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Clinical course and prognosis in ulcerative colitis: results from population-based and observational studies

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Abstract

The clinical course of ulcerative colitis (UC) may range from a quiescent course with prolonged periods of remission to fulminant disease requiring intensive medical treatment or surgery. Disease outcome is often determined by relapse rates, the development of colorectal cancer (CRC) and mortality rates. Early patient classification, identifying those with a high risk of developing complicated disease, is essential for choosing appropriate treatment. This paper reviews the clinical outcomes of UC patients as reported in population-based and observational studies representative of the whole patient population. Extensive colitis, a high level of systemic symptoms and young age at diagnosis are factors associated with a high risk of colectomy. Patients with distal disease who progress to extensive colitis seem to be a subgroup with an especially high risk of colectomy. Some prognostic factors of severe disease have been identified which could be used to optimize treatment and possibly reduce future complications. The overall risk of CRC and mortality was not significantly different from that of the background population. These results may have implications for follow-up strategies, especially regarding endoscopic surveillance of UC patients.

Keywords Ulcerative colitis, natural history, colorectal cancer, mortality

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Introduction

Ulcerative colitis (UC) is characterized by chronic inflammation of the large bowel occurring in genetically susceptible individuals exposed to environmental factors. The disease usually develops in young adults in their third and fourth decade. Due to the generally young age at onset and the chronic nature of UC, the disease burden in each patient may be substantial, with an average disease duration of 40 years.

Many of the published studies on UC were conducted in tertiary referral centers, where only patients with the most complicated disease are treated. The results obtained through these studies may give false predictions of disease outcome for the average patient with UC. Hence, population-based studies, reflecting the entire range of disease from mild proctitis to fulminant extensive colitis, including all age groups, are needed to gain more knowledge about the prognosis of UC. The results based on these studies are likely to give important clues about risk factors of complicated disease and may enable a more optimized treatment of patients.

The clinical course and outcome of UC may have changed over the years. This could be due to better diagnostic tools, a broader spectrum of medical treatments and less invasive surgical procedures. However, some patients are exposed to strong immunomodulators, such as azathioprine and / or biologics over many years, which make them more vulnerable to opportunistic infections and possible carcinogenic processes. Therefore, it is crucial to compare disease outcomes, including relapse, surgery, cancer and mortality, before these drugs were generally used to the current situation, approximately 10 years after biologic drugs became widely used.

The aim of this article is to review the clinical outcomes of UC patients, as reported in population-based and observational studies that are representative of the whole patient population. Predictive factors for clinical outcomes with respect to disease behavior, such as disease extent, relapse, surgery, cancer and mortality, will be discussed.

Methods

This overview will focus on the past 20 years, based mainly on information available from observational and population-based studies published in English. The literature review was performed by searching PubMed, Cochrane and Ovid with the

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appropriate key words ("ulcerative colitis" and "inflammatory bowel disease" combined with a free text search for "diagnosis," "population based," "clinical," "course," "prognosis," "surgery," "complications," "cancer," "colonic cancer" and "mortality").

Importance of classification of disease

Disease classification at diagnosis is of crucial importance, as it may yield valuable information about the subsequent disease course. This information is essential to give optimal medical care for each individual patient.

Currently, the Montreal classification (Table 1) is the most widely implemented [1]. It assesses the extent of disease and severity of symptoms, both of which have important prognostic value. The extent of disease is classified as mucosal changes on endoscopy limited to the rectum (E1), the left side of the colon, (E2) and beyond the splenic flexure (E3). The symptom severity score ranges from none (S0) to severe systemic manifestations (S3).

Colectomy is a solid endpoint regarding disease severity in UC. Several studies have revealed a relationship between the extent of colitis at diagnosis and the risk of colectomy [2-4]. In a recent population-based study from Norway (IBSEN study), extensive colitis at presentation was found to be an independent predictor of colectomy at both 1 year [5] and 10 years [2] after diagnosis. Comparable results were obtained by the European Collaborative Study Group of Inflammatory Bowel Disease (EC IBD) study [3] showing that colectomy was more likely in extensive colitis than in proctitis, with a cumulative hazard ratio of 4.1 (95% confidence interval [CI]: 2.0-8.4).

A high level of systemic symptoms at diagnosis has also been associated with increased risk of colectomy. In a study from Copenhagen, Langholz *et al* reported that patients with extensive colitis and additional signs of systemic disease, such as fever and weight loss at diagnosis, were more prone to undergo colectomy [6]. Similar findings were reported in the IBSEN cohort [2]. In this study, the 2 year cumulative colectomy rate among patients diagnosed with extensive colitis was 3% in the group with an erythrocyte sedimentation rate (ESR) <30 mm/h compared with 21% in the group with elevated ESRs ≥30 mm/h (log-rank test, P=0.001).

Conversely, extensive colitis or severe systemic symptoms at diagnosis were not associated with an increased risk of overall relapse in the abovementioned studies. On the contrary, in the Copenhagen cohort [6], the combination of weight loss and fever was independently associated with a more favorable course with less risk of relapse, provided that the patients avoided a colectomy. Likewise, in the IBSEN cohort, Solberg *et al* reported that non-colectomized patients presenting with ESR ≥30 mm/h at diagnosis were more likely to have a relapse-free course of disease than those initially presenting with ESR <30 mm/h [2]. Because nonsurgical relapse in these studies was solely defined by clinical symptoms, this result might be explained by the fact that clinical symptoms are quite common in patients with limited disease distribution and mild to moderate disease activity. However, as suggested by the Danish authors, this observation may also be explained by a strong immune reaction at the onset of disease that secures a more quiescent course in those who respond to medical treatment. The results from the IBSEN study partially supported this theory: the authors found more frequent endoscopic mucosal healing after 1 year of therapy in patients who were severely ill and had extensive disease at diagnosis [7].

It has been suggested that age should be a part of the clinical classification of UC, as this factor has been shown to influence the disease course. However, the results from population-based studies are not consistent. Both the EC IBD study and the IBSEN study showed a trend toward more frequent relapse in young patients diagnosed with UC [8,9]. Moreover, in the IBSEN study, being aged above 50 years at diagnosis was found to be a protective characteristic against relapse and colectomy [2]. In contrast to this finding, the Copenhagen study did not report any age-related differences regarding the disease course.

Table 1 Montreal classification of extent and severity of ulcerative colitis (UC) [1]

Extent / severity		Anatomy / definition
E1	Ulcerative proctitis	Involvement limited to the rectum (proximal extent of inflammation is distal to the rectosigmoid junction)
E2	Left-sided UC (distal UC)	Involvement limited to a portion of the colorectum distal to the splenic flexure
E3	Extensive UC (pancolitis)	Involvement extends proximal to the splenic flexure
S0	Clinical remission	Asymptomatic
S1	Mild UC	Passage of four or fewer stools / day (with or without blood), absence of any systemic illness and normal inflammatory markers (ESR)
S2	Moderate UC	Passage of more than four stools per day but with minimal signs of systemic toxicity
S3	Severe UC	Passage of at least six bloody stools daily, pulse rate of at least 90 beats/min, temperature of at least 37.5°C, hemoglobin of less than 10.5 g /100 mL and ESR of at least 30 mm/h

ESR, erythrocyte sedimentation rate

Of other factors possibly influencing the disease course in UC, smoking tobacco has been associated with a more quiescent course [10,11]. Lakatos *et al* found that smoking in UC was associated with more extensive colitis (P=0.01) and a tendency for a decreased need of colectomy (P=0.06) [12]. Similarly, the EC IBD study revealed a tendency towards a lower risk of colectomy among smokers within 10 years after diagnosis (hazard ratio [HR] 0.7; 95%CI 0.3-1.4) [3,8]. Other studies have shown that smoking status is associated with a less active disease course. Moreover, smoking cessation has been associated with increased disease activity, reflected in the need for hospitalization and major medical therapy [13,14].

There are some data suggesting that perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) may be a prognostic factor of disease course. In UC patients who had undergone restorative proctocolectomy, preoperative p-ANCA positivity was associated with an increased postoperative occurrence of acute and chronic pouchitis. Pouchitis was seen in 42% of p-ANCA positive patients compared to only 20% of the p-ANCA negative group [15]. In the IBSEN cohort, UC patients with p-ANCA positivity had a four-fold higher risk of receiving azathioprine, a treatment that, in this study, was generally given to steroid-dependent or refractory patients [2]. Moreover, in a pilot study from the Mayo Clinic, Sanborn *et al* reported that the presence of p-ANCA was associated with treatment-resistant left-sided colitis [16]. Finally, recent data might suggest that p-ANCA could be a predictor of the response to immunomodulatory therapy because p-ANCA negativity has been associated with an early response to this treatment.

Disease progression

It has become evident that UC, like Crohn's disease, may be considered a progressive and dynamic disease. Many studies have found that proctitis and left-sided colitis may progress to extensive colitis over time. However, it is difficult to compare results between these studies because they used different methods to assess the extent of disease. In the IBSEN cohort, where endoscopy was the main instrument for determining disease extent, 14% of patients with proctitis had progressed to extensive colitis during the first 10 years after diagnosis [2]. This finding was in line with the results reported by Ayres *et al* and Langholz *et al*. However, the progression rate among those with initially left-sided colitis (28%) during the first 10 years of diagnosis was lower in the IBSEN cohort than reported in many other studies. This observation may be partly due to different modalities of investigation (barium enema and sigmoidoscopy versus colonoscopy).

In the IBSEN study, Solberg *et al* reported that those with proximal disease extension tended to be at a greater risk of undergoing colectomy than those presenting with extensive colitis at diagnosis (crude rate: 28% versus 19%; P=0.07), suggesting that this subgroup of UC patients has a more aggressive course of disease [2]. The patients experiencing proximal extension were of slightly younger age (P=0.04), but apart from age, no other covariates at diagnosis were significantly associated with proximal extension of disease. Likewise, a prospective registry study including 420 UC patients from Barcelona found that young age at diagnosis was an independent predictive factor for proximal disease extension (HR 0.979; 95%CI 0.959-0.999); this result was expressed as age at onset with a reduction of 2.1% for each additional year [17]. In the same study, primary sclerosing cholangitis (PSC) was another, even stronger, predictive factor for proximal disease extension (HR 12.83; 95%CI 1.36-121.10). The median time from diagnosis of distal or left sided colitis to proximal disease extension was 5.25 years (interquartile range [IQR]: 1.87-9.59 years).

Although UC is primarily considered to be a mucosal disease, there is evidence that over time, disease progression also does damage in the deeper layers of the colon in some patients. Such changes were evident already in the past when the colon was assessed by Barium enemas. "Lead-pipe" colon described the x-ray image of a colon with lost haustra, reduced length, caliber and elasticity found after long-standing colitis [18]. Benign colonic strictures were reported in 3.6 to 11.2% of UC patients, in previous studies [19-21]. An extensive study on strictures in UC was conducted by Gamaste *et al* on 1156 UC patients from Mt Sinai [21]. They found benign strictures in 42 patients (3.6%) after mean disease duration of 14.5 years. These structural changes in the deeper layers of the colon include a hypertrophied and permanently contracted muscularis mucosa that is detached from the submucosa, and morphological changes in the neuromuscular compartment with a reduced number of neuroglia cells and interstitial cells of Cajal [22]. These changes in the colonic wall may result in dysmotility and account for persistent diarrhea after mucosal healing. The transmural damages are particularly disabling in the ano-rectal compartment, where they may result in reduced rectal accommodation, leading to urgency and even frank fecal incontinence [23].

In summary, a small portion of UC patients will experience proximal disease extension, predominantly younger patients and those with coexistent PSC. These patients are at an increased risk of a more serious disease course, reflected by the need for immunosuppressive treatment and an increased risk of colectomy.

Colectomy

Even if colectomy in many centers is performed by minimally invasive techniques, such as laparoscopic colectomy or even single-incision laparoscopic colectomy, it is still regarded as a dramatic treatment for young patients. The procedure may be complicated with postoperative complications such as infections, anastomosis leakage, abscesses, reduced fertility, sexual dysfunctions and small bowel obstructions. And, although the general health of the patient often improves significantly after removing the sick colon, and the chance of

developing colorectal cancer (CRC) is reduced to a minimum, many patients experience psychosocial limitations while living with an ileostomy or an ileal pouch anal anastomosis (IPAA). Common complaints among patients with IPAA are frequent- and nightly bowel movements and some degree of fecal incontinence (seeping/soiling) [24]. Furthermore, 70% of UC patients with an IPAA experience one or more episode of pouchitis, a non-specific inflammation of the ileal pouch, during a 20-year period of follow up [24].

Indications for colectomy may be divided into acute and elective procedures. Emergency colectomies are done for life-threatening complications of colitis in hospitalized patients unresponsive to medical treatment, while refractory disease, intolerance to medical treatment and colonic neoplasia are the main indications for elective colectomy. Although mortality related to severe attacks of UC has substantially decreased to less than 1% during the past decades [25], a delay in surgery may increase the risk of postoperative complications and mortality [26]. Concerns have been raised as to whether extensive medical treatments may hamper tissue healing and could expose the patient to postoperative infections. The risk of complications for patients on biologics alone or in combination with other immunomodulatory therapies peri- and postoperatively is still under evaluation.

Although emergency colectomy rates, accounting for approximately 50% of the colectomies performed for UC, seem to remain stable [27], studies have indicated that the overall colectomy rate has declined over the years. In the Copenhagen cohort, Langholz *et al* found that the 1-year colectomy rate for UC patients from 1962-87 was 9% [28], whereas Vind *et al* found, using the same methodology, a some what lower 1-year colectomy rate of 6% from 2003-2005 [29]. The authors stratified for treatment with azathioprine / 6-mercaptopurine and found an inverse association between the use of these medications and the risk of colectomy.

Furthermore, the colectomy rate in UC varies greatly between different cohorts. In the EC IBD study, in which 771 UC patients were followed up for a decade after inception from 1991-1993, the authors reported a cumulative risk of colectomy of 8.7% after 10 years. In this study, there was a significant difference in the risk of colectomy between northern and southern centers (10.4% versus 3.9%, respectively) [3]. Within the northern centers, there were also marked differences between the Copenhagen cohort (25.7%) and the Norwegian and Dutch cohorts (8.2%). Variations in the risk of colectomy may partly reflect different treatment strategies, but apart from that possibility, the authors could not readily explain the geographical differences. However, the different environmental factors, and the underlying immune response are likely to play a role. Earlier work by the EC IBD study group showed that there was a slightly higher incidence of Ulcerative colitis in Northern European- compared to Southern European countries. The fact that the colectomy rate in Northern Europe also was higher, could suggest that the disease burden in this region is greater. Moreover, the severity of the disease could be more pronounced in individuals living in a cooler, less inhabited and more sterile environment.

Many studies have shown that the risk of colectomy is highest during the first years after diagnosis [4,30]. In the IBSEN cohort, 25 out of 49 colectomies were performed during the first 2 years during a 10-year follow-up period [2]. To be able to offer the appropriate treatment in a timely manner and, thereby, possibly avoid colectomy, it is important to identify subgroups of patients with an increased risk of subsequent colectomy.

Recently, a risk matrix model for prediction of complicated disease was developed based on the data from the IBSEN cohort. From these data, it was extrapolated that the risk of colectomy was 15 times higher if the patient was young (<30 years old), had extensive colitis, elevated ESR (>30 mm/h) and a need for corticosteroids at diagnosis [31]. The combination of these risk factors at diagnosis predicted complicated UC correctly in 90.3% of the patients Table 2 depicts the risk of colectomy in UC 10 years after diagnosis in the IBSEN cohort. As shown in the table, ESR >30 mm/h and extensive colitis at diagnosis were independent risk factors of colectomy, while age above 50 years at diagnosis was inversely associated with the risk of colectomy.

CRC in UC

The association between UC and CRC has been a focus of study for many years. According to the present literature, CRC accounts for 10-15% of deaths in IBD. IBD-associated CRC (IBD CRC) affects patients at a younger age than sporadic cancer, but the prognosis is quite similar, with a 5-year survival of approximately 50% [32].

Chronic inflammation is believed to promote carcinogenesis. The genetic features that lead to sporadic CRC chromosome instability and DNA hypermethylation also occur in colitis-associated CRC. However, the carcinogenesis pathway in IBD CRC is less clearly understood than its sporadic counterpart. Unlike the normal colonic mucosa, cells of the inflamed colonic mucosa have genetic alterations before there is any histological evidence of dysplasia or cancer. Oxidative stress is likely to be involved in carcinogenesis through reactive oxygen and nitrogen species [33].

In a national registry study from Belgium [34] including 171 UC patients with CRC, the authors reported that 73% of the patients developed their tumors in the area of the colon affected by colitis. Forty-seven percent of the tumors appeared in the left colon or rectum. Surprisingly, the tumors did not necessarily occur in the area of the colon with persistent inflammation. Moreover, 8 of 23 patients with left-sided colitis developed a tumor in the right side of the colon.

The risk of CRC is thought to be due to a combination of genetic, environmental and acquired factors [35]. The association between inflammation and cancer is well recognized, while the molecular biology, immunopathology and genetic associations between CRC and UC remain unclear [32].

Recently, Jess *et al* published a meta-analysis of population-based cohort studies to determine the risk of CRC in

Table 2 Risk of colectomy 10 years after diagnosis in ulcerative colitis patients. Cox regression analysis. Data from the IBSEN cohort [3]

		Unadjusted			Adjusted		
Variables at diagnosis	N	HR	CI	P-value	HR	CI	P-value
Age groups							
<30 years [ref]	159	1.0					
30-50 years	204	0.59	0.32-1.10	0.096	Excl		
≥50 years	156	0.39	0.17-0.87	0.022	0.28	0.12-0.65	0.003
Sex							
Female [ref]	252	1.0					
Male	267	0.83	0.47-1.45	0.51	Ni		
Extent of colitis							
Proctitis [ref]	171	1.0					
Left-sided colitis	182	1.37	0.59-3.22	0.46	Excl		
Extensive colitis	166	3.46	1.62-7.37	0.001	2.98	1.25-7.08	0.013
Hb g/dL							
≥10.5 [ref]	434	1.0					
<10.5	31	3.11	1.39-6.99	0.006	Excl		
ESR mm/h							
<30 [ref]	366	1.0			1.0		
≥30	98	3.23	1.79-5.84	<0.001	2.94	1.58-5.46	0.001
Temperature °C							
< 37.8 [ref]	457	1.0					
> 37.8	53	3.07	1.56-6.03	0.001	Excl		
Familial IBD (1st degree)							
No [ref]	457	1.0					
Yes	62	0.61	0.22-1.69	0.34	Ni		
Smoking status							
Never smokers [ref]	292	1.0		0.45	Ni		
Current smokers	69	0.54	0.19-1.53				
Ex-smokers	156	0.79	0.41-1.50				

N, number of patients; HR, hazard ratio; CI, 95% confidence interval; Ni, the variable was not entered in the multiple analyses; Excl, the variable was entered in the multiple models but was excluded because of later non-significance; [ref], reference category

patients with UC [36]. In these population-based cohorts, UC increased the risk of CRC by 2.4-fold, accounting for an overall occurrence of 1.6% (including sporadic cases), during the first 14 years of follow up. Male sex, diagnosis at a young age and extensive colitis increased the mortality risk. The authors suggested that the long-term risk of CRC among patients with UC was overestimated in the previous meta-analysis performed by Eaden *et al* In this analysis, the cumulative incidence of CRC was 2% after 10 years and 8% after 20 years of follow-up [37]. The corresponding figures were 0.4% and 1.1%, respectively, in the meta-analysis by Jess *et al*, which was restricted to unselected patients from population-based cohorts [36].

In meta-regression analysis from the aforementioned study by Jess *et al*, only cohort size was associated with the risk of CRC (Fig. 1). The significant heterogeneity between the studies in this meta-analysis might reflect differences in follow-up time, cohort sizes and geography in terms of patient care. Jess and co-investigators analyzed the relative risk (RR) of CRC 1 year after diagnosis among individuals with IBD and without IBD [36]. During 178 million person-years of follow up, 268 patients with UC developed CRC. The overall risk of CRC among UC patients was comparable with the risk in the background population (RR 1.07; 95%CI 0.95-1.121). However, patients diagnosed during childhood or adolescence, those with a long duration of disease and those with coexistent PSC were at increased risk. For patients with UC, the overall RR for CRC decreased from 1.34 (95%CI 1.13-1.58) in 1979-88 to 0.57 (95%CI 0.41-0.80) in 1999-2008. The authors concluded that a diagnosis of UC no longer seemed to increase the patients' risk of CRC, although subgroups of patients remained at increased risk. The national registry study from Belgium found that older age at diagnosis was an independent risk factor for CRC. These older patients presented with early cancer (<8 years from diagnosis) [34].

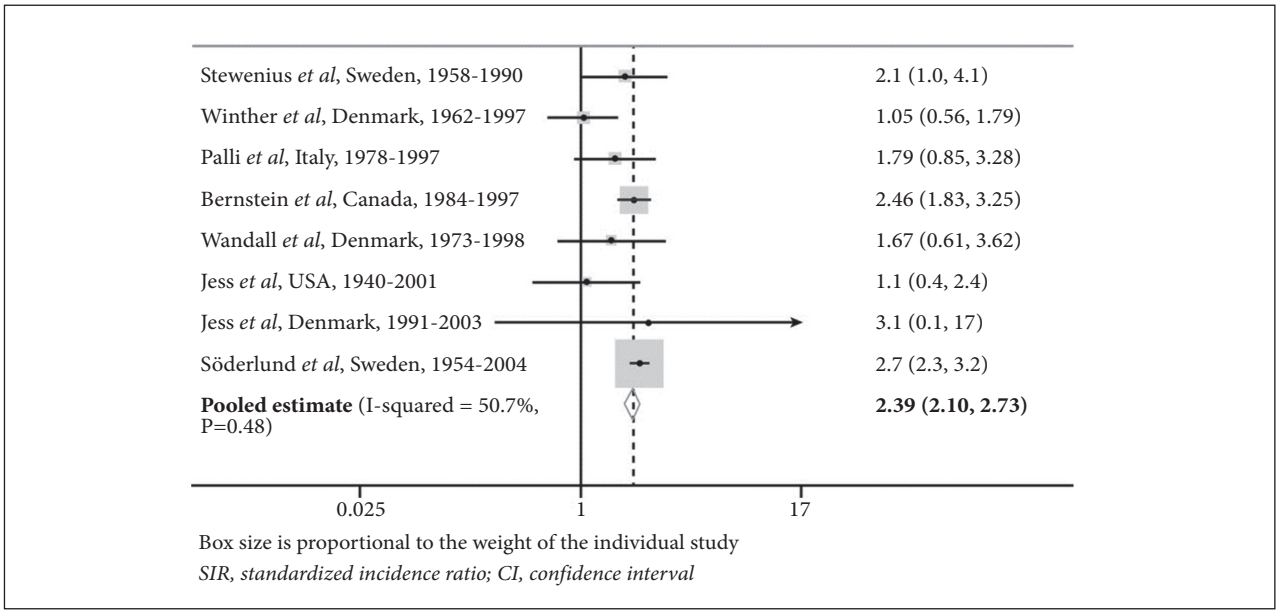

Figure 1 Risk of colorectal cancer in ulcerative colitis. Meta-analysis of population-based studies, Jess *et al* [39]

Data collection in the IBSEN study on the risk of CRC 20 years after diagnosis is currently ongoing; however, no significantly increased mortality risk due to CRC was found 20 years after diagnosis in UC patients compared with their age, sex and geographically matched controls [38].

The EC IBD study also evaluated the occurrence of cancer in IBD in general. In the 15-year follow up of this study cohort [39], the prevalence of all cancers was 9.1%. Most of the patients had a single neoplasm in an extraintestinal location. When comparing northern and southern centers, there was a tendency towards more intestinal neoplasms in the north and more extraintestinal neoplasms in the south, but the frequency of observed cancers was not different from the expected frequency in the background population. Because this study was performed in the years before biologics and combined immunomodulatory therapies were implemented, these findings may be useful historical data when overall safety and long-term effects of these therapies are assessed.

Cancer prevention

Preventing cancer is more favorable than curing it, both for the patient and for society. The decreased cancer rates reported in recent studies compared to earlier studies might be due to improved medical treatment and better patient care.

Chemoprevention

Five-aminosalicylates (5-ASAs) decrease the risk of CRC in UC patients in some studies, although the results are not consistent. Velayos *et al* conducted a meta-analysis of 9 studies including 1932 UC patients [40]. They found that the use of 5-ASA was associated with a lower incidence of CRC (odds ratio [OR] 0.52; 95%CI 0.37-0.69). However, they did not find any decrease in the incidence of dysplasia, although the prevalence of this disorder was only evaluated in 2 of the 9 studies. Tediman *et al* [41] did not find any reduction in CRC in patients using 5-ASA 12 months prior to a CRC diagnosis, suggesting a bias in the abovementioned studies. However, this discrepancy may be explained by the fact that the patients in the latter mentioned study received a short exposure to 5-ASA, indicating that such a time-limited exposure to 5-ASA has minimal effect. The 5-ASA-associated mechanism of cancer prevention is thought to involve mucosal healing. *In vitro* studies revealed the pharmacodynamics of 5-ASA: the drug inhibits the nuclear factor kappa B pathway, which sustains tumor survival and inflammation [42,43].

For UC patients with coexistent PSC, the use of ursodeoxycholic acid (UDCA) has been associated with a lower rate of CRC [44,45]. The increased risk of CRC for these patients may be due to increased levels of bile acids in the colonic lumen. UDCA reduces the amount of luminal bile acids. Tung *et al* [44] found a strong relationship between UDCA and a decreased risk of CRC even when adjusting for the age at UC diagnosis, duration of disease, gender, severity of liver disease and sulfasalazine use (OR 0.18; 95%CI 0.05-0.61).

Screening of CRC in UC

Evidence-based guidelines advise that patients with colitis receive a surveillance colonoscopy 8-10 years after diagnosis, with the interval for further surveillance guided by risk factors [46].

Proposed risk factors for IBD CRC are male gender and young age at diagnosis, whereas UC duration, severe and extensive disease, presence of PSC and a family history of CRC are previously confirmed risk factors [47].

In the national registry study from Belgium, Baars *et al* [34] reported that age at CRC diagnosis was independent of IBD duration. The median age was 40.1 years (IQR: 24-58), and the median age at CRC diagnosis was 56.4 (IQR: 44-65). In this cohort, the investigators found that 35% of patients developed cancer earlier than 8 years after IBD diagnosis, implying that they would have developed cancer already at the suggested time when screening began. After adjusting for possible confounders, the authors reported that age at the onset of IBD (HR 2.29; 95%CI 1.92-2.74) and ongoing active inflammation at follow-up (HR 1.5; 95%CI 1.0-2.29) were significantly associated with a shorter interval between IBD and CRC. In fact, 36 out of 251 (14%) patients were diagnosed with IBD and CRC simultaneously. All of these patients were older than 37 years. The age of the patient at IBD diagnosis was inversely related to the time to CRC diagnosis. In patients diagnosed with IBD at age 60-65, the median time to diagnosis CRC was only 3.5 years (0.9-4.8 years).

For a subset of patients, annual CRC screening from the onset of disease has been recommended [48]. This finding applies to patients with coexistent PSC and UC patients with a first-degree relative diagnosed with CRC before age 50. The national registry study from Belgium did not show any tendency for early cancers in the group of UC patients suffering from PSC, however many studies have shown an overall increased risk of CRC in this group compared to those with UC without PSC [34]. Because PSC patients often have mild colitis with minimal symptoms, it is advised that patients, when diagnosed with PSC, undergo a colonoscopy to determine whether they also have coexistent UC. The adjusted relative risk of dysplasia or cancer is 3.15 (95%CI 1.37-7.27) for UC patients with PSC compared to patients with UC alone. Kornfeld *et al* found [49] that the cumulative risk rates were 33% after 20 years and 40% after 30 years of UC diagnosis. The increased cancer risk of UC patients with PSC is explained by enterocyte damage due to the increased concentrations of bile acids in the lumen of the colon.

UC patients with a first-degree relative with CRC have an increased risk of IBD CRC. It is suggested that this is 2-3 times higher compared to the risk with UC alone. For those with a first-degree relative diagnosed with CRC at a young age, before the age of 50, this risk was estimated to be increased by 9-fold [35]. Comparable findings were reported in a retrospective population-based study from California. In that study, Velayos *et al* [40] found that patients with a family history of CRC were at an increased risk of developing IBD CRC (OR 3.7; 95%CI 1.0-13.2).

The way surveillance colonoscopy should be performed is also a topic of debate. IBD CRC poses different challenges than sporadic CRC, as these lesions tend to be harder to discover because they are often flat and multifocal [32]. It has long been advocated to take random quadrantic biopsies every 10 cm throughout the length of the colon, but this approach represents less than 1% of the colonic mucosa and has shown to miss many dysplasia-associated lesions or masses (DALMs) [32]. To take all these biopsies and later analyze them is time consuming for both the endoscopist and the pathologist. When, in addition, the detection rate of DALM lesions was insufficient, the need to develop alternative strategies seemed pertinent.

Chromoendoscopy is a method in which the colonic mucosa is colored with a dye to enhance the mucosal patterns, thereby making it easier to detect dysplastic lesions. Kiesslich *et al* [50] demonstrated many years ago that chromoendoscopy was superior to conventional colonoscopy in detecting dysplastic lesions. Later, Rutter *et al* [51] reported a similar trend when comparing conventional colonoscopy with random biopsies to indigo carmine-targeted biopsies. Chromoendoscopy found 7 dysplastic lesions out of 157 biopsies, compared to 0 dysplastic lesions in 2904 random biopsies. Moreover, in a case-controlled prospective study of 700 patients, Hurlstone *et al* [52] found a greater number of dysplastic lesions when using indigo carmine compared to conventional colonoscopy with random biopsies.

Narrow-band imaging, which is now available on most endoscopes, is thought to help visualize dysplastic / neoplastic lesions through enhancing vessels, pit patterns and soft tissue structures, but it has not been shown to increase identification of dysplastic lesions compared to conventional colonoscopy [53].

Confocal laser endomicroscopy visualizes the histology during an endoscopy. When spray dye is applied simultaneously, Hurlstone found a 2.5-fold-increased detection of dysplastic lesions in a randomized controlled trial in which endofocal laser chromoendomicroscopy was compared to chromoendoscopy [52]. Furthermore, in a randomized controlled trial comparing conventional colonoscopy with random biopsies to confocal chromoscopic endomicroscopy, Kiesslich *et al* [54] reported a 4.75-fold-increased yield of detecting dysplastic lesions while taking 50% fewer biopsies (P=0.005).

Mortality

Early studies on UC prognosis were not all consistent, but some showed a significant reduction in survival [55].

However, studies conducted during the last two decades have shown that UC patients have no increased mortality compared to the background population [56]. Winther *et al* showed no increased overall mortality in UC patients in the Copenhagen cohort (median follow up of 19 years) [57]. Likewise, in a Finnish population-based registry of 1254 IBD patients established between 1986 and 2007 [58], the overall standardized mortality ratio (SMR) was 0.9 (95%CI 0.77-1.06). In the aforementioned EC IBD study in which a large number of patients were followed up for 10 years after diagnosis, no increase in SMR among UC patients was noted [59]. Similarly, in the IBSEN cohort, no significant overall

Table 3 Mortality in ulcerative colitis. The main articles cited in this section of the review

Author	Inclusion period	Median follow up (years)	Origin	Study population	UC cases	SMR	95% CI
Ekbom [55]	1965-1983	≈ 10	Uppsala, Sweden	Population-based	2509	1.4	1.2-1.5
Farrokhyar [56]	1978-1986	8.3	Wolverhampton, Salisbury, Swindon, England	Hospital-based	356	1.03	0.79-1.40
Hoie [59]	1991-1993	10.3	Europe, Israel	Population-based	775	1.09	0.86-1.37
Manninen [58]	1986-2007	13.5	Tampere, Finland	Population-based registry study	1254	0.90	0.77-1.06
Palli [64]	1978-1992	10.1	Florence, Italy	Population-based	689	0.6	0.4-0.8
Solberg [2]	1990-1993	10.4	South East Norway	Population-based	519	1.24	0.93-1.62

SMR, standardized mortality ratio; UC, ulcerative colitis; CI, confidence interval

increase in mortality risk was found either 10 years [2] or 20 years [38] after diagnosis. Finally, in a meta-analysis of 22 studies published between 1982 and 2010 [60], the authors could not detect any increased risk of death in UC patients compared to community controls. The pooled SMR from the 10 population-based inception studies was 1.1 (95%CI 0.9-1.2).

Although colectomy reduces UC mortality by removing the colorectal dysplasia risk, peri- and postoperative mortality could increase the mortality risk. The mortality rates associated with surgery have been determined in several studies. After elective colectomy and emergency colectomy in the UK, the mortality rates were 3.7% and 13.2%, respectively [61].

In the Danish National Registry of IBD patients from 1996 to 2010, 50% underwent colectomy under emergency hospitalization [62]. The crude mortality rate of patients with UC undergoing emergency surgery was 5.2% among emergency cases compared to 1% among elective cases. After elective surgery, mortality during the first 30 days was 0.9% (8/938). However, the 30-day mortality was as high as 18.4% among patients older than 60 years of age. In addition to older age, comorbidity and low hospital colectomy volume also contributed to higher 30-day mortality in UC patients undergoing emergency surgery.

UC occurs more frequently in non-smokers; therefore, smoking-related mortality, such as from lung cancer (pooled SMR 0.3; 95%CI 0.1-0.9; P=0.04), is decreased [63]. Results from an Italian study by Palli *et al* [64] reported significantly reduced mortality among UC patients (SMR 0.6; 95%CI 0.4-0.8) compared to the background population. The authors suggested that the reduced mortality, especially from cardiac and respiratory disease, was explained by the low incidence of cigarette smoking among these patients, while a meta-analysis showed similar results compared to the background population (pooled SMR 0.9; 95%CI 0.7-1.1). Furthermore, mortality from respiratory disorders was significantly increased (pooled SMR 1.6; 95%CI 0.7-1.1) when pulmonary embolism, asthma and pneumonia were included.

In summary, the overall UC mortality rate has declined over the last 30 years; today, it is similar to the rate of the background population. There is conflicting data on mortality associated with surgery in UC, but increased risk of death is found in older patients with comorbidity when undergoing emergency surgery.

Concluding remarks

1. The classification of disease in newly diagnosed patients is important to predict the clinical course and may also guide medical treatments and follow-up strategies.
2. Some UC patients will experience proximal progress in disease distribution, and there are data suggesting that these patients represent a particular risk group for colectomy.
3. While the colectomy risk overall has decreased over the years, the emergency colectomy rates have remained unchanged. The peri- and postoperative mortality risks are reduced, but delayed surgery is associated with increased risk of postoperative complications and mortality.
4. The overall relative risk of colonic cancer in UC is not significantly increased compared with the background population, but those with coexistent PSC, extensive colitis, long duration of disease and old age at diagnosis (60 years and above) have a greater risk of developing CRC. For patients diagnosed at an older age, CRC often appeared early after diagnosis, before the suggested time for a screening endoscopy, indicating that the current recommendations need to be modified.
5. A conventional surveillance colonoscopy with white light and random biopsies misses many dysplastic lesions. Chromoendoscopy and especially confocal chromoscopic endomicroscopy are more succesful at visualizing dysplastic lesions.
6. The overall mortality from UC has not increased; however, older patients with comorbidities have an increased risk of death when undergoing emergency surgery.

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