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## REVIEW ARTICLE

# Colorectal cancer in inflammatory bowel disease: Results of the 3rd ECCO pathogenesis scientific workshop (I)

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**Abbreviations:** AOM, Azoxymethane; IBD, Inflammatory bowel disease; UC, Ulcerative colitis; CD, Crohn's disease; CRC, Colorectal cancer; CAC, Colitis-associated cancer; CIN, Chromosomal instability; IL, Interleukins; DSS, Dextran sodium sulphate; IC, Indeterminate colitis; PSC, Primary sclerosing cholangitis; OR, Odds ratio; SIR, Standardised incidence ratio; RR, Relative risk; MRR, Mortality rate ratio; TLR, Toll-like receptor; NF- $\kappa$ B, Nuclear factor- $\kappa$ B; TGF $\beta$ , Transforming growth factor- $\beta$ ; MSI, Microsatellite instability; TNF $\alpha$ , Tumour necrosis factor- $\alpha$ ; 5-ASA, 5-amino salicylic acid.

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**KEYWORDS**

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**Abstract**

Epidemiological studies demonstrate an increased risk of colorectal cancer in patients with inflammatory bowel disease (IBD). A detailed literature review was conducted on epidemiology, risk factors, pathophysiology, chemoprevention and outcomes of colorectal cancer (CRC) in IBD as part of the 3rd ECCO scientific pathogenesis workshop.

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**1. Introduction**

We conducted a detailed literature review on epidemiology, risk factors, pathophysiology, chemoprevention and outcomes of colorectal cancer (CRC) in inflammatory bowel disease (IBD) as part of the 3rd ECCO scientific pathogenesis workshop. The results of a literature search are presented here.

**2. Epidemiology of colorectal cancer in IBD****2.1. Methodological considerations**

IBD is associated with an increased risk of CRC, which is thought to be primarily related to long-standing chronic

inflammation.<sup>1</sup> However, the magnitude of the risk has been difficult to estimate, as many factors may bias study results<sup>2</sup> including patient selection, number of patients, completeness of case recruitment and ascertainment and duration of follow-up.<sup>2,3</sup>

Early studies from tertiary referral centres reported a high risk of CRC, but as more severe cases were included, they tended to overestimate the risk. In contrast, population-based studies covering defined geographical areas report a more conservative risk. However, these studies probably included patients with limited and less severe disease, and may have underestimated the risk. In addition, geographical differences have been described, with an increased incidence of IBD-related CRC reported in the USA and in the UK compared with Scandinavia.<sup>4</sup> Similarly, the 10-year follow-up of the European

Collaborative IBD inception cohort showed that Northern European centres had higher rates of IBD-related CRC than Southern centres (prevalence 0.9% vs. 0.25%, respectively;  $p = 0.17$ ),<sup>5</sup> although this North-South gradient was not apparent at 15 year follow-up.<sup>6</sup> Similarly, studies from Asian countries have shown important differences between countries.<sup>7–10</sup>

## 2.2. Epidemiology of colorectal cancer in ulcerative colitis

In 2001, a meta-analysis of cohort and case-controlled studies<sup>4</sup> on the risk of CRC in UC estimated an incidence rate of 3/1000 person years disease duration (PYD), an annual risk of 0.3% and a cumulative risk of 18.4% after 30 years of disease. The incidence rate progressively increased each decade from 2/1000 PYD to 7/1000 for the second and 12/1000 for the third decade.

More recent population-based studies and meta-analyses have shown that the risk is lower than previously described or even similar to that of the general population.<sup>4,11–22</sup> (Table 1). This could be explained by methodological aspects (hospital-based vs. population-based studies), by a true decrease in risk due to better disease control, higher colectomy rates, use of drugs with chemoprotective effects or more widespread endoscopic surveillance in high-risk patients.<sup>2</sup>

Castaño-Milla et al.<sup>21</sup> reported an overall incidence rate of 1.67/1000 PYD and incidence rates per decade were estimated at 1.01/1000, 3.75/1000 and 5.85/1000 PYD for the first, second and third decades, respectively. In a meta-analysis of prospective population-based studies, Jess et al.,<sup>22</sup> found that an average of 1.6% of patients with UC were diagnosed with CRC during the first 14 year follow-up, and the estimated standardised incidence ratio (SIR) was 2.39 (2.1–2.7).

Recent time-trend studies also demonstrate a decreasing risk of CRC in UC patients. Jess et al.<sup>19</sup> found that the relative risk (RR) decreased from 1.34 between 1979 and 1988 to 0.57 between 1999 and 2008. In a meta-analysis by Castaño-Milla et al.,<sup>21</sup> the incidence rate was found to decrease from 4.29/1000 PYD in studies published in the 1950s to 1.09/1000 PYD in the studies published between 2000 and 2011.

## 2.3. Epidemiology of colorectal cancer in Crohn's disease

The role of Crohn's disease (CD) as a risk factor of CRC is controversial and, compared with UC, the risk is modest. In a meta-analysis of population-based studies in CD, Jess et al.<sup>23</sup> estimated a pooled SIR for CRC of 1.9 (1.4–2.5). Canavan et al.<sup>24</sup> found a RR of 2.5 (1.3–4.7) among all CD patients, with a higher risk for CD-colitis (RR 4.5 (1.3–14.9)); this study estimated a cumulative risk of 2.9% at 10 years, 5.6% at 20 years and 8.3% at 30 years. A similar risk (RR 2.44 (1.56–3.82)) was reported in a meta-analysis by von Roon et al.<sup>25</sup> Laukoetter et al.<sup>26</sup> reported an incidence of 0.5/1000 PYD, a 2- to 3-fold increase over the incidence of CRC in an age-matched background population.

Friedman et al. found dysplasia (low or high grade) or CRC in 18.5% of patients, and after a negative screening colonoscopy the probability of developing HGD or CRC was 7% by the 10th surveillance examination.<sup>27</sup> Basseri et al. detected LGD, HGD or CRC in 5.6% of patients,<sup>28</sup> but in this cohort the number of patients with extensive colitis was lower than in Friedman's (55% vs. 90%).

## 2.4. Colorectal cancer in indeterminate colitis

Only one study evaluating the epidemiology of CRC in indeterminate colitis (IC) was identified.<sup>29</sup> Stewenius et al., in 1995, followed an inception cohort of 471 UC patients and 100 IC patients for a mean of 14.8 years. Three of 100 patients with IC developed CRC, an incidence of 2.4/1000 PYD (SIR 8.6, 95% CI 1.8–25.1), compared with an incidence of 1.4/1000 PYD in patients with UC.

## 3. Risk factors for CRC in patients with IBD

Reported risk factors for CRC include extensive disease,<sup>4,30</sup> young age at diagnosis,<sup>4,31</sup> family history of CRC,<sup>32</sup> co-existing primary sclerosing cholangitis (PSC)<sup>33</sup> and persistent inflammation of the colon.<sup>34–36</sup>

**Table 1** CRC risk in UC patients. Population-based studies.

	Annual incidence	Cumulative incidence	Risk (95% CI)
Palli <sup>11</sup>	0.12%		1.79 (0.85–3.28)
Bernstein <sup>12</sup>	Colon 0.16% Rectum 0.06%		Colon, RR 2.75 (1.91–3.97) Rectum, RR 1.90 (1.05–3.43)
Winther <sup>13</sup>	0.06%	2.1% at 30 years	SIR 1.05 (0.56–1.79)
Jess <sup>14</sup>	0.10%	2% at 25 years	SIR 1.1 (0.4–2.4)
Lakatos <sup>15</sup>	0.15%	7.5% at 30 years	SIR 1.74 (1.01–3.0)
Jess <sup>16</sup>			SIR 3.1 (0.1–17) <sup>*</sup>
Soderlund <sup>17</sup>		3.5% at 30 years <sup>**</sup>	SIR 2.7 (2.3–3.2)
Jess <sup>19</sup>	0.051%		RR 1.07 (0.95–1.21)

RR: Relative risk. SIR: Standardised incidence ratio.

<sup>\*</sup> Danish EC-IBD Cohort.

<sup>\*\*</sup> Estimated from Kaplan–Meier curve.

### 3.1. Duration and extent

A meta-analysis by Eaden<sup>4</sup> shows that in UC patients the risk of CRC becomes appreciable after 10 years, and it is assumed that risk increases with disease duration. Guidelines recommend that CRC screening be started 6–10 years after onset of symptoms in extensive colitis.<sup>37–39</sup> However, CRC may develop earlier, with some patients diagnosed simultaneously with CRC and IBD, and about 9–15% presenting with CRC with a disease duration of <6 years.<sup>40</sup> However, data from the St Mark's Hospital London surveillance cohort report that the incidence of CRC remained constant or decreased with increasing disease duration.<sup>41</sup> In a Swedish cohort of 7607 IBD patients followed from 1960 to 2004, the incidence of CRC (adjusted for the type and extent of IBD, sex, age and time since diagnosis) did not show any statistically significant trend over successive calendar periods of follow-up.<sup>17</sup>

The risk of CRC has been found to be higher in extensive UC than in left-sided UC, while in proctitis it is similar to that of the general population,<sup>30</sup> and this has been confirmed in a recent meta-analysis.<sup>22</sup> However, Soderlund et al.,<sup>17</sup> analysing an original Scandinavian cohort,<sup>30</sup> found that the RR of cancer in patients with proctitis was 1.7 (95% CI, 1.2–2.4) compared with that of the general population. Some authors suggested a possible proximal extension of the disease in patients with an initial rectal involvement.<sup>42</sup> In Crohn's colitis, the risk of CRC is similar to that of UC if the extension and duration are comparable.<sup>43–46</sup>

### 3.2. Age of onset

In the original meta-analysis by Eaden et al., young age at onset of IBD showed a trend towards a slightly increased risk of CRC, and the incidence rate of CRC in UC diagnosed in childhood was higher than the incidence in adults<sup>4</sup>; this has been confirmed in a more recent meta-analysis.<sup>22</sup> In CD, young age has also been associated with an increased risk of CRC.<sup>31</sup> However, this has not been confirmed in other studies, with some even suggesting that CRC may develop earlier in patients diagnosed with IBD at older ages.<sup>47–49</sup>

### 3.3. Primary sclerosing cholangitis

PSC is a recognized risk factor for CRC in patients with colitis, with a 4-fold increase in risk compared with UC patients without PSC.<sup>15,19,33</sup> Dysplasia or CRC have also been found to appear soon after the diagnosis of both diseases in some patients (21.5 per 100 patients-years of follow-up during the first two years).<sup>50</sup> Moreover, current evidence emphasizes that the risk of CRC remains after liver transplantation.<sup>51,52</sup>

PSC can also be associated with Crohn's colitis or IC, and it may also carry an increased risk of CRC, especially if colitis is extensive.<sup>53</sup> Two retrospective case-control studies have reported conflicting results, with a Swedish study reporting an increased risk of CRC in CD-PSC (odds ratio [OR] 6.78, 95% CI 1.65–27.9),<sup>54</sup> and a British study reporting no increase in risk (OR 1.64, 95% CI 0.14–18.7).<sup>55</sup>

### 3.4. Other risk factors

Söderlund et al.,<sup>56</sup> in the previously described cohort, found that males had a 60% higher risk of CRC (RR 1.6, 1.2–2.2), and a greater cumulative incidence after 40 years of disease (8.3% vs. 3.5%); the effect of gender was limited to patients with more than 10 years' of follow-up and in those aged <45 years at diagnosis. No differences have been found in CRC incidence between Caucasian and African-American IBD patients.<sup>57</sup>

## 4. The pathophysiology of colitis-associated cancer

### 4.1. Regulatory signals in colitis-associated cancer (CAC)

Numerous positive and negative regulators have been implicated in the development of CRC (see Table 2).

#### 4.1.1. Toll-like receptors (TLRs)

A deficiency in the TLR adaptor, MyD88, has been found to significantly reduce tumour number and size in the *Apcmin/+* mouse model of intestinal tumorigenesis<sup>58,59</sup> and the absence of bacteria in mouse models of inflammation-associated cancer has been shown to prevent dysplasia or cancer.<sup>60</sup>

#### 4.1.2. Cytokines

**4.1.2.1. Tumour necrosis factor- $\alpha$ .** The absence of tumour necrosis factor- $\alpha$  (TNF $\alpha$ ) signalling in mice has been found to be associated with decreases in mucosal damage, inflammatory cell infiltrates, and cytokine expression, in response to azoxymethane (AOM) challenge and dextran sodium sulphate (DSS), as well as a significant reduction in tumour formation.<sup>61</sup>

**4.1.2.2. Interleukin-6.** High levels of interleukin-6 (IL-6) and a soluble IL-6 receptor in IBD patients promote the accumulation of T cells in the lamina propria of the colon by upregulating anti-apoptotic factors.<sup>62,63</sup> Moreover, increased IL-6 levels have been observed in the serum of cancer patients and in tumour biopsies.<sup>64</sup> Finally, expression of IL-6 and STAT3 has been shown to be greater in active UC and after progression to colitis-associated cancer (CAC) than in controls or inactive disease.<sup>65</sup>

**4.1.2.3. Interleukin-21.** Interleukin-21 (IL-21) was recently found to be elevated in the gut of patients with CAC, and in mice with CAC induced by AOM and DSS.<sup>66</sup> IL-21-deficient mice also developed fewer and smaller tumours than wild-type mice.<sup>67</sup>

#### 4.1.3. Chemokines

The atypical chemokine receptor D6 selectively recognizes and efficiently depletes most inflammatory CC chemokines from the extracellular milieu.<sup>68</sup> Furthermore, expression of D6 is increased in the lymphatic vascular bed of colonic sections with IBD-associated colon cancer.<sup>69</sup>

TNF $\alpha$  induces the expression of chemokines from a variety of colonic cells.<sup>70</sup> Indeed, the mucosa of IBD patients

**Table 2** Regulatory signals in colitis-associated cancer.

	Effect	Example	Reference
<i>Positive regulators</i>			
Toll like receptors	Promote carcinogenesis	MyD88 deficiency reduces tumour number and size in the APC <sup>min</sup> mice	58–60
Procarcinogenic cytokines	Promote carcinogenesis	Tumour necrosis factor IL6	61–65
Chemokines	Promote carcinogenesis Direct neoplasia suppression-decreased COX-2, attenuated neovascularization	Atypical chemokine receptor D6 CCL2	68,69 62,72,73
<i>Negative regulators</i>			
IL-10	Prevent IBD related colonic neoplasia, through direct inflammation suppression and through IL-6		73
Transforming growth factor- $\beta$ (TGF $\beta$ ) family	Neoplasia inhibition directly and through inflammation suppression	Transforming growth factor- $\beta$ (TGF $\beta$ ) family, SMAD-7	74,75
Toll-IL-1R8	Inhibits IL-1 and TLR complexes signals, lack of NF- $\kappa$ B activation		76–78
Nuclear factor- $\kappa$ B (NF- $\kappa$ B)	Promotes cell proliferation and survival.		79–83
<i>Molecular pathways</i>			
Chromosomal instability (CIN) pathway	Prominent neoplastic pathway in IBD-related neoplasia, cause unclear	P53 mutations—common, DPC4 and KRAS—less common	89,92,93
Microsatellite instability pathway	Variable frequency, found in inflamed, non-neoplastic mucosa	MLH1-promoter methylation, TGFBR2 and ACVR2 mutation—lower than in sporadic CRC	94–99
Methylation pathway (CpG island methylation)	Questionable role in IBD related neoplasia	p16 INK4 and p14 ARF methylation.	95,100–102
Serrated neoplasia pathway	Present in some IBD-related neoplasia including inflammatory mucosa—contribution unclear	V600E BRAF mutation, serrated lesions in histology	103
Field effect	Multifocal risk for neoplastic transformation as a result of chronic inflammation and dysbiosis that affects mutation pressure	Markers: aneuploidy, p53 mutations, CpG island hypermethylation	89,104,106,107

has been shown to have enhanced mRNA and protein expression of MCP-1/CCL2,<sup>71</sup> a CC chemokine with potent chemotactic and activating activities for monocytes/macrophages. CCL2 mRNA expression has been shown to be enhanced in the colon of the AOM-challenged mouse model, and blocking the TNF $\alpha$ /TNFR axis reduced colorectal carcinogenesis, intracolonic macrophage infiltration, and CCL2 mRNA expression.<sup>72</sup>

#### 4.1.4. Negative regulators

**4.1.4.1. Interleukin-10.** The demonstration that interleukin-10 (IL-10) suppresses IL-6 and controls CAC development in a model of microbial CRC indicates that the control of CAC development by IL-10 may be at least partially mediated through IL-6. Moreover, it was recently demonstrated that patients with IL-10 receptor mutations that abrogate IL-10 signalling develop early and aggressive disease.<sup>73</sup>

**4.1.4.2. Transforming growth factor- $\beta$ .** Transforming growth factor- $\beta$  (TGF $\beta$ ) receptor-deficient transgenic mice were found to develop significantly more tumours than wild-type mice, while the opposite occurred in TGF $\beta$  transgenic mice.<sup>74</sup> Additionally, mechanistic studies showed that TGF $\beta$  inhibited IL-6-dependent tumour formation, reinforcing the concept

that immunoregulatory molecules such as IL-10 and TGF $\beta$  have a protective effect on intestinal inflammation and in CAC formation.<sup>74</sup> Supporting these data, mice transgenic for the TGF $\beta$  inhibitor smad7 with over-expression specifically on T cells, developed more severe colitis in response to AOM/DSS challenge, but only a few small tumors.<sup>75</sup>

**4.1.4.3. Toll-IL-1R8.** A recently identified orphan member of the IL-1 receptor family, Toll-IL-1R8 (TIR8), inhibits signalling from IL-1R/TLR complexes,<sup>76,77</sup> and gene transfer experiments have revealed that it reduces the activation of NF- $\kappa$ B by the IL-1R complex<sup>77</sup> and by members of the TLR family.<sup>76</sup> Moreover, TIR8-deficient mice administered DSS show dramatic weight loss, intestinal bleeding and increased mortality, while susceptibility to CAC in the AOM challenge model was increased.<sup>78</sup>

**4.1.4.4. Nuclear factor- $\kappa$ B.** Activation of nuclear factor- $\kappa$ B (NF- $\kappa$ B) plays a key role in inflammation and cell proliferation and survival.<sup>79</sup> Regulation of NF- $\kappa$ B involves sequestration of NF- $\kappa$ B in the cytoplasm by the inhibitor I $\kappa$ B, which is regulated through phosphorylation by the I $\kappa$ B kinase (IKK $\beta$ ) complex, targeting it for ubiquitin-dependent degradation.<sup>80</sup>

Greten et al.<sup>81</sup> demonstrated that IKK $\beta$  links inflammation and tumorigenesis in a mouse model of CAC in which IKK $\beta$  was

deleted either in intestinal epithelial cells or in myeloid cells. NF- $\kappa$ B has also been shown to induce vascular endothelial growth factor and COX-2, which promote angiogenesis.<sup>80</sup> In addition, a subgroup of NLR proteins, including NLRP12, inhibits transcription factor NF- $\kappa$ B, and it was recently reported that NLRP12 ( $-/-$ ) mice were highly susceptible to colitis and CAC, suggesting that NLRP12 is a checkpoint of noncanonical NF- $\kappa$ B, inflammation and tumorigenesis.<sup>82,83</sup>

**4.1.4.5. Intestinal microbiota.** Recent studies point to alterations in the luminal microbiota in patients with IBD. Adherent-invasive *Escherichia coli* is associated both with IBD and CRC.<sup>84,85</sup> A more recent approach demonstrated microbial changes in tumour-developing IL-10 $^{-/-}$  mice with the prevalence of *E. coli*.<sup>86</sup> Deletion of the bacterial polyketide synthase (pks) genotoxic island from *E. coli* NC101 reduces the development of dysplasia and cancer, independent of inflammation.

## 4.2. Molecular pathways of CAC

CRC has been considered to develop through well defined pathways, including chromosomal instability (CIN), microsatellite instability (MSI) and, most recently, the CIMP pathway.<sup>87</sup> There have been previous attempts to distinguish IBD related to sporadic colonic neoplasia<sup>88</sup> with some success. A few studies looked at different markers and genes related to CIN, such as aneuploidy, loss of heterozygosity (LOH) and genomic gains or losses of various genes<sup>89–91</sup> but observations are not consistent.

Notably, p53 mutations occur earlier in IBD-related neoplasia, probably a key initiating event,<sup>92</sup> than APC mutations, which occur later than commonly observed in sporadic colorectal neoplasia.<sup>93,94</sup> Allelic deletions of p53 were observed in approximately 50% to 85% of colitis-associated tumours.<sup>95</sup> p53 LOH has been shown to correlate with malignant potential in the colon. Mutations in some other commonly mutated CIN pathway genes of sporadic CRC such as DPC4 and KRAS were uncommon in CAC.<sup>96</sup> The CIN pathway can contribute to up to 85% of CAC, while the role of the MSI pathway is less clear. However, MSI has been found in up to 45% of cases.<sup>97–99</sup> MSI has been demonstrated in histologically normal colonic mucosa of patients with UC, perhaps as a risk indicator for neoplastic progression.<sup>100</sup> A paper looking at MSI and methylation status of 124 IBD-related colonic neoplasias from 78 patients,<sup>101</sup> showed 19/124 (9.6%) neoplastic lesions to be MSI-high (MSI-H). Methylation profile, tested by HPP1 and RAB32 methylation, was found to be independent of MSI status, with such methylation found in 28/61 (46%) and 20/60 (33.3%) carcinomas, while HPP1 methylation was frequently (~50%) observed in dysplastic mucosa and even in nondysplastic mucosa (7%). In another study,<sup>102</sup> mutational events secondary to MSI were found to be similar in IBD- and non IBD-related colonic neoplasia. MSI-H IBD neoplasias were not more frequently right sided and there was no age or sex association, whereas sporadic MSI-H CRC was more prevalent in older women. IBD MSI-H tumours were more advanced and less often poorly differentiated than sporadic MSI-H tumours.

Data regarding the methylation pathway are contradictory. Some evidence suggests that the involvement of this pathway is more prevalent in IBD-related neoplasia.<sup>101</sup> Methylation of CPG islands in several genes can precede dysplasia and can be

detected throughout the colon in UC patients.<sup>103</sup> p16<sup>INK4</sup> has frequently been shown to be hypermethylated in patients with UC even in non-dysplastic mucosa, and is considered a marker for the CIMP pathway.<sup>98</sup> An additional methylated gene is p14<sup>RF</sup>, an indirect regulator of p53.<sup>104</sup> Recent evidence does not support the co-occurrence of methylation with IBD CRC neoplasia.<sup>105</sup>

The serrated neoplasia pathway, characterized by V600E BRAF mutations, has been recently shown to explain some of the IBD-related neoplastic colonic lesions.<sup>106</sup> Clonality of colitis-associated neoplasia has been shown in several crypts from the same colitis-associated neoplastic lesions.<sup>92,107</sup> As in sporadic CRC, genomic transformation probably takes place in stem cells at the base of the crypt, as mutations have been shown to spread. These cells apparently sense signals from the microenvironment and the epithelial mesenchymal interaction.<sup>108</sup>

## 4.3. The field effect

One of the main differences between sporadic and IBD-related colonic neoplasia is that in IBD the entire colonic mucosa carries risk for neoplastic transformation that can be multifocal, as opposed to one or few premalignant adenomas or cancers in sporadic cases.<sup>109</sup>

Aneuploidy is a marker for genomic instability and has been shown in morphologically normal mucosal cells in IBD. Studies in UC patients with consecutive colonoscopies indicate that cell populations with aneuploidy expand in location over time.<sup>110</sup> Aneuploidy does not correlate morphologically with dysplasia and is probably more widespread. Many genomic alterations, including methylation, have been shown in morphologically normal colonic mucosa in IBD patients.<sup>92,107</sup> p53 mutations that are an initial event in IBD-associated neoplasia can be found in nondysplastic mucosa.<sup>95</sup> Two recent studies<sup>92,107</sup> looked into individual crypts and found the same mutations, mainly in TP53 KRAS and CDKN2A, present both in neoplasia and in nondysplastic mucosa, even long before tumour development, strongly supporting the concept of a precancerous field effect.

The cause of the field effect can be explained by the constant re-epithelialization of ulcerated and chronically inflamed colonic mucosa by abnormal healing clones that expand,<sup>97</sup> as well as local environmental changes such as dysbiosis of the microflora, which can cause the appearance of these mutations in several spots.<sup>111</sup>

## 5. Outcome of colorectal cancer in IBD

During the last 40 years there have been a few small reports looking at the outcome of CRC in UC<sup>9,112–115</sup> and CD.<sup>116,117</sup> The overall 5-year survival rates in these reports range from 33.5% to 55.1% for UC and 18% to 46% for CD, with no significant differences compared with non-IBD cases of CRC.

Over the last 16 years, a number of larger multi-centre cohort studies and population-based reports have been published. Bansal and Sonnenberg<sup>118</sup> showed a trend ( $p = 0.0681$ ) towards decreased risk of cancer-related death in CRC among patients with IBD ( $n = 371$ ) compared with sporadic CRC ( $n = 52\ 243$ ), but no difference between CD ( $n = 134$ ) and UC ( $n = 237$ ). A 20-year follow-up study from the Mayo Clinic compared IBD-related (UC = 241 and CD = 49) CRC with age-

and sex-matched sporadic CRC.<sup>119</sup> IBD-related cancers were more proximal, with only 55% distal to the splenic flexure, compared with 78% among sporadic CRC. Cases of IBD-related CRC were more often grade 3 or 4 tumours (40%) compared with sporadic tumours (33%), and were also more often mucinous (UC 20%, CD 24% and sporadic 13%). Despite this, no differences were found in overall survival between sporadic and IBD-related CRC. Two Danish population-based studies looked specifically at UC-<sup>120</sup> and CD-<sup>121</sup> related CRC compared with sporadic CRC. In the study on UC by Jensen et al.<sup>120</sup> 71 259 sporadic CRC cases during 1977–1999 were compared with 279 UC-related cancers. Cancer stage, and rates of lymph node and distant metastasis were similar between the two groups. The overall mortality rates at 1 and 5 years after cancer diagnosis were increased in UC-related CRC compared with sporadic cancers (1.24 (95% CI 1.02–1.51) and 1.17 (95% CI 1.01–1.36), respectively). In a similar study by Larsen et al.,<sup>121</sup> 71 438 sporadic CRC cases were compared with 100 CD-related CRC cases. The hazard ratios for death at 1 and 5 years after cancer diagnosis were 1.82 (95% CI 1.36–2.43) and 1.57 (95% CI 1.24–1.99), respectively. Both in UC and CD, CRC diagnosed <60 years of age was shown to have a worse outcome, especially within the first year with a hazard ratio of 1.92 (95% CI 1.29–2.87). Brackmann et al.<sup>122</sup> published a population-based study from 1962 to 2005 on 81 780 sporadic cases of CRC and 60 patients with IBD-related dysplasia or CRC (CD colitis n = 6, UC n = 54). No differences were found regarding cancer stage or distant metastasis at the time of CRC diagnosis. The mortality rate ratio (MRR) was 3.71 (95% CI 2.54–5.42) for IBD-related CRC, compared with sporadic cancers mainly attributable to multifocal dysplasia or cancers, for which the MRR was 4.27 (95% CI 2.83–6). Survival after localised IBD-related CRC was similar to that of sporadic CRC.

In another study, the outcome in UC patients (n = 20) was compared with that in CD patients (n = 14) diagnosed with CRC between 1990 and 2007.<sup>123</sup> CRC in CD was found to be associated with worse outcome in terms of 5-year disease-free survival, 43% and 31% vs. 70% and 63% in UC (p = 0.01 respectively). In a Swedish population-based study,<sup>124</sup> sporadic CRC cases (n = 112 948) were compared with tumours occurring in IBD patients (n = 251), all with similar tumour stage at CRC diagnosis. Apart from rectal cancer in CD, the CRC-related mortality was increased among IBD patients, with hazard ratios for colon cancer of 2.08 (95% CI 1.46–2.96) in CD, 1.32 (95% CI 1.02–1.72) in UC and 1.77 (95% CI 1.22–2.56) for rectal cancer in UC. Furthermore, this study revealed that IBD patients <60 years at time of diagnosis and males had a worse outcome.

Some studies have found no difference between IBD and sporadic CRC in terms of survival. Peyrin-Biroulet et al. analysed data from the Burgundy digestive cancer registry in France during 1976–2008 (sporadic n = 19 413 and IBD related n = 38).<sup>125</sup> As shown previously, IBD patients were younger at the time of CRC diagnosis, 56.9 years vs. 70.9 years (p < 0.001). A trend towards an excess death rate was found among IBD patients with CRC (hazard ratio 1.46 95% CI 0.94–2.27). Another more recent US study<sup>126</sup> compared 29 CRC patients with CD and 53 with UC with 13 938 sporadic CRC patients. Mortality from CRC was 2.3 (95% CI 1.6–3.0) times higher in CD and 2.0 (95% CI 1.3–2.7) times higher in UC.

In summary, the available literature shows an impaired outcome of CRC in IBD, with a 2-fold increase in mortality compared with sporadic cancers, but without major differences between UC and CD except for a more advanced tumour stage at the time of diagnosis in CD patients. It is worth noting that for IBD, the presence of CRC is often not known prior to surgery. Male sex and young age are factors associated with poor outcome.

## 6. Chemoprevention of colorectal cancer in IBD

A number of agents are potential chemopreventives in IBD, such as 5-aminosalicylates (5-ASAs), ursodeoxycholic acid (UDCA), folic acid and azathioprine.

### 6.1. 5-Aminosalicylates

5-ASA compounds, used extensively in the management of IBD, particularly UC, have been identified as candidate chemopreventive agents.<sup>127</sup> The mechanism of action of mesalazine in chemoprevention is diverse, interfering with many pathways in CRC cell biology, rather than simply controlling inflammation. Actions include activation of the PPAR gamma pathway, inhibition of lipoxygenase and cyclooxygenase mediators, free radical scavenger and antioxidant functions, and ability to inhibit interleukins.<sup>128</sup>

Early evidence comes from a community-based study cohort of 175 patients with UC by Moody et al.<sup>129</sup> who demonstrated a 10-fold reduction in the incidence of CRC in patients on long-term sulphasalazine. In a case-controlled study, Pinchowski et al.<sup>130</sup> studied this aspect in IBD patients grouped by the duration of 5-ASA use. Patients who had used sulphasalazine for  $\geq 3$  months had a 62% risk reduction compared with patients with a shorter duration of use. In a further case-controlled study, Eaden et al.<sup>131</sup> compared 102 patients with UC-related CRC with matched controls, finding a 75% risk reduction for CRC among patients with regular 5-ASA use (OR 0.25; 95% CI 0.13–0.48; p < 0.00001). The benefit persisted after adjusting for variables such as disease extent and disease duration (OR 0.19, 95% CI 0.06–0.61; p = 0.006). A more recent large population-based general practise database study from the UK<sup>132</sup> found that regular users of 5-ASAs (defined as >6 prescriptions in the preceding 12 months) had a 40% reduced risk of CRC (adjusted OR 0.60 (0.38–0.96)).

However, not all studies support a protective effect. In a large UC surveillance cohort at St Mark's Hospital, London, primarily designed to examine risk factors for colorectal neoplasia, use of mesalazine for  $\geq 10$  years was associated with a more modest and non-significant decrease in CRC risk (OR 0.65; 95% CI 0.26–1.62).<sup>133</sup> In addition, this study reported an unexpected increase in risk of CRC in patients taking long-term sulphasalazine. Similarly, Ullman et al.<sup>134</sup> found no evidence of an effect of mesalazine exposure on subsequent development of advanced neoplasia. Terdiman<sup>135</sup> compared CRC patients registered on a large administrative claims database in California with controls, finding that 5-ASA therapy of any dose for a duration of 1 year before diagnosis of CRC was not associated with a reduction in CRC risk (OR 0.97, 95% CI 0.77–1.22). Bernstein et al. found a trend towards increased cancer risk associated with the use of 5-ASAs within 2 years of a cancer diagnosis, indicating perhaps that the

benefit only exists if given early in the course of disease in UC.<sup>136</sup>

The most compelling data supporting a beneficial effect of 5-ASAs come from a meta-analysis of 9 observational studies involving a total of 1932 patients, finding a 49% reduction in the risk of CRC or CRC/dysplasia with regular use of 5-ASAs.<sup>137</sup> The pooled analysis showed a protective association between use of 5-ASA and CRC (OR 0.51, 95% CI 0.37–0.69) and for the combined end point of CRC/dysplasia (OR 0.51, 95% CI 0.38–0.69). A recent systematic review<sup>138</sup> including 4 observational studies focused on non-referral studies indicated a chemopreventive benefit with 5-ASAs with an adjusted OR of 0.95 (95% CI 0.66–1.38), but there was moderate heterogeneity ( $I^2 = 58.2\%$ ;  $p = 0.07$ ).

Four studies looked at the dose needed to provide a chemoprevention benefit. A study by van Staa et al.<sup>132</sup> found a doubled risk reduction among those on daily doses above 1.2 g/day compared with those taking <1.2 g/day, but a protective effect was observed in both groups (adjusted OR 0.28 and 0.56, respectively). Similar results were shown by Eaden et al.<sup>131</sup> where mesalazine at doses of 1.2 g or more reduced CRC risk by 91% compared with no treatment (OR 0.09, 95% CI 0.03–0.28) but a protective effect was still found with lower doses (OR 0.08; 95% CI 0.08–0.85). In a more recent case-controlled study involving 1594 IBD patients that included 18 CRC patients, cumulative aminosalicylate dose of over 4500 g reduced the risk of CRC by 97% after adjusting for disease extent and duration.<sup>139</sup>

Overall, despite the lack of good quality prospective randomised trials, there is sufficient evidence now to recommend the use of 5-ASAs for the chemoprevention of CAC. However, a number of unanswered questions remain. There is little data from which to establish recommendations for when to initiate therapy, the duration of therapy needed to achieve the benefit of chemoprevention and whether the effect lasts after cessation of therapy. Future studies should also identify those groups at highest risk among whom the benefit may be higher, and whether 5-ASA can inhibit progression of dysplasia to cancer. The anti-mutational effect of 5-ASA may also be useful in individuals with Lynch syndrome.<sup>140,141</sup>

## 6.2. Ursodeoxycholic acid

The first indication of a potential chemoprotective effect of UDCA in UC came from a retrospective study of 59 patients with PSC and UC, of whom 41 were treated with UDCA<sup>142</sup> in which a lower prevalence of dysplasia was reported in the UDCA-treated group (OR 0.18;  $p = 0.005$ ) with a 40% difference in risk between the two groups. The protective effect appeared to persist after adjusting for age, duration of colitis and concomitant sulfasalazine use (adjusted OR 0.14, 95% CI 0.03–0.64). In a placebo-controlled trial in PSC patients with UC (median disease duration 13 years, follow-up time 6.5 years), designed to detect improvement in liver function, UDCA was associated with a 74% risk reduction for CRC and dysplasia (RR 0.26, 95% CI 0.07–0.99).<sup>143</sup> Due to the limited number of colonic biopsies performed in the study compared to the current surveillance guidelines, the result may be biased.

Further evidence of the benefit of UDCA came from a proof of concept study in IBD patients with pre-existing low-grade

dysplasia and DNA aneuploidy randomised to receive UDCA or placebo.<sup>144</sup> The primary outcome, defined as the need for colectomy for the progression of dysplasia, was reached in 2 patients in the placebo group and none in the UDCA-treated group. This study was limited by very small patient numbers, short treatment duration and the low doses of UDCA used, but it does indicate that UDCA may halt the progression of dysplasia in high-risk patients with extensive colitis and pre-existing premalignant lesions.

The early positive findings for UDCA as a chemopreventive agent have not been replicated in more recent studies, including studies with more patients. In a cohort study that included 120 patients, Wolf et al.<sup>145</sup> found no difference in the risk of developing dysplasia or carcinoma, although they did show a reduction in mortality in the UDCA group. More recent studies suggest that the duration of treatment and the dose of UDCA are important factors in chemoprevention.<sup>146–150</sup> Eaton and et al.<sup>148</sup> examined the effects of high-dose (28–30 mg/kg/day) UDCA on the development of colorectal neoplasia in 56 patients with UC and PSC with a follow-up duration of 235 patient years. Patients who received high-dose UDCA had a significantly higher risk of developing colorectal neoplasia during the study than those who received placebo (HR: 4.44, 95% CI 1.30–20.10;  $p = 0.02$ ). In another study, also using high-dose UDCA (17–23 mg/kg), there was a similar frequency of dysplasia or cancer after 5 years in patients originally assigned to UDCA or placebo (13% vs. 16%), and no difference was detected in dysplasia/cancer-free survival after 5 years of therapy (13% and 16%) or 10 years of follow-up (30% and 27%).<sup>149</sup> In a study in post-transplant patients with PSC, use of 5-ASA or UDCA was shown on multivariate analysis to be associated with an increased risk of CRC.<sup>150</sup> A large randomised study estimating the survival advantage in PSC patients of high-dose 5-ASA failed to demonstrate any reduction in CRC risk.<sup>151</sup> In contrast, a prospective study from Germany in 120 patients with IBD and PSC found that the annual incidence of CRC increased up to 6 years after the start of UDCA but subsequently decreased.<sup>152</sup> A recent meta-analysis of 4 studies, including 281 patients, reported that UDCA was not associated with any improvement in the risk of CRC (OR 0.53; 95% CI: 0.19–1.48;  $p = 0.23$ ) compared with no UDCA or placebo.<sup>153</sup>

Overall, studies so far suggest that the role of UDCA as a chemopreventive agent remains controversial, particularly at high doses. Larger randomised prospective studies including those comparing high doses versus low doses are needed to reach a conclusion. However, this is unlikely given the rarity of treatment-naïve PSC patients with colitis, and the long follow-up necessary.

## 6.3. Immunomodulators

There is increasing evidence that chronic inflammation favours the development of cancer in IBD, and hence mucosal healing with immunomodulators or biologics may prevent CRC in IBD.<sup>154</sup> However, there is insufficient data on the role of immunomodulators in chemoprevention. In a single-centre study of UC patients treated with azathioprine and followed for 17 years, no patient developed cancer.<sup>155</sup> In a further cohort study from New York of 315 patients followed for an average of 8 years, azathioprine (AZA)/6-mercaptopurine



(6MP) use did not have any effect on the development of CRC.<sup>156</sup> Three further studies examined chemoprevention by 6MP and AZA as chemoprophylaxis, although not as the primary endpoint.<sup>133,142,157</sup> Rutter et al.<sup>133</sup> showed a non-significant trend towards a protective effect of azathioprine use for 1–5 years, or greater than 5 years, with ORs of 0.34 (95% CI 0.09–1.25) and 0.73 (95% CI 0.30–1.78), respectively. Lashner et al.<sup>157</sup> reported that the use of azathioprine for  $\geq 6$  months had no protective effect (RR 1.12, 95% CI 0.26–4.17). A similar result was reported by Tung et al.<sup>142</sup> These studies were retrospective cohort studies with no data available on the dose used or duration of treatment. In a nested case–control study using a UK primary care database,<sup>132</sup> among 5-ASA users who had also used oral glucocorticoids or immunosuppressants in the previous 6 months there were no differences in the risk of CRC between regular and irregular 5-ASA use (adjusted OR 1.21 (95% CI 0.43–3.45)). In contrast, regular 5-ASA use was associated with a reduced risk of CRC in non-users of oral glucocorticoids or immunosuppressants (adjusted OR 0.53 (95% CI 0.30–0.92)).<sup>129</sup> In a more recent nested case–control study in North America, using immunosuppressive therapy (OR 0.3; 95% CI 0.16–0.56;  $p < 0.001$ ) or anti-TNF $\alpha$  (OR 0.09; 95% CI 0.01–0.68;  $p < 0.02$ ) was protective in terms of risk of IBD-related CRC.<sup>20</sup> Interestingly, the overall risk of CRC in this cohort was much lower than previously reported, with an overall risk of 0.04%.<sup>20</sup>

The association between thiopurine and/or 5-ASA use and the risk of advanced neoplasia (AN), including high-grade dysplasia and colorectal cancer, was recently investigated in a large cohort of patients with IBD in the Netherlands.<sup>158</sup> Thiopurine use was associated with a significantly decreased risk of AN (adjusted HR 0.10, 95% CI 0.01 to 0.75). 5-ASA therapy also had a protective effect against AN, but this was not statistically significant (adjusted HR 0.56, 95% CI 0.22 to 1.40).

Recent experimental data identifying TNF $\alpha$  as a mediator involved in initiation and progression of CAC has not yet been reflected in clinical trials, and other risks will preclude their use for the sole aim of chemoprevention. The results from the GETAID CESAME cohort have not yet been fully reported, but preliminary data do not support a chemopreventive role of AZA.<sup>159</sup>

#### 6.4. Folic acid

Lashner et al.<sup>157</sup> reviewed data from 99 patients with pancolitis enrolled in a 7-year surveillance programme and studied the effect of folate supplementation on the rate of neoplasia development using case–control methodology. Folate supplementation was associated with a 62% lower incidence of neoplasia but this was not statistically significant (OR, 0.38; 95% CI, 0.12–1.20). The same group also reported a similar non-significant trend towards a protective effect and dose–response effect of folate supplementation of  $\geq 6$  months in a subsequent cohort study.<sup>160</sup> In this study, the adjusted RR of neoplasia for patients taking folate was 0.72 (95% CI 0.28–1.83). The risk of neoplasia varied with folate dose (RR, 0.54 for 1.0 mg folate; RR, 0.76 for 0.4 mg folate in a multi-vitamin, compared with no folate). The degree of dysplasia also varied with folate use (RR for cancer, 0.45; RR for high-grade dysplasia, 0.52; RR for

low-grade dysplasia, 0.75, compared with patients without dysplasia) ( $p = 0.08$ ). An experimental study on cell kinetics using immunohistochemistry following 3 months of folic acid or placebo supplementation in 12 colitis patients revealed a reduction in cell proliferation.<sup>161</sup> However, the role of folic acid has not yet been tested in large randomised controlled trials.

Overall, while there is no clear data to support routine the use of folic acid, there appears to be a trend towards benefit. Since folic acid is inexpensive and safe it may be considered in selected patients at the clinician's discretion.

#### 6.5. Statins

Experimental data from mice indicate that statins may have a protective effect against colitis-associated carcinogenesis, primarily by the induction of selective apoptosis of colon cancer cells.<sup>162</sup> In a population-based case–control study,<sup>163</sup> statin therapy was associated with a modest reduction in CRC in the non-IBD population, but a substantial 94% risk reduction in patients with IBD was observed in a subset analysis of 55 IBD patients. Furthermore, a recent meta-analysis of 18 trials on statin use in hypercholesterolemia showed only limited benefit in the setting of general population.<sup>164</sup> Overall, further studies are needed in high-risk IBD patients to test the results of initial experimental studies.

#### 6.6. Chemoprevention in CD

The role of chemoprevention in CD has not been well studied, and available data comes from studies with small numbers of CD patients and do not give any firm conclusions. However, a non-significant trend for a protective effect has been reported with regular 5-ASA use (OR 0.30; 95% CI 0.05–1.17;  $p = 0.10$ ) in at least one study.<sup>165</sup>

### 7. Conclusions and areas for future research

Recent data show that CRC risk is decreasing but it still remains a major clinical problem in IBD patients. Better control of intestinal inflammation is likely to be the major reason. Future areas of investigation should focus on understanding better the key pathogenic pathways. In addition, the impact of all the novel medications including anti-TNF in decreasing CRC risk needs to be better assessed, even though interventional studies appear to be unethical and not feasible when it is a matter of choosing between treating or not inflammation. Large prospective cohorts can help us to further investigate and identify the risk factors to develop CRC and to assess the efficacy of IBD related drugs in reducing the risk. Finally, from a surgical point of view the collection of data from cohort studies and managing CRC in similar pathways of care can provide better data on survival and disease related outcomes.

#### Conflict of interest

Silvio Danese has served as a speaker, a consultant and an advisory board member for Schering-Plough, Abbott

Laboratories, Merck & Co, UCB Pharma, Ferring, Cellierix, Millenium Takeda, Nycomed, Pharmacosmos, Actelion, Alphawasserman, Genentech, Grunenthal, Pfizer, Astra Zeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor, and Johnson and Johnson.

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