Dysplasia and colorectal cancer in inflammatory bowel disease : a result of inflammation or an intrinsic risk ?

C. Breynaert[1], S. Vermeire[2], P. Rutgeerts[2], G. Van Assche[2,3]

(1) Department of Internal Medicine ; (2) Department of Gastroenterology, University Hospital Gasthuisberg, Leuven, Belgium.

Abstract

Patients with inflammatory bowel disease (IBD) face an increased lifetime risk of developing colorectal cancer (CRC). Although CRC in IBD only accounts for 1-2% of all cases of CRC in the general population, it is responsible for approximately 15% of the mortality of patients with Crohn's disease (CD) and ulcerative colitis (UC). Independent factors associated with increased risk include long disease duration, extensive colonic involvement, young age at onset of IBD, severity of inflammation, primary sclerosing cholangitis, backwash ileitis and a family history of CRC. Many of these factors emphasise the role of inflammation as an underlying mechanism. Despite the differences between the molecular abnormalities found in colitis-associated dysplasia in comparison with sporadic CRC, IBD-associated cancer has a similar dysplasia-cancer sequence, similar frequencies of major chromosomal abnormalities, microsatellite instability and similar glycosylation changes. These similarities seem to outweigh the differences and make it reasonable to suggest that not only IBD-associated CRC but even sporadic colon cancer might be largely secondary to inflammation. Oxidative stress, apoptosis, COX-2 activity and a possible common inherited defective glycosylation are thought to play a key role in the pathogenesis of colitis-associated CRC. DNA alterations initiated in colonic crypts can expand to adjacent crypts through crypt fission.

There seems little doubt that the increased risk of cancer in inflammatory bowel diseases is a result of the disease rather than an inherited phenomenon. An understanding of the definition and pathogenesis of CRC in IBD is crucial to optimise patient management. Further investigation is therefore necessary. (Acta gastroenterol. belg., **2008**, 71, **367-372**).

Introduction

Colorectal cancer is the third most common cancer and the fourth most frequent cause of death due to cancer worldwide. The WHO estimates that yearly 945 000 new cases occur, with 492 000 deaths (1). Patients with IBD face an increased lifetime risk of developing colorectal cancer compared to the normal population. Although CRC in IBD only accounts for 1-2% of all cases of CRC in the general population, it is considered as a serious complication of the disease and accounts for approximately 15% of all deaths in IBD patients (2,3). The risk of CRC increases with the extent and the duration of the disease. This is best known in patients with UC. Recent findings show that the malignant potential in Crohn's colitis and UC is of the same order for patients with equal extent and duration of disease (4). In a meta-analysis of 116 studies, Eaden *et al.* showed that the risk of CRC for people with IBD increases by 0.5-1.0% yearly, 8-10 years after diagnosis. The cumulative risk of CRC in patients with UC rates 2% by 10 years, 8% by 20 years, and 18% by 30 years of disease (3,5). However, more recent studies suggest that the risk of CRC is considerably lower than previously described : Rutter *et al.* report a cumulative incidence of UC-associated CRC of 2.5% at 20 years, 7.6% at 30 years and 13.5% at 45 years (6). The cumulative risk of CRC in patients with CD is 2.9% after 10 years (4). Furthermore, the mean age at diagnosis of IBD-associated CRC is 40-50 years : this is 10-20 years earlier compared to the mean age at diagnosis of sporadic CRC (7,8).

CRC is an important cause of morbidity and mortality in patients with IBD, so knowledge of the underlying mechanisms of dysplasia and CRC are crucial to optimise patient management in terms of cancer prevention and screening. The question if CRC in patients with IBD is only a consequence of mucosal inflammation is still open. This would implicate that in the prevention of cancer optimal anti-inflammatory therapy would be efficient. Alternatively chronic IBD colitis could be a primary premalignant condition or a hitherto unidentified inherited phenomenon predisposing to inflammation as well as to oncogenesis, meaning that the development of dysplasia and CRC is an intrinsic risk (9-11).

The aim of this review is to summarize all clinical and molecular features of IBD-associated CRC. Recent literature is used to answer the question whether IBD-associated CRC is a consequence of inflammation or an intrinsic risk of IBD.

Clinical risk factors associated with an increased risk of developing CRC

Extent of inflammation

Several independent factors are associated with an increased risk of developing CRC. These risk factors are summarized in table 1. In both UC and CD, strong associations exist between the duration and extent of

Correspondence to : Prof. Dr. Gert Van Assche, Department of Gastroenterology, University Hospital Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium. E-mail : Gert.Vanassche@uz.kuleuven.be

Submission date : 09/09/2008
Revised version : 17/10/2008
Acceptance date : 29/10/2008

Table 1. — **Clinical risk factors associated with an increased risk of developing CRC in patients with IBD**

Extent of colitis
Duration of disease
Severity of inflammation / endoscopic findings
Young age at onset of IBD
Backwash ileitis
Primary sclerosing cholangitis
Family history of sporadic CRC

mucosal inflammation and the risk of cancer. In the landmark study of a population-based cohort of 3117 UC-patients followed from 1922 to 1983, Ekbom *et al.* showed that the risk of CRC increases with the extent of mucosal inflammation (12). For patients with ulcerative proctitis, the standardized incidence ratio (SIR) was 1.7 (95% confidence interval (95%-CI) 0.8-3.2), for those with left-sided colitis 2.8 (95%-CI 1.6-4.4) and for those with pancolitis 14.8 (95%-CI 11.4-18.9). The meta-analysis of Eaden *et al.* confirmed these results : the overall prevalence of CRC among patients with UC in all 116 studies was 3.7% (95%-CI 3.2-4.2%), which increased to 5.4% for patients with pancolitis (3). A recent meta-analysis of Canavan *et al.* estimated a relative risk for CRC in CD of 2.5 (95%-CI 1.3-4.7). The relative risk increased to 4.5 (95%-CI 1.3-14.9) for patients with extensive colonic disease (4,7).

Duration of disease

IBD-associated CRC is only rarely encountered before seven years disease duration. Thereafter the risk increases at a rate of 0.5-1.0% per year. So there is an increasing risk of CRC with longer duration of disease. Eaden *et al.* observed that the cumulative risk for any patient with UC was 2% at 10 years, 8% at 20 years and 18% at 30 years (3,5). A recent Dutch trial showed that 22% of the observed patients developed CRC before the surveillance guideline starting points of 8 or 15 years duration of disease. In 11 of the 149 patients, IBD and CRC were even diagnosed simultaneously (13). In some studies, the risk rises exponentially with duration beyond 30 years (14). However, new estimates of the magnitude of the cancer risk in IBD hint to a changing picture. Some studies suggest that the relative risk of CRC is considerably lower than previously believed : Rutter *et al.* found a cumulative incidence of CRC that was lower than that in the meta-analysis by Eaden *et al.* : 2.5% after 20 years of disease, 7.6% after 30 years, 10.8% after 40 years and 13.5% after 45 years (6). Another study shows that the risk of CRC in UC of CD did not increase compared to the reference population (15). The reason for the apparent decline in incidence remains unclear, but would be consistent with a combination of improved therapies, prevention strategies or earlier proctocolectomy in patients with IBD.

These risk factors link the severity and duration of inflammation with CRC. The extent of the inflammation needs also to be factored in, since patients who have inflammation limited to the rectum do not have a significantly increased risk for developing rectal cancer compared to the general population (12,16).

Age at diagnosis

Another risk factor is age at diagnosis : a younger age at onset of IBD-colitis is associated with a higher risk for CRC. Ekbom *et al.* found that the cumulative colorectal cancer risk in patients with extensive colitis after 35 years of follow-up was 40% for patients with a disease starting before the age of 15 and 25% for patients developing colitis between the age of 15 and 39 (12). However, young patients have a longer potential lifespan, so the higher risks reported in this age group could simply reflect the duration of the disease (3,5,16). Furthermore, a recent study of Brackmann *et al.* showed that age at onset of IBD is the strongest predictive variable for dysplasia at cancer diagnosis ($p = 0.025$). They identified two distinct groups of CRC in IBD : widespread neoplasia was associated with early onset of IBD and localized neoplasia was associated with late-onset IBD (17).

Severity of inflammation

As inflammation is the underlying mechanism for IBD-associated carcinogenesis, it is likely that the severity of inflammation is related to the risk of CRC. No study has convincingly showed that severity of disease correlates with the degree or duration of inflammation, with the exception of a single study in 1964 (18). In this study, Prior *et al.* found that there was a constant increased risk for colorectal cancer 15 years after diagnosis, rather than a constantly rising risk (19). These data plead against the role of inflammation as culprit for the increased risk on CRC in patients with IBD. Probably, the reason for these findings has to do with the determination of disease activity in the past. When activity of disease is measured according to the frequency of symptomatic exacerbations, it does not appear that there is a correlation with CRC risk (20,21). However, a recent study, in which colitis activity is defined histologically, found that a higher degree of histologically active inflammation was indeed associated with a significant increased risk of CRC (22). The same authors demonstrated that macroscopic colonoscopic features correlate with the risk of developing colorectal neoplasia : severe active inflammation, features indicative of previous severe inflammation such as post-inflammatory polyps, 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 colorectal neoplasia. Conversely, they also showed a strong correlation between a normal colonoscopic appearance and a reduced risk of neoplasia (22). However, these data are not confirmed by Jess *et al.* (24).

Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) in combination with UC is associated with an increased risk of colorectal dysplasia and CRC. In a case-control study, the absolute cumulative risk for developing colon cancer or dysplasia for UC patients with PSC was 9% after 10 years of colitis, 31% after 20 years, and 50% after 25 years, compared with rates of 2%, 5%, and 10%, respectively, in UC controls representing a fivefold increase in risk at 25 years ($p < 0.001$) (25). This association is supported by evidence from other centers with exception of the study of Loftus *et al.* (26-28). The increased risk for CRC subsists with approximately 1% per person per year after orthotopic liver transplantation (29). There has been some debate about the mechanism of this association. Potentially, PSC could be a marker for subclinical long-standing pan-colitis, supporting the mechanism of inflammation as a predisposing factor to CRC in IBD. On the other hand, PSC could be a risk factor independent of the duration and extent of IBD. However, regardless of the exact mechanism of the association, a colonoscopic surveillance program is crucial, independent of the duration of UC-colitis or presence of symptoms (8).

Backwash ileitis

The presence of mild mucosal inflammation of the extremely distal terminal ileum in patients with UC and pancolonic involvement is called backwash ileitis. Heuschen *et al.* (30) found that the prevalence of CRC in patients with backwash ileitis was 29% compared with a CRC prevalence of only 9% in patients with pancolitis without backwash ileitis and 1.8% in those with left-sided colitis ($p < 0.001$). Other studies, however, have not been able to reproduce these findings (23,31,32).

Family history of CRC

Lastly, a positive family history of sporadic CRC is independently associated with a twofold or threefold risk of sporadic CRC (33). Several studies confirmed the same association for patients with IBD : a positive family history of CRC confers a twofold greater risk of developing CRC to the patient with IBD (34-36). However, first-degree relatives of patients with IBD do not have an increased risk for CRC. These findings plead against a common inherited susceptibility underlying both the inflammation and neoplasia (35).

Molecular pathogenesis of colitis-associated CRC

Inflammation-dysplasia-carcinoma sequence

Regardless of the underlying condition, every CRC develops essentially from a dysplastic precursor lesion. In sporadic CRC, the dysplastic precursor is the adenomatous polyp, a discrete focus of neoplasia that is removed by simple endoscopic polypectomy. In contrast, dysplasia in patients with IBD can be polypoid or flat, localized, diffuse or multifocal (37). When IBD-associated CRC is compared to its sporadic counterpart, colitis-associated carcinogenesis (CAC) can be summarized as the *inflammation-dysplasia-carcinoma sequence* (10). However, CRC can arise in colitic colons without any apparent prior dysplasia or aneuploidy (38). Sporadic adenomas require 10 to 15 years to evolve in carcinomas, whereas IBD-associated dysplasia generally progresses within 3 years after diagnosis (37).

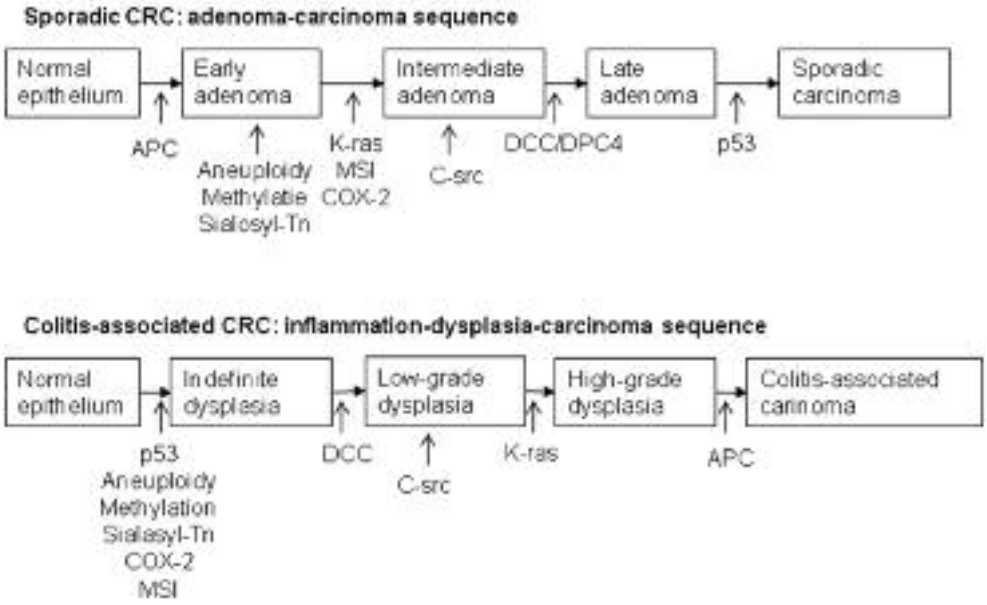
Genomic instability

As in sporadic CRC, the two main types of *genomic instability* that contribute to CAC are chromosomal instability (CIN) and microsatellite instability (MSI) (37). Emerging evidence suggests that the two major pathways of CIN and MSI also apply to CAC with roughly the same frequency as for sporadic CRC, respectively 85% and 15% (38). In addition, hypermethylation of the promoter region of specific genes plays a role in the carcinogenesis of CRC (37,40). However, multiple differences have been observed in time and frequency of these mutations (9-11,37,40). This is summarized in figure 1. Loss of tumor suppressor genes such as *adenomatous polyposis coli* (APC) is typically an early event in the carcinogenesis of sporadic CRC, whereas it is much less frequent and usually occurs late in CAC. *p53 Gene alterations* occur early in CAC, whereas it is a late phenomenon in the classical adenoma-carcinoma sequence. Allele loss or duplication of chromosome 17p, which contains p53, is remarkably common even in the non-dysplastic colitic epithelium of UC patients affecting 22% of epithelial cells compared with 10% of cells in normal controls and rising to 25% in low-grade dysplasia and 37% in the presence of high-grade dysplasia or cancer (41). Considerable evidence implicates that p53 plays an instrumental role in UC carcinogenesis, apparently at an early stage in CAC. Furthermore, it seems that chronic inflammation itself may predispose to these early mutations (42). K-ras oncogene mutations have been shown to be infrequent in IBD-associated cancers, whereas they are frequent events in sporadic CRC. It is believed that mutations of k-ras predisposes to the development of sporadic adenomas by inducing polypoid growth. The relative infrequency of k-ras mutations in IBD dysplasia may in part explain the flat growth pattern of CAC (43).

The role of inflammation in colon carcinogenesis

Oxidative stress and cellular damage

Oxidative stress produced by chronic inflammation is thought to play a key role in the pathogenesis of colitis itself as well as in colonic carcinogenesis. Chronic inflammation of the colon is associated with increased mucosal production of pro-inflammatory cytokines,



Abbreviations : APC, adenomatosis polyposis coli ; DCC, deleted in colorectal cancer ; DPC4, deleted in pancreatic cancer ; COX-2, cyclooxygenase-2 ; MSI, microsatellite instability.

Fig. 1. — Molecular pathogenesis of sporadic CRC and colitis-associated CRC

chemokines and growth factors of infiltrating mononuclear cells. However, these inflammatory cells generate reactive oxygen and nitrogen species causing oxidative stress and cellular damage in terms of oxidation of proteins and DNA. Reactive oxygen species play a role in early p53 mutations. They also interfere with the function of the DNA mismatch repair enzymes, thereby promoting MSI at an early stage (11,44,45).

Crypt fission

Chen *et al.* (46) postulate that at the initiation of CAC, DNA alterations caused by oxidative damage accumulate through clonal succession in individual crypts and spread from one crypt to another in a process of *duplication* or crypt fission. On the one hand, widespread genomic instability is present in the entire colon of UC patients with cancer. On the other hand, important chromosomal damage in inflamed colonic mucosa without dysplasia shows that these changes are induced by inflammation and that *apoptosis* most likely is important in the prevention of malignancy of inflamed mucosa. Failure of apoptosis is likely to be a critical step in the development of IBD-associated CRC (9). These findings are supported by the observation of morphologic changes like dysplasia found in the regenerative crypts of colonic mucosa of UC-patients without association with the development of cancer. Crypt cells are a dynamic populatation, and probably abnormal cells are removed by apoptosis while migrating to the surface, which indicates that dysplasia and CRC arise from surface epithelia rather than crypts (47).

Cyclooxygenase-2

Cyclooxygenase-2 (COX-2) activity plays an important role in sporadic carcinogenesis, inhibiting apoptosis and promoting angiogenesis (9,11). It has been shown that normal colonic mucosa does not express COX-2, but the enzyme is induced in premalignant and malignant lesions of the colon. Several epidemiologic studies have observed that the use of nonsteroidal anti-inflammatory drugs can decrease the risk of sporadic CRC and adenomatous polyps significantly in patients with familial adenomatous polyposis (48). Inflammation in IBD leads to increased expression of COX-2. Eaden *et al.* (20) demonstrated that *5-aminosalicylate* (5-ASA) use in patients with UC is associated with reduced CRC risk of 53-75%. A dose of at least 1.2 g of 5-ASA leads to a lower incidence of dysplasia and cancer. These findings were confirmed by several studies (49-51). Some recent studies however do not support this association (23,51). These data suggest that inflammation plays a crucial role in sporadic CRC as well as in CAC and may be a common causal mechanism in the carcinogenesis of CRC. Important to notice is that immunosuppressive use as azathioprine conversely doesn't lead to a lower incidence of CRC in patients with IBD (4,36,52). Only one study describes a non-significant reduction of the risk of CRC in case of UC (21). Recent data show that immunosuppressive use and treatment with infliximab of patients with IBD lead tot healing of the colonic mucosa. This could have important bearings on the risk of dysplasia if chronic inflammation is the underlying mechanism, although prospective studies demonstrating the link

between mucosal healing and reduction of CRC are lacking (54). Finally, recent research in mouse models of colitis indicates that TNF inhibition reduces carcinogenesis through a reduction of inflammatory pathways including prostaglandins and beta-catenin (55).

Inherited defective glycosylation

Finally, according to Rhodes' hypothesis, UC, CD, and CRC are all caused by *inherited defective glycosylation*. This defect would on the one hand act to increase the binding of lectins, leading to increased cell proliferation and cancer, and on the other hand result in weak mucus that would, dependent on the presence of environmental factors such as smoking and bacteria, lead to either CD or UC. If, as postulated, there is a genetically mediated common glycosylation defect linking IBD and CRC, an autosomal recessive inheritance would be a likely inheritance pattern. However, this could not be directly demonstrated (56-58). Moreover, we would expect a higher prevalence of CRC in relatives of patients with IBD and this is not the case (58).

Summary

All data seem to suggest that inflammation and associated processes play a critical role in the carcinogenesis of CAC. The increased risk of CRC for patients with IBD-colitis is associated with localisation, extent en duration of inflammation. A family history of CRC increases this risk further for patients with IBD suggesting the importance of both genetic and acquired factors in the carcinogenesis like in sporadic CRC. As in the adenoma-carcinoma sequence of sporadic CRC, CAC can be described as the inflammation-dysplasia-carcinoma sequence. There are important differences between the molecular pathogenesis like a lower frequency of mutations of APC and early p53 gene alterations in comparison with sporadic CRC. However, the similarities between the molecular mechanisms of CAC en sporadic CRC seem to outweigh the differences and make it reasonable to suggest a common underlying mechanism of carcinogenesis. This makes it possible to speculate that not only CAC but also sporadic CRC is a consequence of inflammation. Several studies seem to confirm these findings.

Understanding the underlying mechanism of CAC will be crucial to optimise counselling, prevention, screening for cancer and surveillance of dysplasia, as well as the ideal time for performing proctocolectomy in patients with chronic colitis**.**

Research agenda for the future

Large prospective cohort studies ideally inception cohorts are needed with emphasis on advanced imaging and histology including molecular markers. Only such a large effort will enable to optimise patient management of surveillance and will emphasise the role of inflammation.

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