td>
</tr>
<tr>
<td>Familial history of CRC2</td>
<td>2 to 26</td>
</tr>
<tr>
<td>Presence of stenosis</td>
<td></td>
</tr>
<tr>
<td>Treatment by salicylates</td>
<td>(protective)</td>
</tr>
<tr>
<td>Folate supplementation</td>
<td>(protective)</td>
</tr>
<tr>
<td>Severity of inflammation</td>
<td></td>
</tr>
<tr>
<td>Backwash ileitis</td>
<td></td>
</tr>
</tbody>
</table>

Table 1 Factors associated to colorectal cancer risk in ulcerative colitis (and by extension in Crohn’s disease) patients.

Age of onset and duration of IBD

Some studies indicate that patients for whom the onset of disease occurs at an early age have a higher risk of developing CRC. This is the case for UC, for which the risk of CRC 35 years after disease onset was estimated by Ekbom et al. at 40% among patients diagnosed before the age of 15, whereas it was estimated at only 25% for those aged from 15 to 39 years at diagnosis [24], but also for CD, for which the RR of CRC among patients with isolated colitis increased from 5.6 to 20.9 for those aged under 30 years at diagnosis [24]. The role of age at onset, alone, remains however controversial. Most authors agree that the increased incidence among patients having developed IBD early in life results probably, or at least partly, from a longer duration of disease: before 8 to 10 years of disease progression, CRC risk is generally assumed to be not higher than in the general population [1, 5, 7]. It is only later that it increases by approximately 0.5 to 1% each year, reaching cumulative incidence rates reported in Section Epidemiology. However, a recent study shows that a substantial proportion of CRCs may occur before 8-10 years of disease [25].
Disease extension
Colonic extent of the disease has been identified as an independent risk factor. In UC, CRC occurs essentially in patients presenting with pancolitis or a history of colitis beyond the left angle of the colon (extensive colitis). When colitis does not affect beyond the left angle, the risk of CRC is low with a RR of 2.8 (95% CI: 1.6-4.4) in the case of left-sided colitis [versus 14.8 (95% CI: 11.4-18.9) in the case of pancolitis], very low when disease is limited to the rectosigmoid (RR = 1.7, 95% CI: 0.8-3.2), and virtually nonexistent in the case of proctitis [24].

Chronic inflammation
The link between persistent inflammation and risk of CRC has long been controversial. Nevertheless, as stated earlier (see Section PATHOPHYSIOLOGY), recent clinical and experimental data demonstrate that chronic inflammation is a key factor contributing to colon carcinogenesis in IBD. In addition, features indicative of previous severe inflammation, such as pseudopolyps, and features indicative of chronically active colitis, such as a shortened or tubular colon and stricture formation are all associated with a significant increase in the risk of CCR [26].

Family history of colorectal cancer
A family history of CRC increases the risk of CRC in UC [27,28] and in CD [28]. Conversely, the presence of a first-degree relative presenting with an IBD does not increase the risk of developing CRC among other healthy family members [29].

Presence of reflux ileitis
Heuschen et al. suggested that the presence of reflux ileitis may be an independent risk factor for CRC in UC [30]. These results were, however, not reproduced in a recent case-control study published by Rutter et al. [26].

Association with primary sclerosing cholangitis
Many studies have demonstrated that patients with primary sclerosing cholangitis (PSC) associated with UC have a higher risk of developing CRC [31-33]. For example, a case-control study conducted by Broome et al. [32] observed a cumulated risk of CRC of 9% after 10 years of disease progression among patients presenting both diseases, of 21% after 20 years and 50% after 25 years, compared with 2%, 5% and 10% respectively among patients with UC, but not PSC. This risk remains even after liver transplantation for PSC [33].

Prevention
Today, prevention of CRC in IBD is principally based on endoscopic surveillance for the detection of dysplastic lesions. Nevertheless, preventive medical treatment, especially using 5-aminosalicylates (5-ASA), has also proved to be efficient in most studies.

Medical prevention
5-aminosalicylates
5-aminosalicylates are currently the most acknowledged medical treatment for CRC prevention in UC patients or patients with colonic CD (although, the studies have mostly been performed in UC patients). Pinczowski et al. provided the first evidence of a protective role for 5-ASA against colitis-associated CRC [34]. In a case-control study, they compared 102 UC patients with CRC with 196 cancer-free matched controls, and found that treatment with sulfasalazine or corticosteroids for a duration of at least 3 months was associated with a protective effect against CRC development, an effect more pronounced in patients taking sulfasalazine (RR = 0.38, 95% CI: 0.20-0.69 after adjusting for disease activity) [34].

Several years later, Eaden et al. [35] demonstrated in a case-control study of 102 patients with UC, that regular treatment by 5-ASA (defined as a treatment for 5-10 years) reduced the risk of CRC by 75% (OR = 0.75, 95% CI: 0.13-0.48) [35]. They further analysed CRC risk associated with specific medications and doses, and showed that mesalamine at a dose of 1.2 g/d or greater reduced the risk by 81% (OR = 0.19, 95% CI: 0.06-0.61) whereas sulfasalazine at a dose of 2 g/d or more was less effective (OR = 0.85, 95% CI: 0.32-2.26) [35]. This study, however, had two methodological drawbacks as (i) cases and controls were not drawn from the same population (throughout the United Kingdom for cases, and only from the Leicestershire General Hospital — a referral centre — for controls), and as (ii) case and control populations differed by the ethnic composition.

The three most recent studies published in extenso are those from van Staa et al. [36], Velayos et al. [37] and Terdiman et al. [38]. Van Staa et al. conducted a large population-based study including 18,969 patients (100 having developed a CRC during 5-ASA use), and defined those considered as 5-ASA regular users if they had six or more 5-ASA prescriptions in the previous 12 months. They found (i) that regular users had a lower risk of CRC than irregular users (OR = 0.7, 95% CI: 0.44-1.03), (ii) that this protective effect does not occur in sulfasalazine users, and (iii) that for mesalamine users this effect was only significant for patients having 13-30 prior prescriptions (OR = 0.30, 95% CI: 0.11-0.83) or more than 30 prior prescriptions (OR = 0.31, 95% CI: 0.11-0.84) [36]. Velayos et al. published a case-control study of 188 patients with UC-related CRC compared to 188 matched controls [37]. Use of 5-ASA for 1 to 5 years resulted in a decreased risk of CRC compared to 5-ASA use for less than one year (OR = 0.4, 95% CI: 0.2-0.9). However, when 5-ASA were used for more than 6 years, the protective effect tends to decrease and the advantage was no longer statistically significant (6 to 10 years: OR = 0.6, 95% CI: 0.3-1.4; >10 years: OR = 0.6, 95% CI: 0.3-1.3) [37]. Finally, Terdiman et al., in a stratum-specific case-control study, found a trend toward a decreased risk of CRC with increasing number of mesalamine prescriptions, but statistical significance was not achieved (P = 0.08) [38].

Nevertheless, not all studies showed this protective effect [39], and given the important heterogeneity of individual study results and the fact that a randomised controlled clinical trial probably will never been performed, the best available data interpretation appears to be that of published meta-analysis. Beside Eaden’s et al. meta-analysis, in 2005, Velayos et al. analysed nine studies evaluating the effect of exposure to 5-ASA on CRC or dysplasia outcomes [40]. Pooled analysis showed a protective effect of 5-ASA for CRC (OR =
The mechanisms of action put forward to explain this potentially protective effect have been detailed in several reviews [41, 42]. Anti-proliferative and pro-apoptotic effects of 5-ASA appear to be mediated through numerous pathways including inhibition of reactive oxygen species and oxidative DNA damage, inhibition of COX-1 or -2, of NF-κB activation, of MAP kinases and of Bcl-2 [41, 42]. It has also been demonstrated that 5-ASA acts as a peroxisome proliferator-activated receptor-gamma (PPAR-γ) ligand [43]. Rousseaux et al., using both in vitro and in vivo experiments, showed that 5-ASA increased PPAR-γ expression, thereby reducing inflammation in experimental colitis in mice [43], and Schwab et al. provided additional data demonstrating that 5-ASA anti-proliferative and pro-apoptotic effects were both mediated through PPAR-γ-dependent and - independent mechanisms [44].

**Folate**

Experimental and epidemiologic studies have suggested that low folate levels may represent a risk factor for sporadic CRC [45, 46], probably by inducing DNA strand breaks in the p53 gene [47]. Patients with IBD have an increased risk of folate deficiency, and recently, Phelp et al. reported that the risk of CRC is 17 times higher in IBD patients with hyperhomocysteinemia and folate deficiency [48]. Nevertheless, until now only one small case-control study (including 6 cases and 61 controls) found a statistically significant protective effect of folate supplementation [49] and one small pilot randomised controlled trial comparing folic acid supplementation to placebo in 12 UC patients showed that a 3 month supplementation resulted in reduction of cell proliferation analysed by immunohistochemistry [50]. All other case-control studies found no statistically significant effect of folate supplementation [18, 51-53]. Therefore, until now, folate supplementation could not be considered as an effective chemopreventive treatment in colitis, despite folate deficiency has to be corrected in IBD patients.

**Ursodesoxycholic acid**

Ursodeoxycholic acid (UDCA) would appear to play a protective role in UC associated with PSC. In patients with PSC, UDCA given at high doses (13-15 mg/kg/d) has been shown to increase the 4-year survival [54]. As UDCA has been suggested to have antioxidant and antiproliferative effects in colorectal carcinogenesis [55-57], several authors studied its potential protective role against CRC development in UC patients. Pardi et al. studying 52 patients with both PSC and UC (mean 13 years) previously enrolled in a placebo-controlled randomised trial of UDCA in PSC, reported that patients treated with UDCA (n = 29, 13-15/mg/kg/d for a median of 42 months) had a lower risk of developing dysplasia or CRC (10% of patients after an average follow-up of 6.5 years) compared to those receiving placebo (35%, RR = 0.26, 95% CI: 0.07-0.99) [53]. However, the main drawback of this study was the generally low number of colonic biopsies taken at each surveillance colonoscopy, which might interfere with data interpretation. In a small randomised controlled pilot study, 19 patients (13 with UC and 6 with CD), not all with concomitant PSC, but with prior findings of LGD, were randomised to receive 500 mg twice daily of UDCA (n = 10) or placebo, and were followed for 2 years [58]. Using a scoring system based on histological and DNA content studied by flow cytometry, the authors found no significant differences between both treatment groups [58]. However, this study also has several limitations such as the short treatment time (2 years) and the use of a non-validated score. Finally, Wolf et al. reported their results on a historical cohort study of 120 patients with UC and PSC, 28 patients receiving UDCA daily for at least 6 months (mean duration: 3.4 years), whereas the remaining 92 patients did not [59]. Although there were significantly fewer deaths (from all causes) among the UDCA-treated patients, UDCA had no significant effect on the risk for developing CRC or dysplasia [59]. Therefore, at the present time, we do not know whether UDCA may protect from colorectal carcinogenesis in IBD patients with or without concomitant PSC.

**Statins**

Despite statins have been shown to inhibit colorectal carcinogenesis in animal models, the clinical relevance of these data remains unclear. In a population-based case-control study, Poynter et al. [60] reported a significant association between the use of statins for at least five years and reduced relative risk of CRC, even after adjustment for other potentially protective factors [60]. This protective effect appears impressive in the small subset of patients having IB with a 94% risk reduction [60]. However, other studies found no protective effects in the general population [61], and a recent meta-analysis of 18 studies showed no strong reduction of CRC in patients taking statins for hypercholesterolemia [62].

**Prevention by endoscopic screening**

The known association of dysplasia and CRC in UC has been the basis for defining endoscopic screening and surveillance strategies. Current guidelines result principally on retrospective and case-control studies as well as expert-opinion and consensus. Several questions have to be answered such as: how to best detect dysplasia in flat mucosa? How to proceed with polyps in UC? How should dysplasia be managed? During endoscopic examination, it is essential to examine the whole colon in search for all visible lesions, which can be classified as either (i) raised mucosal lesions easier to detect with the naked eye, and (ii) flat mucosal lesions, more difficult to diagnose, hence requiring complementary endoscopic methods.

**Dysplasia in flat mucosa**

By contrast to sporadic CRC, dysplasia in IBD is more frequently detected in flat mucosa. Often, there is no detectable macroscopic abnormality when conventional colonoscopy is performed. Special attention should be given to slight distortion of mucosal blood vessels, compared to what one would expect to observe in normal tissue, to achromic areas or, conversely, flat or barely raised erythematous plaques. Mucosa can also appear slightly thickened, with a granulous appearance or fine nodularities and occasionally discretely
Villous upon thorough examination [63-65]. Therefore, dysplasia can easily be overlooked during standard colonoscopy, and several reports estimate that only 20 to 50% of intraepithelial neoplasms are detected by standard colonoscopy [66]. The introduction of in vivo staining methods (chromoendoscopy) has significantly improved dysplasia screening in IBD. Such methods use predominantly methylene blue or indigo carmine [67-71] and have been incorporated in recent guidelines [72]. These techniques as well as virtual chromoendoscopy using narrow band imaging [73-75], and in vivo microscopy using confocal endomicroscopy [76, 77], are detailed elsewhere in this special issue [78].

Before the development of chromoendoscopy, considering both the fact that the entire involved colon might be at risk for neoplastic transformation in IBD patients, and the high neoplasia miss-rate of white light colonoscopy, extensive sampling by random biopsies in addition to targeted biopsies of suspicious lesions have been recommended, in order to decrease the risk to miss dysplasia [72, 79-82]. Current guidelines recommend at least 33 biopsies as a retrospective analysis reported a 90% positive predictive value for dysplasia diagnosis after 33 biopsies [83]. To increase the predictive positive value to 95%, this study showed that at least 56 random biopsies may be performed [83]. However, in general gastroenterology practice, these numbers of biopsies are often not achieved [84, 85]. Since the development of chromoendoscopy, the need for random biopsies has been questioned by several authors [71, 73, 86]. In fact, all available studies showed that using methylene blue or indigo carmine increased the number of targeted biopsies and the detection of dysplasia [67-69, 87, 88]. Dysplasia was rarely found in random biopsies, and usually identification of dysplasia in random biopsies did not modify patients' surveillance strategy or treatment. For example, in the study by van den Broek et al. evaluating tri-modal imaging for surveillance in 50 patients, only two random biopsies (out of a total of 1,992 random biopsies) were positive for dysplasia, both taken in a patient in whom targeted biopsies (in that case using autofluorescence) revealed three neoplastic lesions confirmed by proctocolectomy [75]. Other studies are ongoing to evaluate if using new imaging techniques might allow avoiding random biopsies. If so, it remains to be determined which technique will be the most relevant in daily practice, in terms of diagnostic performance, availability by the largest majority of endoscopists, and cost/benefit ratio.

**Dysplasia in raised mucosa**

Dysplasia may also be detected in raised lesions, the so-called Dysplasia-Associated Lesions or Masses (DALMs). Such lesions can be in the form of (i) raised plaques with irregular surface, occasionally comprising poorly-delimited and slightly nodular zones, (ii) polypoid lesions or isolated nodules, generally sessile, and more rarely pediculated [89-92], with a matt surface or slightly inflammatory mucosa, and roughly circumscribed in the case of sessile lesions, or (iii) a group of several polyps, generally sessile and usually found within the same area of colonic mucosa, size varying from 5 mm to several centimetres [64, 67].

Nevertheless, all raised or polypoid lesions are not necessarily DALMs, and it can prove difficult to distinguish them from inflammatory pseudopolyps (which do not have specific cancerous potential) or sporadic colonic adenomas which can develop as frequently among IBD patients as in the general population. Some inflammatory pseudopolyps can only be conclusively distinguished from DALMs following the formal exclusion of dysplasia by histological analysis. Differential diagnosis is all the more difficult when doubt remains between DALM and colonic adenoma. Several authors have suggested considering polypoid dysplastic lesions as DALMs in patients aged under 40, and as sporadic adenomas (still referred to by certain authors as ALMs - Adenoma-Like Masses) in older patients [93]. Nevertheless, this viewpoint is difficult to justify, and all the more difficult to recommend, given the major risk of associated CRC in patients presenting with a DALM which may have been inadequately considered as a sporadic adenoma. Other authors have attempted to identify the clinical, endoscopic and/or pathological characteristics (including molecular analysis) of DALMs, without for as much succeeding in providing a conclusive answer to this issue [89, 92-94].

**Current recommendations for endoscopic surveillance strategy**

These various points have led to recommendations for a screening strategy, initially among UC patients [79-82], then, by extension, among those presenting with CD. In view of risk factors, such surveillance essentially concerns patients with extensive colonic disease, beyond the left colonic angle for UC patients, or involving more than 1/3 of colonic surface in CD patients, for whom disease onset occurred early in life and has progressed for over 8 to 10 years.

Surveillance strategy consists in the systematic and thorough search for dysplasia on endoscopic biopsies, following a clearly defined calendar. Colonoscopy should be total and performed during the quiescent period of disease progression, in order to avoid histological confusion between dysplastic and regenerative lesions. In this case, adequate medical therapy is necessary to reduce active inflammation followed by short-term repeat surveillance colonoscopy (usually 3 to 6 months later). Biopsies (2 to 4 according to authors, covering the 4 quadrants) should be performed every 10 cm on macroscopically normal mucosa, as well as in areas of mucosal irregularity, areas with altered mucosal colour, raised plaques or polypoid lesions. The probability of detecting dysplasia naturally increases with the number of biopsies performed. On the other hand, the cost of the examination also increases proportionately. As stated earlier, chromoendoscopy using indigo carmine or methylene blue has now to be considered as being a full part of screening and surveillance endoscopy.

Recommended surveillance frequency varies from one author to another: colonoscopy every one or two years for some, colonoscopy every three years after 10 years disease progression, then every 2 years after 20 years progression and finally annual examination after 30 years for others. For patients with associated PSC, in view of the increased incidence of CRC in this particular clinical setting, most authors recommend annual colonoscopic surveillance following the time of PSC diagnosis.

However, this strategy is often difficult to implement since it is not only inconvenient for the patient, but is also
costly and involves a rate of morbidity which is by no means insignificant, all of which reduce its long-term observance. Of course, the ideal solution would be to identify other, more accessible, risk markers for neoplastic degeneration, hence enabling the number of patients involved in endoscopic surveillance to be further reduced. An interesting prospect has been reported, based on the detection of molecular markers in faeces, potentially providing, in the future, a more accurate selection of patients with a high risk of presenting with CRC [95-97].

Surveillance results
Analysis of surveillance results is difficult, particularly in view of the methodological demands of such studies, requiring the inclusion of large numbers of patients and long-term follow-up (15 to 20 years), and of the difficulty in maintaining patient compliance to the study programme, possible refusal to undergo colectomy by patients for whom LGD or HGD has been detected, and especially the impossibility, for ethical reasons, to conduct control studies involving groups of patients without colonoscopic surveillance.

Despite contradictory results, some studies offer the optimism that CRC mortality is likely to reduce among regularly monitored patients. This is suggested, for example, in a retrospective study by Choi et al. [98] demonstrating that, in their series, surveillance enabled the detection of early-stage CRC in 80% of patients against 41% in unmonitored UC patients. In this study, the mortality of the two groups, 5 years after CRC diagnosis, was also significantly improved in the group of monitored patients (77% versus 36%, P = 0.026). Other studies have reported globally similar results [34, 99]. In addition, other data strongly suggest that patients who comply with surveillance colonoscopy have CRC detected at an earlier stage [100].

Management of dysplasia
There are several possible scenarios and we report here the conclusions of the French recommendations, summarised in Figure 2 [81].

“Given the difficulty and the consequences of this diagnosis, any dysplasia, be it low-grade, high grade or indefinite for dysplasia, must be confirmed by a second anatomopathologist (grade C recommendation).” This recommendation is principally based on the fact that poor inter-observer agreement and intra-observer reliability have been reported, even among expert gastrointestinal pathologists, especially for histological diagnosis and classification of indefinite dysplasia or LGD [101, 102]. “The discovery of high grade dysplasia in flat colonic mucosa, confirmed by a second pathologist, should lead to coloproctectomy (grade C recommendation) with, ideally, ileoanal anastomosis and mucosectomy, given the high risk of synchronous CRC on the remaining colon.” This risk of concurrent CRC has been found to be as high as 67% [5, 85].

“The action to be taken in the case of detection of low-grade dysplasia in flat mucosa, following confirmation by a second pathologist, remains a subject of debate, several authors advocating coloproctectomy, others close endoscopic surveillance. No recommendation can be put forward.” Up to recently, the most frequently adopted attitude was to repeat colonoscopy with aggressive follow up. However, other authors encourage more and more physicians to consider coloproctectomy as the most logical option, and consequently the one which should be adopted in clinical situations, all the more so since: (i) dysplasia is unquestionably a precancerous lesion, (ii) concurrent CRC is discovered based on colectomy samples in 19-20% of patients for whom LGD is detected on systematic biopsy [103], (iii) in a third of cases, LGD is the only histological anomaly detected on colectomy samples for patients operated on for CRC [104], (iv) the LGD/HGD/CRC sequence is not systematically observed [85], and, in particular, (v) in most studies, 30 to 70% of LGD, be they uni- or multifocal, progress towards HGD, DALM or CRC within 5 years [85, 104-108] (despite the fact that two other studies report far lower percentages [109, 110]).

“The discovery of indefinite dysplasia in flat colonic mucosa should lead, after confirmation by a second pathologist, to close endoscopic surveillance (grade C recommendation), for example after 6 months.”

“After polypectomy, in the case of the discovery of dysplasia on a raised pedunculated or sessile lesion within an area which has never been macroscopically or histologically affected by colitis, the raised lesion should be considered as a sporadic adenoma, requiring only the customary surveillance...
for such lesions (grade C recommendation)." If the lesion has not been removed, it should, of course, be totally resected.

“When a polyloid lesion is localised within an area currently or previously affected by colitis, and if it bears resemblance to a sporadic polypl, polypectomy will suffice, provided (i) that the lesion is a simple adenoma and has been totally removed or can be removed later, (ii) that there is neither any dysplasia at the base of the lesion, nor any other dysplastic area in the colon, (iii) that the latter may be easily monitored by surveillance colonoscopy and, for certain authors, (iv) that the patient be aged over 40 years (grade C recommendation).”

“If the dysplastic lesion does not resemble a commonplace adenomatous polypl and if dysplasia is also detected around the lesion or at other colonic areas, the lesion should be considered as a DALM. It therefore requires, following confirmation by a second pathologist, the performance of coloproctectomy (grade C recommendation).”

In that case, independently of the histological staging of dysplasia, synchronous CRC in other colonic areas has been demonstrated to be frequent. For example, Blackstone et al. observed 7 cases of CRC among 12 colectomies for DALMs, 5 of which only presented with moderate dysplasia [89], representing around 50% of associated cancers at DALM diagnosis [89, 103].

In the case of negative biopsy, surveillance alone is sufficient.

Conclusion
The risk of developing CRC during the progression of UC or colonic CD is significantly increased, particularly among patients presenting with, or having previously presented with, extensive colitis, and for whom disease onset occurred early in life or for whom disease progression dates from over 8 to 10 years. Consequently, colonoscopic surveillance is recommended, the essential aim of which, along with the detection of macroscopic lesions, is the identification of precancerosis microscopic lesions (dysplasia), with the help, until recently, of systematic multilevel biopsies. However, recent improvement of imaging technologies, especially the development of chromoendoscopy, increases the yield of dysplasia, thus raising the question of the relevance of systematic biopsies. Ongoing studies may help to decide whether by using these techniques, random biopsies still remain necessary. Additionally, it is of outstanding importance to note, that despite the studies showing a chemopreventive effect of 5-aminosalicylates, rigorous colonoscopic surveillance could not be avoided.

Other research directions may explore the usefulness of molecular diagnostic tools currently in development, such as the identification of mutations in stool extracts of DNA which may allow a better definition of the target population supposed to undergo endoscopic screening.

Nevertheless, at the final step, we have to answer the question of how the improvements of chemopreventive and diagnostic strategies may decrease IBD-associated CRC related morbidity and mortality, taking into account patients‘participation, physician compliance to guidelines, and finally cost/benefit effectiveness of recommended strategies.

Conflict of interest:
The Authors have no conflict of interest.

References
Colon cancer in inflammatory bowel disease


Colon cancer in inflammatory bowel disease


