Inflammatory Bowel Disease

Historical Perspective, Epidemiology, and Risk Factors

Talha A. Malik, MD, MSPH[a,b,*]

KEYWORDS

• Inflammatory bowel disease • Crohn's disease • Ulcerative colitis
• Historical perspective • Epidemiology • Risk factors

KEY POINTS

- Inflammatory bowel disease describes 2 well-established but not entirely discrete disease entities, Crohn's disease (CD) and ulcerative colitis (UC), which are represented by an uncontrolled immune-mediated inflammatory response in genetically predisposed individuals to an unknown environmental trigger that interacts with the intestinal flora and primarily affects the alimentary tract.
- Approximately 1.5 million persons in North America have inflammatory bowel disease.
- Several potential risk factors of inflammatory bowel disease have been studied and include particular environmental triggers, intestinal immune mechanisms, heritable factors, gut flora, diet, mesenteric fat, medications, nicotine, infectious agents, immunization, hygiene, pregnancy, breastfeeding, stress, and lifestyle.
- There are data to suggest a higher mortality in CD compared with the general population; however, there is no definitive evidence to suggest higher mortality among patients with UC compared with the general population.
- Epidemiologic studies have expanded understanding of the occurrence, distribution, determinants, and mechanisms of inflammatory bowel disease and this allows clinicians to identify safer and more effective approaches to management and therapeutics.

INTRODUCTION

Inflammatory bowel disease (IBD) consists of 2 well-established but not entirely discrete disease entities, Crohn's disease (CD) and ulcerative colitis (UC). They together are a group of closely related but heterogeneous disease processes. The

Conflicts of interest: None.

[a] Department of Medicine-Gastroenterology, University of Alabama at Birmingham, 1808 7th Avenue South, BDB 391, Birmingham, AL 35294, USA; [b] Department of Epidemiology, University of Alabama at Birmingham, 1808 7th Avenue South, BDB 391, Birmingham, AL 35294, USA
* Department of Medicine-Gastroenterology, University of Alabama at Birmingham, 1808 7th Avenue South, BDB 391, Birmingham, AL 35294.
E-mail address: tmalik@uabmc.edu

Surg Clin N Am 95 (2015) 1105–1122
http://dx.doi.org/10.1016/j.suc.2015.07.006 **surgical.theclinics.com**
0039-6109/15/$ – see front matter

mechanism of IBD involves an uncontrolled immune-mediated inflammatory response in genetically predisposed individuals to an unknown environmental trigger that interacts with the gut microbiome (intestinal flora) and primarily affects the alimentary tract (Fig. 1).[1–6] It is estimated that more than 1.5 million Americans have IBD, approximately half represented in each of these 2 discrete IBD subgroups.[2]

HISTORICAL PERSPECTIVE

Background

It is thought that Alfred the Great, who is commonly considered to be the first King of England (849–899 CE), may have had CD.[7] However, it was not until 1913 that a discrete disease condition resembling what is now considered to be CD was identified, when Kennedy Dalziel, a British physician, described patients with transmural inflammation of the small and large intestines.[7,8] Subsequently in 1932, Dr Burrill Crohn, Dr Leon Ginzburg, and Dr Gordon Oppenheimer published articles describing a condition that caused inflammation of the terminal ileum and which they called regional or terminal ileitis. This disease entity later began to be referred as CD.[7–10]

UC was first described in ancient Greece by Hippocrates as a condition characterized by chronic diarrhea and bloody stools.[7,8] This condition was thought to be related to ulceration and inflammation of the large intestine. In the 1600s, Thomas Sydenham, a British physician, named this disease bloody flux. In 1859, Samuel Wilks, another British physician, identified UC as a discrete disease entity.[7,8]

The first breakthrough that established IBD as the prime intestinal autoimmune disease occurred in the 1950s when it was noted that symptoms in patients with both CD and UC responded to corticosteroids.[3] In the 1970s, traditional immune modulators, predominantly thiopurine analogues, began to be used and eventually became first-line steroid-sparing agents.[3] In 1997, Targan and colleagues[11] published findings of the so-called Crohn's Disease cA2 Study, which assessed the effectiveness of the biologic antibody against tumor necrosis factor (TNF) cA2 (infliximab) in induction of remission in luminal CD. This study began the era of biologics. During the first decade of the twenty-first century, biologics began to gradually emerge as the most effective

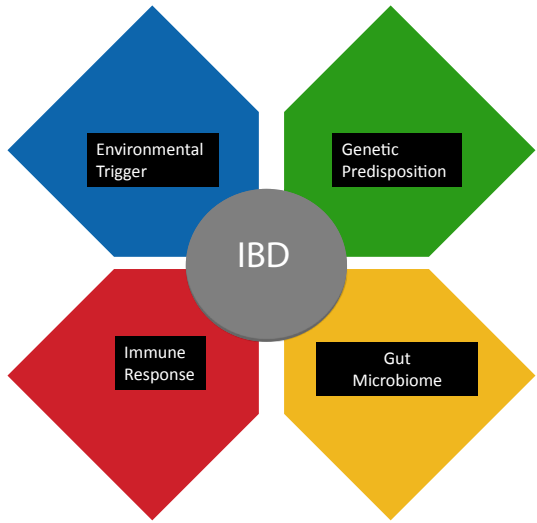

Fig. 1. IBD mechanism.

and central therapeutic agents used to induce and maintain remission in moderate to severe CD and UC.[12–16]

Trends in Occurrence and Distribution

In the past, IBD had been considered a condition that mainly occurred in white populations of Europe, North America, and Australia.[1] For this reason earlier data on CD and UC emanated from these regions.[1] The incidence of CD and UC has stabilized in these regions but still remains higher than it is in the rest of the world.[1] There has been an increasing incidence predominantly of CD in parts of the developing world that include the Middle East, south and southeast Asia, and the Asia-Pacific region.[17,18] However, South America and Africa still have very low incidence rates despite a few case reports that have suggested increasing incidence (**Fig. 2**).[19,20]

Trends in Classification

In 2000, the Working Party for the World Congresses of Gastroenterology proposed the Vienna classification, which attempted to classify CD based on objective variables that included age of onset, disease location, and disease behavior (**Table 1**).[21] In 2005, Silverberg and colleagues[22] presented the report of the Working Party of the Montreal World Congress of Gastroenterology, in which they put forth the Montreal classification of IBD (see **Table 1**; **Table 2**). The Montreal group added classification of UC based on the extent and severity of the disease (see **Table 2**).[3]

Trends in the Course of Disease

With regard to phenotype by location, of all patients diagnosed with CD at the time of their diagnosis, one-third have ileal involvement, one-third have colonic involvement, and one-third have ileocolonic disease.[2] At diagnosis, about 10% to 20% have perianal disease, whereas in 5% to 10% inflammation occurs in the region proximal to the terminal ileum.[2] With regard to phenotype by behavior of disease, of all patients diagnosed with CD, at the time of their diagnosis, 80% have nonpenetrating/nonstricturing disease and the remaining 20% have stricturing or penetrating disease.[23] Although location of CD has been noted to largely remain stable through the disease course, up to one-third of those who are diagnosed with nonpenetrating/nonstricturing disease go on to

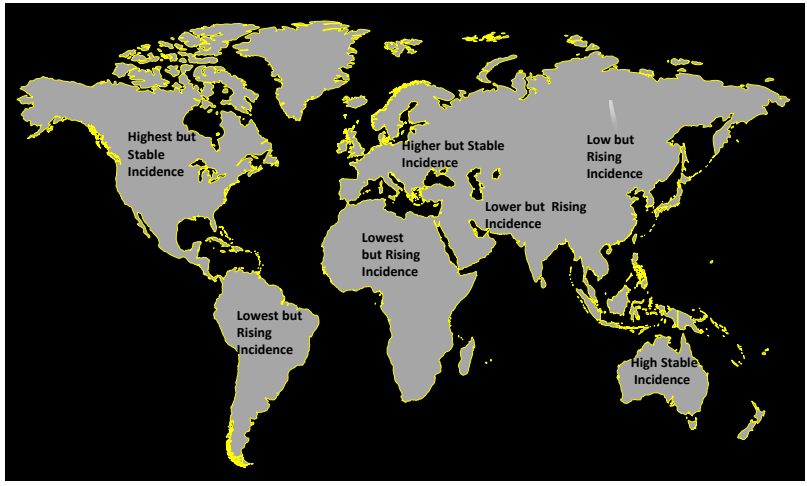

Fig. 2. Trends in incidence of IBD across the globe.

Table 1
Vienna and Montreal classification of CD

	Vienna Classification	Montreal Classification
Age at Diagnosis (y)	A1: <40 A2: >40	A1: <16 A2: b17–40 A3: >40
Location	L1: ileal L2: colonic L3: ileocolonic L4: upper	L1: ileal L2: colonic L3: ileocolonic L4: upper disease modifier or isolated upper disease
Behavior	B1: nonstricturing, nonpenetrating B2: stricturing B3: penetrating	B1: nonstricturing, nonpenetrating B2: stricturing B3: penetrating P: perianal disease modifier

Adapted from Gasche C, Scholmerich J, Brynskov J, et al. A simple classification of Crohn's disease: report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998. Inflamm Bowel Dis 2000;6(1):8–15; and Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol 2005;19(Suppl A):5A–36A.

develop penetrating or stricturing complications by 5 years, with half of all patients with CD having complicated disease at 20 years of follow-up.[24] With regard to disease activity, based on data from the prebiologic era, of all patients diagnosed with CD, approximately two-thirds have a remitting and relapsing coarse, one-fifth remain active most of the time, and about 13% go into long-term remission.[25]

With regard to patients with UC, at the time of diagnosis, one-third have inflammation that does not extend proximal to the rectosigmoid junction; one-third have disease up to the splenic flexure, and the remaining third has UC pancolitis (contiguous inflammation extending proximal to the splenic flexure).[2] Although data are variable, it has been observed that up to 50% of patients diagnosed with proctitis or proctosigmoiditis progress to more extensive disease by 25 years of follow-up.[26] In the same cohort, up to 75% of patients diagnosed with extensive colitis or pancolitis experienced variable degrees of disease extent regression during the same follow-up period.[27] With regard to disease activity, based on data from the prebiologic era, of all patients diagnosed with UC, more than one-half (57%) have a remitting and relapsing

Table 2
Montreal classification of UC

Class	Extent	Description
E1	Ulcerative proctitis	Proximal extent of inflammation distal to rectosigmoid junction
E2	Left-sided UC (distal UC)	Involvement limited to proportion of colorectum distal to the splenic
E3	Extensive UC (pancolitis)	Involvement extending proximal to splenic flexure

From Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol 2005;19(Suppl A):5A–36A.

disease course, about one-quarter go into long-term remission, and about one-fifth of patients have disease activity most of the time.[28]

Trends in Goals of Management

The historical goals of IBD treatment were to induce and maintain clinical remission.[29] However, it is now evident that the natural course of disease progression of CD and UC is not affected if clinicians only focus on induction and maintenance of clinical remission. Therefore the goals of treatment have changed during the past years.

Conventional therapy for IBD has not accomplished a reduction in the need for surgical intervention. Goals of medical management of IBD now include inducing and maintaining endoscopic remission; decreasing rates of hospitalization, surgery and infection; avoiding steroids; improving health-related quality of life; and decreasing risk of cancer and mortality.[29]

EPIDEMIOLOGY

Incidence

There is a lot of variation in data with regard to the incidence of CD and UC across the globe based on geographic region, environment, immigration trends, and ethnic group.[1–3] There is variation in data even within the same geographic region. In the past, UC was generally considered to be slightly more common; however, with increasing incidence of CD in the past few decades, this trend has changed. The annual incidence in North America of both CD and UC is now fairly stable and estimated to be between 0 and 20 per 100,000 persons.[30]

Prevalence

There is also a lot of variation in prevalence data with regard to CD and UC across the globe based on geographic region, environment, immigration trends, and ethnic group.[1–3] As is the case with the incidence of CD and UC, there is variation in prevalence data even within the same geographic region. Although in the past UC was considered to be slightly more prevalent, with the increase in incidence that occurred in CD in the past few decades more recent prevalence data show that CD and UC may be equally prevalent in North America. The estimates for prevalence of CD and UC in North America are 25 to 300 per 100,000 and 35 to 250 per 100,000 respectively.[31–33]

Distribution by Age

Although CD and UC can occur at any age, the peak age of onset for CD is generally considered to be between 20 and 30 years of age and for UC, it is between 30 and 40 years.[1,3,5,30]

There is another peak, especially for UC between 60 and 70 years of age based on some European cohorts.[34–36]

Based on earlier North American population cohorts, the median age of diagnosis of CD was estimated at around 30 years whereas the mean age of diagnosis of CD ranged between 33 and 45 years.[37,38] According to North American UC cohorts, median and mean age of diagnosis of UC ranged between 40 and 45 years.[37,38]

Distribution by Gender

A consistent significant difference has not been observed in the incidence and prevalence of CD and UC between North American men and women.[1,39] Note that several cohorts have indicated a female predominance in CD and a male predominance in UC. However, these findings are not consistent, especially in some low-incidence areas, where CD may be more prevalent among men.[32,40]

The overall incidence of UC has stabilized. A study from northern France suggested a higher incidence of UC versus CD among boys between the ages of 14 and 17 years compared with girls, although at a younger age the reverse was noted.[41] Moreover, men are more likely to be diagnosed with IBD, specifically UC, later in life compared with women.[5]

Racial and Ethnic Disparity

IBD was first studied specifically in African Americans (AAs) by Mendeloff and colleagues[42] in 1966. They observed a lower incidence of IBD among AAs compared with white Americans. Whether the incidence of IBD was low or whether its true incidence and prevalence were under-reported is unclear; however, a higher incidence of both CD and UC has since been observed.[42] In 1992, Kurata and colleagues[31] found a higher incidence of CD among AAs than had previously been noted. This finding was later confirmed by Ogunbi and colleagues[43] in 1998. In a 1986 study of 15 AA patients with CD, Goldman and colleagues[44] noted that disease in AAs was more aggressive with earlier age of onset and resulted in more complications over time. In a 2000 case-control study that attempted to adequately match and control for confounders, Straus and colleagues[45] concluded that disparities in disease severity were a result of social and economic inequalities, such as affordability of health care, delayed appointments because of financial concerns, and difficulties with traveling to provider's office, rather than biological or genetic differences. These results were later confirmed by other studies, including a 2008 systematic review by Mahid and colleagues,[46] which pooled more than 2000 patients with IBD from 8 different studies.

A particularly vulnerable ethnic group has been the Ashkenazi Jewish population. IBD is more common among Ashkenazi Jews than among the Sephardim and the general population, with estimates of prevalence being 17 and 80 per 100,000 among the Ashkenazi in Israel versus 19 and 55 per 100,000 among the Sephardim living in Israel.[47] Moreover, North American Jewish populations are more likely to have IBD than their counterparts living in the Middle East.[1]

RISK FACTORS

Cause and Pathogenesis

The most popular theory regarding pathogenesis of IBD considers it to be a result of an uncontrolled immune-mediated inflammatory response in genetically predisposed individuals to an unknown environmental trigger that interacts with the intestinal flora and primarily affects the alimentary tract.[6]

Postulated Environmental Triggers

Different triggers have been implicated, both external antigens and autoantigens. External antigens include infectious agents such as viruses and bacteria as well as dietary components.[1,6,17] Autoantigens on bacterial flora have also been implicated in the pathogenesis of IBD.[1,6]

Intestinal Immune Mechanism

The main mechanism of inflammatory injury in IBD is immune mediated. There are various mechanisms by which immune-mediated injury takes place. An important factor is abnormal or exaggerated immune response.[6,17,29] For example, human leukocyte antigen (HLA) class II molecules that mediate autoimmune injury are found in high numbers within the intestinal epithelial cells of patients with active IBD. The HLA class II molecules are responsible for antigen processing and presentation. Activated macrophages, which are also sites of HLA class II molecules, also secrete

increased amounts of proinflammatory cytokines, including interleukin (IL)-1, IL-6, IL-8, and TNF-alpha, within the lamina propria of the intestinal wall. IFN-gamma is also produced and it increases intestinal permeability. There is decreased production of IL-2, IL-10, TNF-beta, and transforming growth factor beta, which are downregulatory cytokines, in patients with IBD, and this may explain chronic inflammation in these patients.[4,6,17]

Genetic Predisposition

Up to 15% persons with IBD (both CD and UC) have a first-degree relative who also has IBD.[1,48] The lifetime risk of developing IBD in first-degree relatives has been estimated at 5% in CD and about 2% in UC among non-Jewish populations and 8% and 5% among Jewish populations respectively.[48] In children and siblings, it is generally estimated to be approximately 8% in both CD and UC.[6]

In CD, the concordance rates among monozygotic and dizygotic twins are 50% and 10% respectively, which is suggestive of significant but not complete genetic predisposition. In UC, the concordance rates among monozygotic and dizygotic twins are 16% and 4% respectively, which is suggestive of weaker, albeit definite, genetic predisposition.[48,49]

Gut Flora

Several reviews on the topic of gut flora have suggested that the unknown environmental trigger in IBD (from the external environment) interacts with the intestinal flora within the internal environment to cause disease.[50–52]

Some clues to the veracity of this association emanate from the observations that bigger family size, early life exposure to pets and farm animals, and greater number of siblings is inversely associated with risk of IBD.[1] It has been shown that patients with IBD have reduced diversity of gut microbiota.[1] Another postulated mechanism of pathogenesis of IBD includes the proinflammatory properties of certain microbiota.[53] For example, a 2004 study revealed that adherent-invasive *Escherichia coli* were found in the ileum of 22% of patients with CD versus 6% of controls.[53] It has also been postulated that Firmicutes may confer protection against IBD.[1,51] The study of gut flora and IBD is in flux and it can safely be assumed that, in addition to gut bacteria, viruses and fungi may also play a role.[1]

Role of Diet

Martini and Brandes[54] published a case-control study in 1976 that suggested higher incidence of IBD in those who took larger amounts of refined carbohydrates in their diets. In addition to increased intake of refined sugars, it was also observed that newly diagnosed patients with IBD consumed less dietary fiber, raw fruit, and vegetables compared with healthy controls.[55] Asakura and colleagues[56] subsequently performed a systematic review of past epidemiologic surveys and case-control studies done to study the effect of diet on pathogenesis of CD in Japanese patients and noted an association between increased consumption of animal meat in addition to carbohydrates as potential risk for development of active CD.

Role of Mesenteric Fat and Obesity

Adipose tissue is an active endocrine organ that is made up of elements of connective tissue as well as cells represented by preadipocytes and adipocytes that can be prominent mediators of inflammation in the human body.[57–60] Blain and colleagues[61] found an association between obesity and rapid progression of disease (measured clinically) in patients with CD. In a subsequent study by Hass and colleagues[62] overweight or

obese patients with CD experienced more rapid progression to first surgical intervention compared with underweight patients.

Role of Smoking

The association between smoking and IBD was first noted in 1982.[63] Smoking has been associated with a 2-fold increase in the risk for CD and this association includes early-life exposure as well as passive smoking. In addition to causing exacerbations of CD, smoking has been linked to earlier age of onset, increased need for immunosuppression, overall more aggressive disease, increased requirement for surgery, and higher risk of postresection recurrence of disease.[64–66]

With regard to UC, it has been observed that it is smoking cessation that may cause an exacerbation.[67] Moreover, studies have shown that smokers with UC may have a milder disease course, may require less immune suppression, and have reduced need for surgery.[66,68,69] However, the mechanism underlying these divergent effects on the 2 subtypes of IBD is not well understood.[1] Nicotine replacement in UC has not been reliably found to reduce disease activity, suggesting an effect of smoking on IBD that is independent of nicotine.[70,71]

Medications and Inflammatory Bowel Disease

Medications suggested to be potential risk factors for IBD include oral contraceptives, hormonal replacement therapy, nonsteroidal antiinflammatory drugs (including aspirin), as well as antibiotics.[72–77] There is a single study that implicates the role of excess iron in the water supply in the development of IBD.[78] Zinc has been noted to potentially protect against relapses in IBD based on another unpublished study.[1] Studies of the relationship between vitamin D and development of IBD have been equivocal.[1]

Infections and Inflammatory Bowel Disease

There has been interest in studying the association between *Mycobacterium avium* subspecies *paratuberculosis* and CD but this association has not been consistent.[79,80] Other studies have suggested an association between salmonella and campylobacter infections with an increased risk of IBD.[81] With regard to viruses, measles virus was initially thought to be a risk factor for subsequent development of IBD. However, subsequent studies were not able to detect an association.[82–84] *Clostridium difficile* infection, cytomegalovirus infection, and other causes of sepsis have been noted to cause exacerbation of IBD but no causal link between them has been detected.[85,86]

Role of Immunization

In addition to the measles infection, it was proposed in the 1960s that the attenuated live measles virus vaccine might be associated with IBD because prevalence of IBD had been noted to be much higher in a cohort of patients who received the vaccines compared with those who had not.[82] However, subsequent studies did not confirm this finding and several questions were raised about the methodology used to conduct that study.[87,88] A more recent study noted an inverse relationship between measles vaccination and the risk of IBD.[84]

Hygiene Hypothesis

Some observational studies have shown a protective role of poor hygiene against the development of IBD.[89–92] For example, large number of siblings, large family size, not having access to running water, drinking unpasteurized milk, living on a farm, and early exposure to pets have all been associated with a reduced risk of IBD.[1,39,90–92]

However, these studies have been done in the West. The few studies that have assessed this association in the developing world have been inconclusive.[1,93]

Pregnancy, Breastfeeding, and Inflammatory Bowel Disease

Mode of childbirth (studied because of its influence on the gut microbiota in infancy) has not been found to be significant associated with development of IBD.[94] Studies have also shown that breastfeeding may protect against development of IBD later in life, especially for UC.[1]

Role of Stress and Lifestyle in Inflammatory Bowel Disease

There is observational evidence for the association between stress, anxiety, and depression with a high risk of development of IBD.[95] Depression and anxiety have also been associated with a more severe course of disease, higher rate of surgery, decreased quality of life, as well as reduced responsiveness to immunosuppression.[1,95]

With regard to lifestyle, there seems to be a higher incidence of IBD among people who are in professions that lead them to be more sedentary compared with those whose profession requires increased activity.[96] Moreover, observational evidence suggests that there is an increased incidence of IBD among people with disruptive sleep pattern.[1,97]

Inflammatory Bowel Disease and Surgery

Recently, risk of surgery has decreased in patients with CD and UC.[2] This phenomenon has largely been attributed to the more aggressive medical therapy being used now compared with what was the case just a decade ago, but long-term results are not known.[1,2,34,98–100]

Although, traditionally, the cumulative probability of patients with CD undergoing surgery was 35%, 61%, and 82% after 1, 10, and 20 years respectively, there has been significant reduction in these probabilities in recent studies, with recent estimates of rates of surgery being approximately 10% to 14% and 18% to 35% after 1 and 5 years respectively.[34,98,101–104] With regard to age, location, and behavior of CD, the greatest risk of surgery is with ileocecal location and stricturing or penetrating/fistulizing behavior.[2,102,103] Permanent fecal diversion in the form of a stoma is eventually required in about 10% of patients with CD.[3,64] The risk factors for permanent fecal diversion include colonic and perianal CD.[3,105]

The traditional likelihood of colectomy in UC was slightly less than 10% at 1 year and slightly less than 25% at 10 years after diagnosis.[2,34,102,106] However, even lower rates of colectomy have recently been reported, with rates of 6% and 10% after 1 and 5 years respectively.[27,34,106–108] With regard to age and extent of UC among patients who undergo colectomy, most of these patients have had fairly recent diagnosis and have pancolitis.[2]

Also, more severe disease leads to earlier colectomy.[3] The likelihood of colectomy has been reported generally to be higher in studies on populations emanating from tertiary referral centers.[28,109,110] Medications used for medical management of severe fulminant UC, such as infliximab and cyclosporine, may delay or, less commonly, prevent colectomy.[3,111,112] Among patients with UC, definitive surgery is usually represented by total proctocolectomy and formation of ileal pouch–anal anastomoses. The most frequent form of ileal pouch–anal anastomoses used at present is the J pouch. The risk of acute pouchitis in these patients is about 50%, whereas, in about 5% to 10% of patients, pouchitis becomes chronic.[113]

Inflammatory Bowel Disease and Cancer

With regard to risk factors for colorectal cancer (CRC) in IBD, the primary drivers of risk are persistent active inflammation and immunosuppression followed by long-standing disease, extensive disease, young age at diagnosis, family history of CRC, and coexisting primary sclerosing cholangitis.[2,114]

Of all CRCs, CRCs that occur in UC and, by extension, in Crohn colitis account for about 1% of all CRCs, which means that in patients with UC or Crohn colitis there is a 10 to 25 times higher risk of CRC compared with the general population. Most commonly, CRC occurs in patients with UC or Crohn colitis in their 40s.[115–117]

Risk factors for CRC in patients with UC/Crohn colitis include extent of disease, duration of disease longer than 8 years, and younger age at diagnosis.[117] Other risk factors for CRC in UC include family history of CRC, concomitant primary sclerosing cholangitis, active histologic inflammation, and presence of colonic pseudopolyps.[115,117]

Because of this increased risk of CRC in UC, surveillance colonoscopies are recommended yearly in patients with UC (other than UC proctitis/proctosigmoiditis) after 8 years of disease. In Crohn colitis, this can be done at about 10 to 12 years after diagnosis. It is estimated that the risk of CRC after 10 years of UC or Crohn colitis is about 1%, at 20 years it is about 8%, and at 30 years it is approximately 18%.[115–117] Moreover, any colonic stricture in UC should raise suspicion for cancer because up to one-third of these may be harboring a malignancy. The pathogenesis of carcinogenesis in UC involves sequential somatic gene mutations and clonal expansion. These gene alterations include aneuploidy, mutations of oncogenes, tumor suppressor genes, and DNA repair genes.[116,117]

The risk of extraintestinal cancers, including lymphoproliferative as well as skin cancers, is significantly higher among patients with IBD compared with the general population.[2,118–120]

Inflammatory Bowel Disease and Mortality

Increased mortality is a concern in patients with CD based on most, but not all, data compared with the general population.[121–125] In patients with CD, surgical complications and malnourishment are prominent causes of direct CD-related mortality compared with other factors, including small bowel neoplasm.[121,126,127] As smoking is more common among patients with CD, sequelae related to smoking in the form of respiratory infection and diseases are additional causes of death among patients with CD.[127]

There is no definitive evidence to suggest a higher mortality among patients with UC compared with the general population.[124,125,128–130] Among patients with UC, colorectal neoplasia accounts for most of the mortality compared with surgical or other complications.[126,129] A population-based cohort from Copenhagen County comprising 1160 patients with UC noted that there was increased mortality within the first 2 years of diagnosis among patients who were older than 50 years of age at diagnosis and who had extensive colitis. The increased mortality was associated with postoperative pulmonary embolism and development of pneumonia.[129]

CONCLUDING REMARKS

A lot of information continues to emanate from epidemiologic studies, providing expanded insight into the occurrence, distribution, determinants, and mechanisms of IBD. This knowledge should be used to identify new approaches to management and therapeutics that move away from merely immunosuppressing patients with

IBD and advance their health using methods that involve prevention, preemption, and immunomodulation.

REFERENCES

1. Ananthakrishnan AN. Epidemiology and risk factors for IBD. Nat Rev Gastroenterol Hepatol 2015;12:205–17.
2. Burisch J, Munkholm P. The epidemiology of inflammatory bowel disease. Scand J Gastroenterol 2015;50(8):942–51.
3. Cosnes J, Gower-Rousseau C, Seksik P, et al. Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology 2011;140(6):1785–94.
4. Abraham C, Cho JH. Inflammatory bowel disease. N Engl J Med 2009;361(21): 2066–78.
5. Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. Gastroenterology 2004;126(6): 1504–17.
6. Malik T, Mannon P. Inflammatory bowel diseases: emerging therapies and promising molecular targets. Front Biosci 2012;4:1172–89.
7. Kirsner JB. Historical aspects of inflammatory bowel disease. J Clin Gastroenterol 1988;10(3):286–97.
8. Kirsner JB. Historical origins of current IBD concepts. World J Gastroenterol 2001;7(2):175–84.
9. Crohn BB, Ginzburg L, Oppenheimer GD. Landmark article Oct 15, 1932. Regional ileitis. A pathological and clinical entity. By Burril B. Crohn, Leon Ginzburg, and Gordon D. Oppenheimer. JAMA 1984;251(1):73–9.
10. Ginzburg L. X-ray diagnosis of acute intestinal obstruction without the use of contrast media. Ann Surg 1932;96(3):368–80.
11. Targan SR, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J Med 1997;337(15):1029–35.
12. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999;340(18):1398–405.
13. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002;359(9317): 1541–9.
14. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med 2004;350(9):876–85.
15. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005;353(23):2462–76.
16. Sandborn WJ, Feagan BG, Stoinov S, et al. Certolizumab pegol for the treatment of Crohn's disease. N Engl J Med 2007;357(3):228–38.
17. Podolsky DK. Inflammatory bowel disease. N Engl J Med 2002;347(6):417–29.
18. Sood A, Midha V. Epidemiology of inflammatory bowel disease in Asia. Indian J Gastroenterol 2007;26(6):285–9.
19. Archampong TN, Nkrumah KN. Inflammatory bowel disease in Accra: what new trends. West Afr J Med 2013;32(1):40–4.
20. Ukwenya AY, Ahmed A, Odigie VI, et al. Inflammatory bowel disease in Nigerians: still a rare diagnosis? Ann Afr Med 2011;10(2):175–9.
21. Gasche C, Scholmerich J, Brynskov J, et al. A simple classification of Crohn's disease: report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998. Inflamm Bowel Dis 2000;6(1):8–15.

22. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol 2005;19(Suppl A):5A–36A.
23. Dressel U, Allen TL, Pippal JB, et al. The peroxisome proliferator-activated receptor beta/delta agonist, GW501516, regulates the expression of genes involved in lipid catabolism and energy uncoupling in skeletal muscle cells. Mol Endocrinol 2003;17(12):2477–93.
24. Thia KT, Sandborn WJ, Harmsen WS, et al. Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. Gastroenterology 2010;139(4):1147–55.
25. Munkholm P, Langholz E, Davidsen M, et al. Disease activity courses in a regional cohort of Crohn's disease patients. Scand J Gastroenterol 1995; 30(7):699–706.
26. Bengtson MB, Solberg C, Aamodt G, et al. Clustering in time of familial IBD separates ulcerative colitis from Crohn's disease. Inflamm Bowel Dis 2009;15(12): 1867–74.
27. Solberg IC, Lygren I, Jahnsen J, et al. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). Scand J Gastroenterol 2009;44(4):431–40.
28. Langholz E, Munkholm P, Davidsen M, et al. Course of ulcerative colitis: analysis of changes in disease activity over years. Gastroenterology 1994;107(1):3–11.
29. Sands BE. Inflammatory bowel disease: past, present, and future. J Gastroenterol 2007;42(1):16–25.
30. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012;142(1):46–54.e42 [quiz: e30].
31. Kurata JH, Kantor-Fish S, Frankl H, et al. Crohn's disease among ethnic groups in a large health maintenance organization. Gastroenterology 1992;102:1940–8.
32. Bernstein CN, Wajda A, Svenson LW, et al. The epidemiology of inflammatory bowel disease in Canada: a population-based study. Am J Gastroenterol 2006;101(7):1559–68.
33. Pinchbeck BR, Kirdeikis J, Thomson AB. Inflammatory bowel disease in northern Alberta. An epidemiologic study. J Clin Gastroenterol 1988;10(5):505–15.
34. Vind I, Riis L, Jess T, et al. Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County, 2003-2005: a population-based study from the Danish Crohn colitis database. Am J Gastroenterol 2006;101(6):1274–82.
35. Langholz E, Munkholm P, Nielsen OH, et al. Incidence and prevalence of ulcerative colitis in Copenhagen county from 1962 to 1987. Scand J Gastroenterol 1991;26(12):1247–56.
36. Moum B, Vatn MH, Ekbom A, et al. Incidence of ulcerative colitis and indeterminate colitis in four counties of southeastern Norway, 1990-93. A prospective population-based study. The Inflammatory Bowel South-Eastern Norway (IBSEN) Study Group of Gastroenterologists. Scand J Gastroenterol 1996;31(4):362–6.
37. Loftus EV Jr, Silverstein MD, Sandborn WJ, et al. Crohn's disease in Olmsted County, Minnesota, 1940-1993: incidence, prevalence, and survival. Gastroenterology 1998;114(6):1161–8.
38. Loftus EV Jr, Silverstein MD, Sandborn WJ, et al. Ulcerative colitis in Olmsted County, Minnesota, 1940-1993: incidence, prevalence, and survival. Gut 2000; 46(3):336–43.

39. Bernstein CN, Rawsthorne P, Cheang M, et al. A population-based case control study of potential risk factors for IBD. Am J Gastroenterol 2006;101(5):993–1002.
40. Devlin HB, Datta D, Dellipiani AW. The incidence and prevalence of inflammatory bowel disease in North Tees Health District. World J Surg 1980;4(2):183–93.
41. Auvin S, Molinie F, Gower-Rousseau C, et al. Incidence, clinical presentation and location at diagnosis of pediatric inflammatory bowel disease: a prospective population-based study in northern France (1988-1999). J Pediatr Gastroenterol Nutr 2005;41(1):49–55.
42. Mendeloff AI, Monk M, Siegel CI, et al. Some epidemiological features of ulcerative colitis and regional enteritis. A preliminary report. Gastroenterology 1966;51(5):748–56.
43. Ogunbi SO, Ransom JA, Sullivan K, et al. Inflammatory bowel disease in African-American children living in Georgia. J Pediatr 1998;133:103–7.
44. Goldman CD, Kodner IJ, Fry RD, et al. Clinical and operative experience with non-Caucasian patients with Crohn's disease. Dis Colon Rectum 1986;29(5):317–21.
45. Straus WL, Eisen GM, Sandler RS, et al. Crohn's disease: does race matter? The Mid-Atlantic Crohn's Disease Study Group. Am J Gastroenterol 2000;95(2):479–83.
46. Mahid SS, Mulhall AM, Gholson RD, et al. Inflammatory bowel disease and African Americans: a systematic review. Inflamm Bowel Dis 2008;14(7):960–7.
47. Karban A, Waterman M, Panhuysen CI, et al. NOD2/CARD15 genotype and phenotype differences between Ashkenazi and Sephardic Jews with Crohn's disease. Am J Gastroenterol 2004;99(6):1134–40.
48. Yang H, McElree C, Roth MP, et al. Familial empirical risks for inflammatory bowel disease: differences between Jews and non-Jews. Gut 1993;34(4):517–24.
49. Halme L, Paavola-Sakki P, Turunen U, et al. Family and twin studies in inflammatory bowel disease. World J Gastroenterol 2006;12(23):3668–72.
50. Kostic AD, Xavier RJ, Gevers D. The microbiome in inflammatory bowel disease: current status and the future ahead. Gastroenterology 2014;146(6):1489–99.
51. Jostins L, Ripke S, Weersma RK, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature 2012;491(7422):119–24.
52. Nagalingam NA, Lynch SV. Role of the microbiota in inflammatory bowel diseases. Inflamm Bowel Dis 2012;18(5):968–84.
53. Darfeuille-Michaud A, Boudeau J, Bulois P, et al. High prevalence of adherent-invasive *Escherichia coli* associated with ileal mucosa in Crohn's disease. Gastroenterology 2004;127(2):412–21.
54. Martini GA, Brandes JW. Increased consumption of refined carbohydrates in patients with Crohn's disease. Klin Wochenschr 1976;54(8):367–71.
55. Thornton JR, Emmett PM, Heaton KW. Diet and Crohn's disease: characteristics of the pre-illness diet. Br Med J 1979;2(6193):762–4.
56. Asakura H, Suzuki K, Kitahora T, et al. Is there a link between food and intestinal microbes and the occurrence of Crohn's disease and ulcerative colitis? J Gastroenterol Hepatol 2008;23(12):1794–801.
57. Bedford PA, Todorovic V, Westcott ED, et al. Adipose tissue of human omentum is a major source of dendritic cells, which lose MHC Class II and stimulatory function in Crohn's disease. J Leukoc Biol 2006;80(3):546–54.

58. Geerling BJ, v Houwelingen AC, Badart-Smook A, et al. Fat intake and fatty acid profile in plasma phospholipids and adipose tissue in patients with Crohn's disease, compared with controls. Am J Gastroenterol 1999;94(2):410–7.
59. Karmiris K, Koutroubakis IE, Kouroumalis EA. Leptin, adiponectin, resistin, and ghrelin–implications for inflammatory bowel disease. Mol Nutr Food Res 2008; 52(8):855–66.
60. Yamamoto K, Kiyohara T, Murayama Y, et al. Production of adiponectin, an anti-inflammatory protein, in mesenteric adipose tissue in Crohn's disease. Gut 2005; 54(6):789–96.
61. Blain A, Cattan S, Beaugerie L, et al. Crohn's disease clinical course and severity in obese patients. Clin Nutr 2002;21(1):51–7.
62. Hass DJ, Brensinger CM, Lewis JD, et al. The impact of increased body mass index on the clinical course of Crohn's disease. Clin Gastroenterol Hepatol 2006; 4(4):482–8.
63. Harries AD, Baird A, Rhodes J. Non-smoking: a feature of ulcerative colitis. Br Med J 1982;284(6317):706.
64. Cosnes J. Crohn's disease phenotype, prognosis, and long-term complications: what to expect? Acta Gastroenterol Belg 2008;71(3):303–7.
65. Cosnes J, Nion-Larmurier I, Afchain P, et al. Gender differences in the response of colitis to smoking. Clin Gastroenterol Hepatol 2004;2(1):41–8.
66. Lakatos PL, Szamosi T, Lakatos L. Smoking in inflammatory bowel diseases: good, bad or ugly? World J Gastroenterol 2007;13(46):6134–9.
67. Higuchi LM, Khalili H, Chan AT, et al. A prospective study of cigarette smoking and the risk of inflammatory bowel disease in women. Am J Gastroenterol 2012; 107(9):1399–406.
68. Cosnes J, Carbonnel F, Beaugerie L, et al. Effects of cigarette smoking on the long-term course of Crohn's disease. Gastroenterology 1996;110(2): 424–31.
69. Cosnes J, Carbonnel F, Carrat F, et al. Effects of current and former cigarette smoking on the clinical course of Crohn's disease. Aliment Pharmacol Ther 1999;13(11):1403–11.
70. Biedermann L, Brulisauer K, Zeitz J, et al. Smoking cessation alters intestinal microbiota: insights from quantitative investigations on human fecal samples using FISH. Inflamm Bowel Dis 2014;20(9):1496–501.
71. Persson PG, Hellers G, Ahlbom A. Use of oral moist snuff and inflammatory bowel disease. Int J Epidemiol 1993;22(6):1101–3.
72. Shaw SY, Blanchard JF, Bernstein CN. Association between the use of antibiotics in the first year of life and pediatric inflammatory bowel disease. Am J Gastroenterol 2010;105(12):2687–92.
73. Chan SS, Luben R, Bergmann MM, et al. Aspirin in the aetiology of Crohn's disease and ulcerative colitis: a European prospective cohort study. Aliment Pharmacol Ther 2011;34(6):649–55.
74. Ananthakrishnan AN, Higuchi LM, Huang ES, et al. Aspirin, nonsteroidal anti-inflammatory drug use, and risk for Crohn disease and ulcerative colitis: a cohort study. Ann Intern Med 2012;156(5):350–9.
75. Cornish JA, Tan E, Simillis C, et al. The risk of oral contraceptives in the etiology of inflammatory bowel disease: a meta-analysis. Am J Gastroenterol 2008; 103(9):2394–400.
76. Khalili H, Higuchi LM, Ananthakrishnan AN, et al. Hormone therapy increases risk of ulcerative colitis but not Crohn's disease. Gastroenterology 2012; 143(5):1199–206.

77. Khalili H, Higuchi LM, Ananthakrishnan AN, et al. Oral contraceptives, reproductive factors and risk of inflammatory bowel disease. Gut 2013;62(8):1153–9.
78. Aamodt G, Bukholm G, Jahnsen J, et al. The association between water supply and inflammatory bowel disease based on a 1990-1993 cohort study in southeastern Norway. Am J Epidemiol 2008;168(9):1065–72.
79. Bernstein CN, Blanchard JF, Rawsthorne P, et al. Population-based case control study of seroprevalence of *Mycobacterium paratuberculosis* in patients with Crohn's disease and ulcerative colitis. J Clin Microbiol 2004;42(3):1129–35.
80. Selby W, Pavli P, Crotty B, et al. Two-year combination antibiotic therapy with clarithromycin, rifabutin, and clofazimine for Crohn's disease. Gastroenterology 2007;132(7):2313–9.
81. Gradel KO, Nielsen HL, Schonheyder HC, et al. Increased short- and long-term risk of inflammatory bowel disease after salmonella or campylobacter gastroenteritis. Gastroenterology 2009;137(2):495–501.
82. Thompson NP, Montgomery SM, Pounder RE, et al. Is measles vaccination a risk factor for inflammatory bowel disease? Lancet 1995;345(8957):1071–4.
83. Bernstein CN, Rawsthorne P, Blanchard JF. Population-based case-control study of measles, mumps, and rubella and inflammatory bowel disease. Inflamm Bowel Dis 2007;13(6):759–62.
84. Davis RL, Kramarz P, Bohlke K, et al. Measles-mumps-rubella and other measles-containing vaccines do not increase the risk for inflammatory bowel disease: a case-control study from the Vaccine Safety Datalink project. Arch Pediatr Adolesc Med 2001;155(3):354–9.
85. Ananthakrishnan AN, Issa M, Binion DG. *Clostridium difficile* and inflammatory bowel disease. Gastroenterol Clin North Am 2009;38(4):711–28.
86. Singh S, Graff LA, Bernstein CN. Do NSAIDs, antibiotics, infections, or stress trigger flares in IBD? Am J Gastroenterol 2009;104(5):1298–313 [quiz: 1314].
87. Feeney M, Ciegg A, Winwood P, et al. A case-control study of measles vaccination and inflammatory bowel disease. The East Dorset Gastroenterology Group. Lancet 1997;350(9080):764–6.
88. Morris DL, Montgomery SM, Thompson NP, et al. Measles vaccination and inflammatory bowel disease: a national British Cohort Study. Am J Gastroenterol 2000;95(12):3507–12.
89. Strachan DP. Hay fever, hygiene, and household size. BMJ 1989;299(6710):1259–60.
90. Timm S, Svanes C, Janson C, et al. Place of upbringing in early childhood as related to inflammatory bowel diseases in adulthood: a population-based cohort study in Northern Europe. Eur J Epidemiol 2014;29(6):429–37.
91. Radon K, Windstetter D, Poluda AL, et al. Contact with farm animals in early life and juvenile inflammatory bowel disease: a case-control study. Pediatrics 2007;120(2):354–61.
92. Van Kruiningen HJ, Joossens M, Vermeire S, et al. Environmental factors in familial Crohn's disease in Belgium. Inflamm Bowel Dis 2005;11(4):360–5.
93. Sood A, Amre D, Midha V, et al. Low hygiene and exposure to infections may be associated with increased risk for ulcerative colitis in a North Indian population. Ann Gastroenterol 2014;27(3):219–23.
94. Bager P, Simonsen J, Nielsen NM, et al. Cesarean section and offspring's risk of inflammatory bowel disease: a national cohort study. Inflamm Bowel Dis 2012;18(5):857–62.

95. Bernstein CN, Singh S, Graff LA, et al. A prospective population-based study of triggers of symptomatic flares in IBD. Am J Gastroenterol 2010;105(9): 1994–2002.
96. Sonnenberg A. Occupational distribution of inflammatory bowel disease among German employees. Gut 1990;31(9):1037–40.
97. Ananthakrishnan AN, Long MD, Martin CF, et al. Sleep disturbance and risk of active disease in patients with Crohn's disease and ulcerative colitis. Clin Gastroenterol Hepatol 2013;11(8):965–71.
98. Nguyen GC, Nugent Z, Shaw S, et al. Outcomes of patients with Crohn's disease improved from 1988 to 2008 and were associated with increased specialist care. Gastroenterology 2011;141(1):90–7.
99. Ramadas AV, Gunesh S, Thomas GA, et al. Natural history of Crohn's disease in a population-based cohort from Cardiff (1986-2003): a study of changes in medical treatment and surgical resection rates. Gut 2010; 59(9):1200–6.
100. Lakatos PL, Golovics PA, David G, et al. Has there been a change in the natural history of Crohn's disease? Surgical rates and medical management in a population-based inception cohort from Western Hungary between 1977-2009. Am J Gastroenterol 2012;107(4):579–88.
101. Lakatos L, Kiss LS, David G, et al. Incidence, disease phenotype at diagnosis, and early disease course in inflammatory bowel diseases in Western Hungary, 2002-2006. Inflamm Bowel Dis 2011;17(12):2558–65.
102. Burisch J, Pedersen N, Cukovic-Cavka S, et al. Initial disease course and treatment in an inflammatory bowel disease inception cohort in Europe: the ECCO-EpiCom cohort. Inflamm Bowel Dis 2014;20(1):36–46.
103. Solberg IC, Vatn MH, Hoie O, et al. Clinical course in Crohn's disease: results of a Norwegian population-based ten-year follow-up study. Clin Gastroenterol Hepatol 2007;5(12):1430–8.
104. Sands BE, Arsenault JE, Rosen MJ, et al. Risk of early surgery for Crohn's disease: implications for early treatment strategies. Am J Gastroenterol 2003; 98(12):2712–8.
105. Galandiuk S, Kimberling J, Al-Mishlab TG, et al. Perianal Crohn disease: predictors of need for permanent diversion. Ann Surg 2005;241(5):796–801 [discussion: 801–2].
106. Hoie O, Wolters F, Riis L, et al. Ulcerative colitis: patient characteristics may predict 10-yr disease recurrence in a European-wide population-based cohort. Am J Gastroenterol 2007;102(8):1692–701.
107. Vester-Andersen MK, Prosberg MV, Jess T, et al. Disease course and surgery rates in inflammatory bowel disease: a population-based, 7-year follow-up study in the era of immunomodulating therapy. Am J Gastroenterol 2014;109(5): 705–14.
108. Vester-Andersen MK, Vind I, Prosberg MV, et al. Hospitalisation, surgical and medical recurrence rates in inflammatory bowel disease 2003–2011—a Danish population-based cohort study. J Crohns Colitis 2014; 8(12):1675–83.
109. Hoie O, Wolters FL, Riis L, et al. Low colectomy rates in ulcerative colitis in an unselected European cohort followed for 10 years. Gastroenterology 2007; 132(2):507–15.
110. Henriksen M, Jahnsen J, Lygren I, et al. Ulcerative colitis and clinical course: results of a 5-year population-based follow-up study (the IBSEN study). Inflamm Bowel Dis 2006;12(7):543–50.

111. Campbell S, Travis S, Jewell D. Ciclosporin use in acute ulcerative colitis: a long-term experience. Eur J Gastroenterol Hepatol 2005;17(1):79–84.
112. Jarnerot G, Hertervig E, Friis-Liby I, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. Gastroenterology 2005;128(7):1805–11.
113. Shen B, Fazio VW, Remzi FH, et al. Comprehensive evaluation of inflammatory and noninflammatory sequelae of ileal pouch-anal anastomoses. Am J Gastroenterol 2005;100(1):93–101.
114. Beaugerie L. Inflammatory bowel disease therapies and cancer risk: where are we and where are we going? Gut 2012;61(4):476–83.
115. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut 2001;48(4):526–35.
116. Basseri RJ, Basseri B, Papadakis KA. Dysplasia and cancer in inflammatory bowel disease. Expert Rev Gastroenterol Hepatol 2011;5(1):59–66.
117. Farraye FA, Odze RD, Eaden J, et al. AGA medical position statement on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. Gastroenterology 2010;138(2):738–45.
118. Pedersen N, Duricova D, Elkjaer M, et al. Risk of extra-intestinal cancer in inflammatory bowel disease: meta-analysis of population-based cohort studies. Am J Gastroenterol 2010;105(7):1480–7.
119. Kandiel A, Fraser AG, Korelitz BI, et al. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. Gut 2005;54(8):1121–5.
120. Long MD, Herfarth HH, Pipkin CA, et al. Increased risk for non-melanoma skin cancer in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2010;8(3):268–74.
121. Jess T, Frisch M, Simonsen J. Trends in overall and cause-specific mortality among patients with inflammatory bowel disease from 1982 to 2010. Clin Gastroenterol Hepatol 2013;11(1):43–8.
122. Wolters FL, Russel MG, Sijbrandij J, et al. Crohn's disease: increased mortality 10 years after diagnosis in a Europe-wide population based cohort. Gut 2006; 55(4):510–8.
123. Hovde O, Kempski-Monstad I, Smastuen MC, et al. Mortality and causes of death in Crohn's disease: results from 20 years of follow-up in the IBSEN study. Gut 2014;63(5):771–5.
124. Romberg-Camps M, Kuiper E, Schouten L, et al. Mortality in inflammatory bowel disease in the Netherlands 1991-2002: results of a population-based study: the IBD South-Limburg cohort. Inflamm Bowel Dis 2010; 16(8):1397–410.
125. Manninen P, Karvonen AL, Huhtala H, et al. Mortality in ulcerative colitis and Crohn's disease. A population-based study in Finland. J Crohns Colitis 2012; 6(5):524–8.
126. Jess T, Gamborg M, Munkholm P, et al. Overall and cause-specific mortality in ulcerative colitis: meta-analysis of population-based inception cohort studies. Am J Gastroenterol 2007;102(3):609–17.
127. Bewtra M, Kaiser LM, TenHave T, et al. Crohn's disease and ulcerative colitis are associated with elevated standardized mortality ratios: a meta-analysis. Inflamm Bowel Dis 2013;19(3):599–613.
128. Jess T, Loftus EV Jr, Harmsen WS, et al. Survival and cause specific mortality in patients with inflammatory bowel disease: a long term outcome study in Olmsted County, Minnesota, 1940-2004. Gut 2006;55(9):1248–54.

129. Winther KV, Jess T, Langholz E, et al. Survival and cause-specific mortality in ulcerative colitis: follow-up of a population-based cohort in Copenhagen County. Gastroenterology 2003;125(6):1576–82.
130. Hoie O, Schouten LJ, Wolters FL, et al. Ulcerative colitis: no rise in mortality in a European-wide population based cohort 10 years after diagnosis. Gut 2007; 56(4):497–503.