REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Cancers Complicating Inflammatory Bowel Disease

Laurent Beaugerie, M.D., Ph.D., and Steven H. Itzkowitz, M.D.

Crohn's disease and ulcerative colitis are lifelong inflammatory bowel diseases of unknown origin that generally begin in young adulthood. It is estimated that at least 0.4% of Europeans and North Americans live with inflammatory bowel disease.[1] Life expectancy is reduced in patients with Crohn's disease and in patients with ulcerative colitis that is diagnosed when colitis is extensive or that is diagnosed in childhood.[2-4] There are excess deaths from infection, cardiovascular diseases, and cancers in patients with inflammatory bowel disease.[3] Some differences in the risk of cancer between patients with inflammatory bowel disease and the general population may be the result of differences in the distribution of lifestyle factors. For example, smokers are overrepresented among patients with Crohn's disease, and this overrepresentation results in an excess rate of smoking-related cancers in the total population with Crohn's disease.[2] Conversely, nonsmokers are overrepresented among patients with ulcerative colitis, so there is a decreased rate of such cancers in the total population with ulcerative colitis.[4] The focus of this review is on the epidemiologic characteristics, carcinogenesis, and prevention of excess cancers that can be attributed to chronic intestinal inflammation or to the carcinogenic effects of the immunosuppressive drugs used to treat inflammatory bowel disease.

From the Department of Gastroenterology, Assistance Publique–Hôpitaux de Paris, Hôpital Saint-Antoine, and Equipe de Recherche Labellisée 1057 INSERM Unité Mixte de Recherche 7203 and Groupe de Recherche Clinique–Université Pierre et Marie Curie (UPMC) 3, UPMC Université Paris 6, Paris (L.B.); and Samuel Bronfman Department of Medicine, Dr. Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York (S.H.I.). Address reprint requests to Prof. Beaugerie at Service de Gastroentérologie et Nutrition, Hôpital Saint-Antoine,184 Rue du Faubourg Saint-Antoine, 75571 Paris CEDEX 12, France, or at laurent.beaugerie@sat.aphp.fr.

This article was updated on April 9, 2015, at NEJM.org.

N Engl J Med 2015;372:1441-52.
DOI: 10.1056/NEJMra1403718

CANCERS COMPLICATING INTESTINAL INFLAMMATION

COLORECTAL CANCER

Epidemiology

Colorectal cancer is the third most common cancer worldwide.[5] Sporadic colorectal cancers and colitis-associated cancer may develop in patients with inflammatory bowel disease. The main risk factors for sporadic colorectal cancer are increasing age after 50 years, male sex, and a history of colorectal cancer in first-degree relatives (Table 1). Although lifestyle factors are associated with as much as a 20% alteration in the risk of sporadic colorectal cancer, these have not been assessed in patients with inflammatory bowel disease.

Risk factors for colorectal cancer that are specific to patients with inflammatory bowel disease have been identified in studies of population-based registries,[6] nationwide cohorts,[7,8] and referral-center cohorts.[9,10] Patients with inflammatory bowel disease without colonic inflammation and patients with ulcerative colitis limited to the rectum are not at excess risk for colorectal cancer.[6] In contrast, patients with primary sclerosing cholangitis associated with inflammatory bowel disease are at high risk for colorectal cancer, beginning at the time of the diagnosis.[7] In other patients with inflammatory bowel disease, the excess risk of colorectal cancer, as compared with the risk among persons of the same age and sex without inflammatory bowel disease, is driven by the extent, duration, and severity of colonic inflammation. Up to 15% of colorectal cancers that occur in patients with inflammatory bowel disease are diagnosed within the first 7 years of disease,[8,11] but the

Table 1. Risk Factors for Colorectal Cancer in Patients with Inflammatory Bowel Disease.

Risk factors established in the general population
Increasing age*
Male sex*
History of colorectal cancer in first-degree relatives*
Increased body-mass index†
Low level of physical activity†
Cigarette smoking†
High consumption of red meat†
Consumption of alcohol†
Risk factors specific to patients with inflammatory bowel disease
Coexisting primary sclerosing cholangitis
Increasing cumulative extent of colonic inflammatory lesions‡
Increasing duration of inflammatory bowel disease§
Active chronic endoscopically assessed inflammation
Active chronic histologically assessed inflammation
Anatomical abnormalities
Foreshortened colon
Strictures
Pseudopolyps
Personal history of flat dysplasia

* This factor has been confirmed as a risk factor in epidemiologic studies that were restricted to patients with inflammatory bowel disease.
† This factor has not been specifically assessed in studies restricted to patients with inflammatory bowel disease.
‡ In ulcerative colitis, there is no excess risk of proctitis, an intermediate excess risk for left-sided colitis, and a maximal excess risk for pancolitis. In Crohn's disease, the excess risk appears when more than 30 to 50% of the colonic surface is ever involved.
§ The excess risk becomes significant from the time of diagnosis for patients with primary sclerosing cholangitis and becomes significant 7 to 10 years after diagnosis for other patients.

excess risk of colitis-associated cancer becomes epidemiologically apparent thereafter[12] and increases linearly, with a steeper slope in patients with extensive colitis. In addition, features of previous or currently active colitis,[9,10,13] including pseudopolyps and mucosal inflammation, are independent risk factors for colorectal cancer. Whether a young age at diagnosis of inflammatory bowel disease is a risk factor independent of disease duration is controversial (see the Supplementary Appendix, available with the full text of this article at NEJM.org).

In contrast to the relatively high risk of colorectal cancer (approximately 0.5 to 1% per year) suggested in a 2001 meta-analysis,[14] a progressive decrease in the excess risk of colorectal cancer in patients with inflammatory bowel disease has been noted over time, with no excess risk found in a Danish population-based study.[7] This trend, confirmed in another meta-analysis,[12] was attributed to better control of inflammation, better implementation of colonoscopic surveillance, increased implementation of colectomy in some countries, and the possible chemopreventive effect of 5-aminosalicylates (5-ASAs).

Still, as compared with the risk in the general population, the risk of colorectal cancer in patients with inflammatory bowel disease is 1.5 to 2 times greater in North America[15] and some European countries.[8] Stratification of the population with inflammatory bowel disease according to the duration of disease and the extent of colitis gives insight into incidence rates and the standardized incidence ratio of colorectal cancer among patients with inflammatory bowel disease (Table 2): teenagers with pancolitis have a lifetime risk of colorectal cancer that exceeds 15%.

Pathogenesis

Much is known about the molecular genetic events that drive the onset and progression of sporadic colorectal cancer,[16] although the environmental factor or factors that trigger the carcinogenesis remain to be elucidated. The molecular pathogenesis of colitis-associated cancer shares many features with sporadic colorectal cancer, but there are differences with respect to the timing and frequency of some alterations in the dysplasia–carcinoma sequence (Fig. 1).[17] Chronic inflammation is assumed to underlie the cause of colitis-associated cancer, with oxidative stress–induced DNA damage resulting in the activation of procarcinogenic genes and silencing of tumor-suppressor pathways. Insights from the study of animal models suggest that both the initiation and the progression of colonic neoplasia can be exacerbated or expedited by an inflammatory insult.[18] Moreover, mucosal-mapping studies indicate that the chronically inflamed colonic mucosa of patients with inflammatory bowel disease undergoes a "field change" of cancer-associated molecular alterations before there is any histologic evidence of dysplasia.[19,20] This suggests that the chronically inflamed colonic mucosa is primed to develop multifocal precancerous and cancerous changes. For example, *TP53* mutations occur before the onset of dysplasia as a field change in human colitic mucosa.[21] Microsatellite instability, CpG island methylation, and microRNA alterations have been described in the early phases of both sporadic and colitis-associated neoplasia.[22]

Table 2. Crude Incidence Rate and Standardized Incidence Ratio of Colorectal Cancer in Patients with Inflammatory Bowel Disease.

Disease	Colorectal Cancer Incidence Rate		Colorectal Cancer Standardized Incidence Ratio (95% CI)*	
	Population-Based Studies†	French Cohort‡	Population-Based Studies†	French Cohort‡
	cases per 1000 patient-years			
Inflammatory bowel disease				
All patients	0.8	0.8	1.7 (1.2–2.2)	2.2 (1.5–3.0)
Disease duration				
<10 yr	0.8	—	—	—
10 to 20 yr	1.4	—	—	—
>20 yr	2.4	—	—	—
Age at diagnosis of inflammatory bowel disease				
<30 yr	0.9	—	8.2 (1.8–14.6)	—
≥30 yr	2.0	—	1.8 (0.9–2.7)	—
Ulcerative colitis				
All patients	1.2	1.0	1.7 (1.0–2.4)	1.9 (1.1–3.1)
Patients with long-standing extensive colitis§	—	3.5	—	5.2 (2.4–9.9)
Patients without long-standing extensive colitis	—	0.6	—	1.2 (0.5–2.3)
Crohn's disease				
All patients	0.7	0.7	1.7 (1.0–2.5)	2.4 (1.5–3.8)
Patients with long-standing extensive colitis	—	3.0	—	9.0 (4.8–15.5)
Patients without long-standing extensive colitis	—	0.3	—	1.0 (0.4–2.1)

* Ratios are in comparison with persons in the age-matched and sex-matched general population.
† Data are from a meta-analysis of population-based studies from 1949 through 2011.[12]
‡ Data are from a prospective study of a French cohort from 2004 through 2007.[8]
§ Long-standing extensive colitis is defined as a duration of inflammatory bowel disease longer than 10 years and an estimated cumulative proportion of mucosal area macroscopically or microscopically affected by inflammatory bowel disease of 50% or greater.

An altered microbiota probably contributes to colitis-associated cancer by promoting chronic inflammation, producing carcinogenic factors, or both. In studies of genetically engineered mouse models of colitis-associated cancer that are susceptible to inflammation or cancer, cancer did not develop when the mice were either germ-free or treated with antibiotics.[23-25] Although certain bacteria (e.g., enterotoxigenic *Bacteroides fragilis*, fusobacterium, and *Enterococcus faecalis*) have been shown to play a procarcinogenic role, it is predicted that the complex interplay between the various bacterial communities in the colon is what creates a predisposition to carcinogenesis. The interaction between the host genome, colonic epithelial-cell receptors, and the luminal microbiota is the subject of intense research.

Management of the Risk of Colorectal Cancer in Inflammatory Bowel Disease

Successful surveillance for colorectal neoplasia depends on adequate cooperation from the patient, adequate bowel cleansing, sufficient mucosal sampling, and the ability of the endoscopist to recognize and, if possible, to resect dysplastic lesions. The presence of strictures, actively inflamed mucosa, and inflammatory pseudopolyps makes surveillance colonoscopy more difficult. As in sporadic colorectal cancer, in which the precursor dysplastic lesion is usually a visible polyp, in colitis, most dysplasia is also visible in the colon.[26] However, colitis-associated dysplastic lesions are often flatter and have less distinct borders, and they can even be invisible when standard endoscopic techniques are used. This

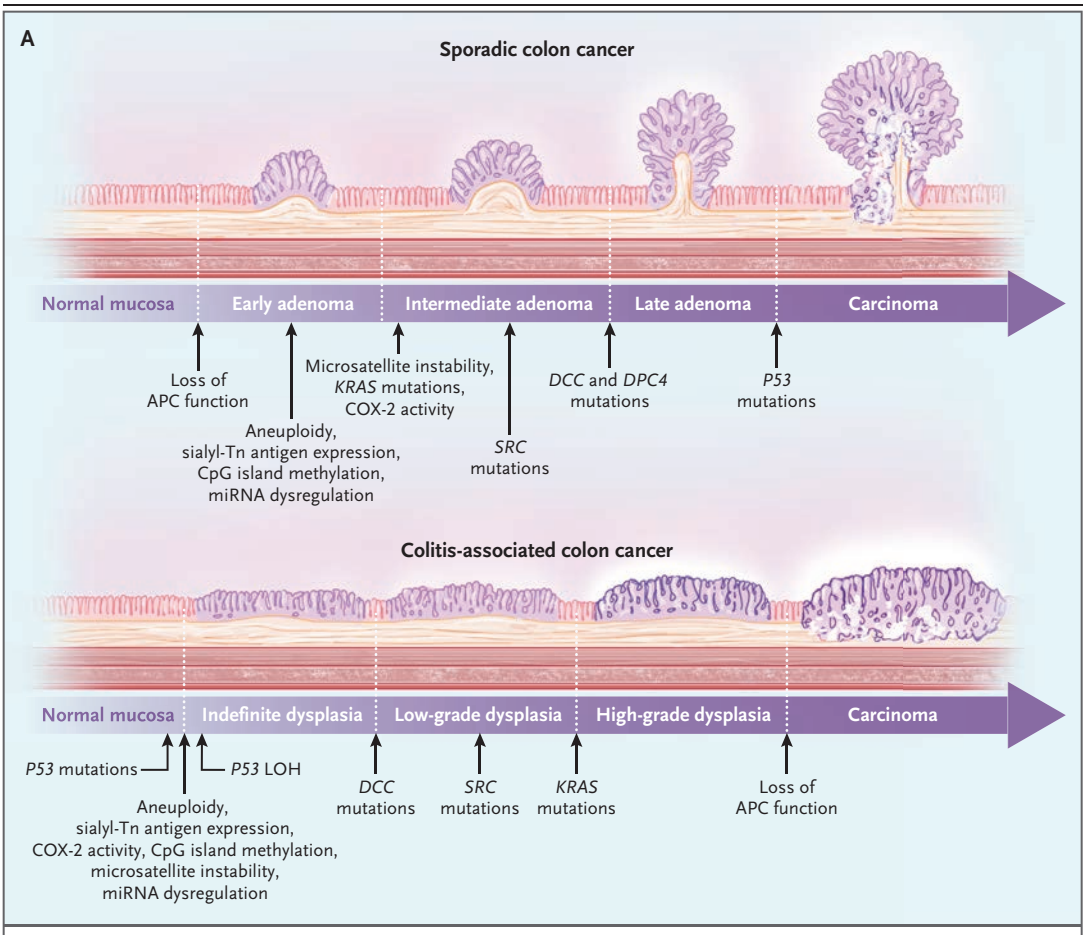

Figure 1. Pathogenesis of Colorectal Carcinoma.

Panel A shows the molecular steps of carcinogenesis of sporadic colorectal cancers and colitis-associated colorectal cancers. Most sporadic colorectal cancers arise from an adenoma precursor lesion that progresses through various stages until it becomes carcinoma. Loss of adenomatous polyposis coli (APC) function is considered the crucial first step ("gatekeeper") that sets the stage for other molecular alterations, with *TP53* mutations driving the later stages of carcinogenesis. In colitis-associated cancer, a dysplastic precursor lesion arises in the colitic mucosa and progresses through various grades of dysplasia. Although many of the same overall molecular alterations occur in colitis-associated cancer, the timing and sequence of events often differs. For example, mutations in *TP53* or a loss of p53 function are seen early, whereas the loss of APC function is a late and less common event. COX-2 denotes cyclooxygenase 2, DCC deleted in colon cancer, DPC4 deleted in pancreatic cancer, locus 4, KRAS Kirsten rat sarcoma viral oncogene homolog, LOH loss of heterozygosity, and miRNA microRNA. Panel B shows endoscopic images of sporadic versus colitis-associated dysplastic lesions. Sporadic adenomas in the general population are usually raised and readily visible with the use of standard white-light colonoscopy (left). However, dysplasia in colitis is often flat and less visible with the use of white-light colonoscopy (center), which justifies the use of image-enhancing techniques, such as chromoendoscopy (right), to better identify the presence and the borders of the dysplasia (arrows). Images were provided by Drs. Jerome Waye, Tonya Kaltenbach, and Roy Soetikno.

has prompted the recommendation to perform extensive biopsies throughout the colorectum, taking care to target any raised or suspicious lesions. Newer endoscopic techniques, especially high-definition white-light colonoscopy and chromoendoscopy with mucosal dye-spraying, enhance the detection of dysplasia, as compared with standard-light colonoscopy (Fig. 1). This is why most international authorities now favor chromoendoscopy with targeted biopsies over random biopsies,[27,28] although the latter approach, alone or in combination with targeted biopsies, has not yet been fully abandoned.[28]

There are only minor differences in the recommendations from medical societies for colonoscopic surveillance (Fig. 2).[27-30] After a dysplastic lesion is found, whether of a low-grade or high-grade histologic type, if it can be completely resected endoscopically and no dysplasia is noted elsewhere in the colon, the patient should remain under close colonoscopic surveillance. A meta-analysis has confirmed that after endoscopic removal of polypoid dysplasia, the risk of subsequent colorectal cancer is relatively low (5 per 1000 patient-years), but the risk of dysplasia remains high (65 per 1000 patient-years).[31] Colectomy is indicated in cases of carcinoma and in cases of high-grade dysplasia that is not endoscopically resectable. Colectomy should also be considered for patients who have low-grade dysplasia that cannot be resected endoscopically; patients with anatomical difficulties, such as stricture or dense pseudopolyps, that limit the accuracy of surveillance; and patients who cannot or will not undergo regular surveillance exams. The decision to undergo a colectomy is highly individualized, and the physician must take into consideration the patient's coexisting conditions, life expectancy, and preferences.

Chemopreventive agents inhibit, delay, or reverse carcinogenesis. In theory, if reducing inflammation leads to a reduced incidence of colitis-associated cancer, all antiinflammatory drugs used in inflammatory bowel disease, including 5-ASA, thiopurines, and tumor necrosis factor α (TNF-α) antagonists, are potential chemopreventive agents. In addition, a specific anticarcinogenic effect of 5-ASA has been advocated on the basis of molecular data.[32]

To date, however, none of the medicines used to treat inflammation in inflammatory bowel disease have been firmly established as being chemopreventive (Table S1 in the Supplementary Appendix). 5-ASA agents were the first drugs to be assessed for this purpose. Case–control and cohort studies, as well as an initial meta-analysis,[33] had suggested that there is a significant reduction in the risk of colorectal cancer in patients with inflammatory bowel disease who are exposed to 5-ASA. However, this was not confirmed in a more recent meta-analysis of nonreferral studies.[34] Nationwide cohort studies[8,35,36] and meta-analyses[37,38] of chemoprevention with thiopurines have also had conflicting results. The first data for TNF-α antagonists are also conflicting (Table S1 in the Supplementary Appendix). With regard to drugs that are not used for the treatment of inflammatory bowel disease, a potential preventive role of low-dose aspirin in persons with previous adenoma or dysplasia has not been assessed in patients with inflammatory bowel disease.

Given the lack of evidence, gastroenterologists are not comfortable prescribing inflammatory bowel disease drugs for the sole purpose of chemoprevention, even though this has been suggested for 5-ASA in some ulcerative colitis guidelines.[39] The feasibility of performing prospective randomized trials designed to show the chemopreventive effect of drugs for inflammatory bowel disease is questionable, because many thousands of patients would have to be enrolled. Alternatively designed prospective observational studies may be feasible if multiple adjustments are made (Table S2 in the Supplementary Appendix), including adjustments for the use of (and propensity to use) all potentially chemopreventive drugs, as well as risk factors for colorectal cancer in inflammatory bowel disease, including markers of colonic inflammation.

SMALL-BOWEL ADENOCARCINOMA

In the general population, small-bowel adenocarcinoma is rare. In patients with Crohn's disease, the risk of small-bowel adenocarcinoma is 20 to 30 times that in patients without Crohn's disease.[40] Small-bowel adenocarcinoma typically arises in the ileal lesions of patients with Crohn's disease more than 8 years after diagnosis. It is often associated with previous or synchronous ileal dysplasia,[41] which suggests that it may complicate chronic ileal inflammation in Crohn's disease through a dysplasia–adenocarcinoma sequence. In the Cancers et Surrisque Associé aux Maladies Inflammatoires Intestinales en France (CESAME) cohort, the subgroup of patients who had small-

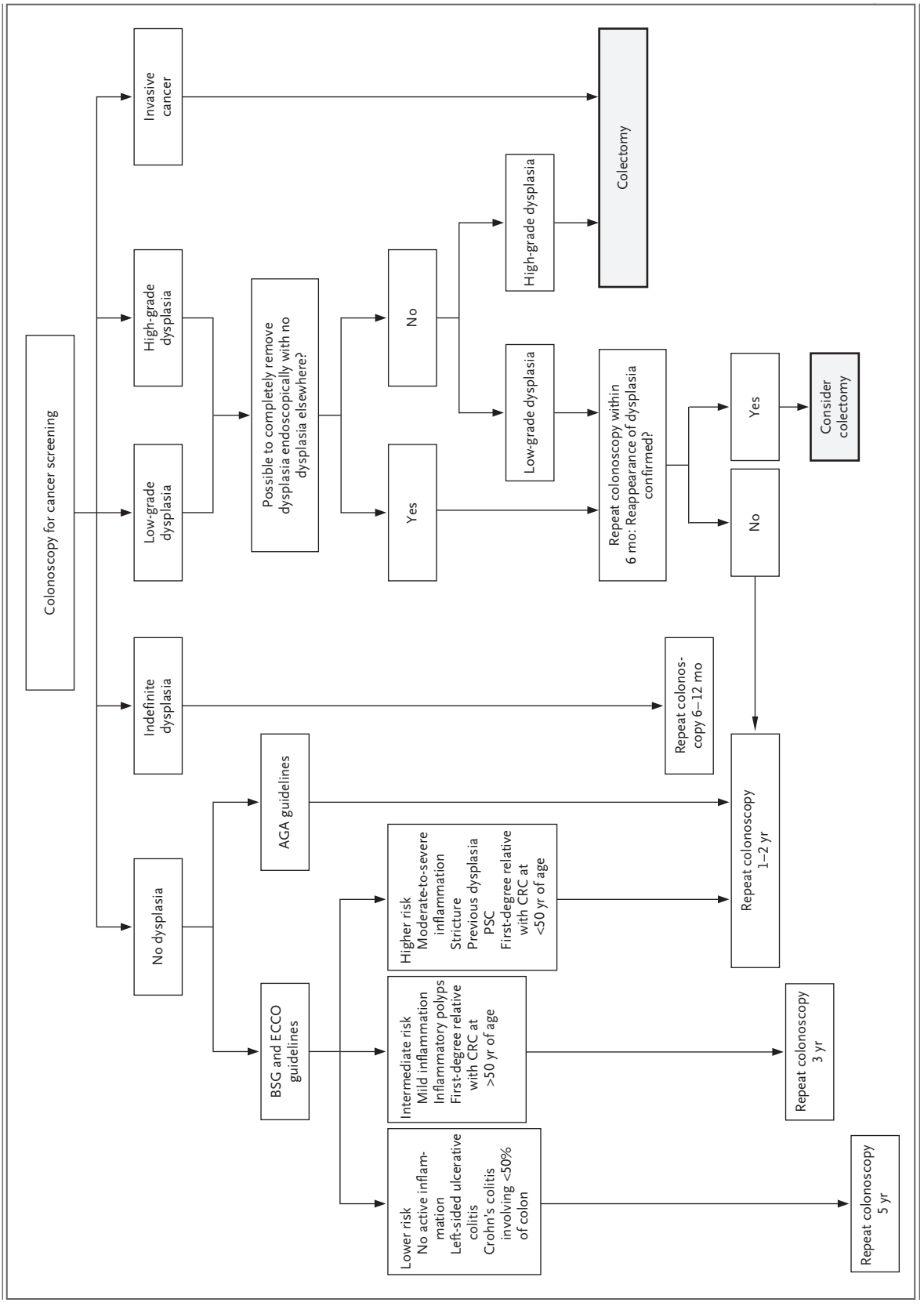

Figure 2 (facing page). Suggested Algorithm for Colorectal Cancer Surveillance in Inflammatory Bowel Disease.

The American Gastroenterological Association (AGA)[29] and European Crohn's and Colitis Organisation (ECCO)[27] recommend that initial surveillance colonoscopy begin after 8 years of colitis or from the time of diagnosis of primary sclerosing cholangitis, at which time random biopsies of the colorectum — or if the expertise is available, chromoendoscopy with targeted biopsies — should be performed. The British Society of Gastroenterology (BSG)[30] recommends beginning surveillance colonoscopy after 10 years of colitis, with chromoendoscopy as the preferred method. For the ECCO and BSG, subsequent surveillance intervals are determined by stratifying patients into low-risk, intermediate-risk, and high-risk groups on the basis of clinicopathological features. The overall clinical management depends on the histologic findings and whether lesions are endoscopically resectable. CRC denotes colorectal cancer, and PSC primary sclerosing cholangitis.

bowel Crohn's disease for more than 8 years had a small-bowel adenocarcinoma incidence rate of 0.5 per 1000 patient-years,[42] which is similar to the risk of sporadic colorectal cancer. Findings on computed tomography and magnetic resonance imaging can be suggestive of the diagnosis of small-bowel adenocarcinoma,[43] but most cases are diagnosed incidentally during laparotomy performed for intestinal obstruction or perforation.[42,43]

Surgical excision of ileal lesions prevents the risk of subsequent malignant transformation, but no other preventive approach is currently available. One case–control study suggests that 5-ASA has a potential chemopreventive effect for small-bowel adenocarcinoma,[44] but no data exist for immunosuppressants. Consideration of an endoscopic surveillance program for patients at higher risk for small-bowel adenocarcinoma is problematic, because extensive and stricturing lesions make ileoscopy for the full visualization of the segments of the small bowel affected by Crohn's disease difficult or impossible.

INTESTINAL LYMPHOMAS

The risk of primary intestinal lymphomas is significantly higher in patients with inflammatory bowel disease, but the absolute risk (0.1 per 1000 patient-years) is low.[45] Excess intestinal lymphomas in inflammatory bowel disease are mainly B-cell non-Hodgkin's lymphomas, typically arising in the chronically inflamed intestinal lesions of middle-aged men with Crohn's disease after 8 years of disease.[45] Epstein–Barr virus (EBV) is often identified in lymphoma cells,[45] which suggests that local inflammation-promoted EBV replication plays a role in lymphomagenesis in these cases.[46]

ANAL CANCERS

Anal squamous-cell carcinoma occurs with a low annual incidence of approximately 0.01 to 0.02 per 1000 person-years in the general population and in patients with inflammatory bowel disease.[47] Persons at higher risk include men who have sex with men, as well as women with high-grade cervical dysplasia. Although immunosuppression after organ transplantation promotes human papillomavirus (HPV)–related anal carcinoma, the risk in patients with inflammatory bowel disease who are receiving immunosuppressants is unknown. Anal cancers may also arise in the fistulae of patients with long-standing (>10 years) fistulizing perianal Crohn's disease, with an incidence rate of approximately 0.2 per 1000 patient-years.[48] These cancers include adenocarcinomas and squamous-cell carcinomas that have no consistent relationship with HPV infection. Diagnosis is often delayed because of a nonspecific clinical presentation and because access to lesions is difficult in the presence of stenosis. A change in anal symptoms and unexplained pain should alert the clinician. The overall prognosis for patients with fistula-associated cancers is poor.

CHOLANGIOCARCINOMA

The risk of cholangiocarcinoma in patients with inflammatory bowel disease is approximately 2 to 4 times as high as in the general population, although the absolute risk is low, with an incidence of approximately 0.08 per 1000 person-years.[49] Most but perhaps not all[50] of the increased cholangiocarcinoma risk in patients with inflammatory bowel disease is seen in patients with associated primary sclerosing cholangitis; these patients have a risk that is approximately 160 times as high as that in the general population, as well as a 5 to 10% lifelong risk.[51] Most experts recommend noninvasive annual imaging of the biliary tract (magnetic resonance cholangiopancreatography or ultrasonography) and serum CA 19-9 measurement. If the results are abnormal, clinical judgment is used to decide on diagnostic confirmation and consideration for liver transplantation. Despite this approach, the prognosis of cholangiocarcinoma remains poor.

Table 3. Risks of Cancer in Patients with Inflammatory Bowel Disease Exposed to Thiopurines and TNF-α Antagonists.*

Cancer Type	Patients at Risk	Current Thiopurine Users			Current TNF-α Antagonist Users	
		Standardized Incidence Ratio (95% CI)	Incidence Rate *cases per 1000 person-years*	Adjusted Rate Ratio vs. Nonusers (95% CI)	Incidence Rate *cases per 1000 person-years*	Adjusted Rate Ratio vs. Nonusers (95% CI)
Hematologic cancers	All	—	—	—	0.4†	0.9 (0.4–1.9)†
All lymphomas	All	5.7 (3.7–10.1)‡	0.9§	5.3 (2.0–13.9)§	—	—
Posttransplant-like lymphoma	Patients seropositive for EBV (nearly all adults >30 yr of age)	—	1¶	—	—	—
Early post-mononucleosis lymphoma	Young men (<35 yr of age) seronegative for EBV	—	3¶	—	—	—
Hepatosplenic T-cell lymphoma	Young men (<35 yr of age)	—	0.1¶ to 0.3‖	—	0.1¶ to 0.3‖	—
Acute myeloid leukemia and myelodysplastic syndromes	All	1.5 (0.1–8.5)**	0.06**	—	—	—
Skin cancers						
Nonmelanoma skin cancers	All	7.0 (4.2–11.2)††	1.1††	2.3 (1.5–3.5)‡‡	—	1.1 (1.0–1.4)§§
Melanomas	All	1.1 (0.1–3.9)¶¶	0.1¶¶	1.1 (0.7–1.7)§§	0.5†	1.3 (0.6–2.7)† to 1.9 (1.1–3.3)§§
Urinary tract cancers	All	—	0.5‖‖	2.8 (1.2–6.5)‖‖	0.3†	1.6 (0.6–4.2)†
All cancers	All	—	6.8§ to 7.5‖‖	1.4 (1.2–1.7)‖‖ to 1.7 (1.3–2.1)***	4.4†	1.1 (0.8–1.4)†

* EBV denotes Epstein–Barr virus.
† Data are from Nyboe Andersen et al.[60]
‡ Data are from Kotlyar et al.[61]
§ Data are from Beaugerie et al.[56]
¶ Data are an estimate from Beaugerie et al.[56]
‖ Data are an estimate from Kotlyar et al.[59]
** Data are from Lopez et al.[62] In this study, the standardized incidence ratio and incidence rate in past users of thiopurines are 7.0 (95% CI, 1.4 to 20.3) and 0.3 per 1000 person-years, respectively.
†† Data are from Peyrin-Biroulet et al.[63]
‡‡ Data are from Ariyaratnam and Subramanian[64]
§§ Data are from Long et al.[65]
¶¶ Data are from Peyrin-Biroulet et al.[66]
‖‖ Data are from Pasternak et al.[36]
*** Data are from Beaugerie et al.[67]

OTHER CANCERS RELATED TO INFLAMMATORY BOWEL DISEASE

Early and sustained healing of intestinal lesions has become the ultimate objective of treatment in inflammatory bowel disease. Achieving this objective involves the long-term use of conventional immunomodulators (thiopurines [azathioprine or mercaptopurine] or methotrexate), TNF-α antagonists, or both in an increasing proportion of patients with Crohn's disease, as well as in patients with moderately to severely active ulcerative colitis. Immunosuppressants may be carcinogenic by directly altering cell DNA,[52] impairing immune control of chronic infection by mutagenic viruses,[53] or reducing immunosurveillance of tumor cells.[54] Here, we review the cancers for which a higher risk has been established or suggested in patients with inflammatory bowel disease who have long-term exposure to immunosuppressants.

HEMATOLOGIC CANCERS

Lymphomas

Non-Hodgkin's lymphomas are frequent cancers; the risk of these cancers is greater in men and increases with age. There is no overt excess risk of non-Hodgkin's lymphoma due to inflammatory bowel disease itself.[55,56] Thiopurines were shown in the 1970s to increase the incidence of non-Hodgkin's lymphoma after kidney transplantation. This phenomenon was established in the early 2000s in patients with inflammatory bowel disease.[56,57] Most of the thiopurine-promoted lymphomas are posttransplant-like EBV-associated B-cell lymphomas.[56] These lymphomas may occur in patients seropositive for EBV (i.e., almost all adults >30 years of age); in these patients, non-Hodgkin's lymphoma is attributed to the cytotoxic effects of thiopurines on EBV-specific immune cells that prevent the proliferation of EBV-infected B lymphocytes.[58]

Young men (<35 years of age) who are seronegative for EBV may also have fatal early postmononucleosis lymphomas develop; these lymphomas mimic those encountered in X-linked lymphoproliferative disease.[56] Finally, non–EBV-related hepatosplenic T-cell lymphomas may occur in patients exposed to thiopurines alone or in combination with TNF-α antagonists. These very rare lymphomas are most typically seen in young men after 2 years of therapy with thiopurines and TNF-α antagonists.[59]

The epidemiologic aspects of the three subtypes of thiopurine-induced lymphoproliferation are detailed in Table 3. The resulting standardized incidence ratio for patients with inflammatory bowel disease to have any lymphoproliferation develop is 5 to 6 in current thiopurine users and is not significantly increased in patients who used thiopurines in the past or never used them.[56,61] The highest absolute risk is observed in patients older than 65 years of age (5 per 1000 patient-years),[56] and the highest standardized incidence ratio is seen in men younger than 30 years of age.[61] In current users, the excess risk becomes apparent from the second year of treatment and appears to be roughly constant thereafter.[61] The excess risk disappears after thiopurine withdrawal.[61]

The risk of lymphoproliferation associated with methotrexate use is unknown in inflammatory bowel disease. In rheumatoid arthritis, reversible polyclonal EBV-associated lymphoproliferation has been reported, but no excess risk of lymphoma has been demonstrated in nationwide cohorts.[68]

Whether TNF-α antagonists promote lymphomas by themselves in patients with inflammatory bowel disease is difficult to assess because of the substantial proportion of patients who have previously been treated with immunomodulators.[69] However, after adjustment for cotreatments, no excess risk of lymphoma was found in a recent adequately powered study involving a cohort of patients with inflammatory bowel disease who had been exposed to TNF-α antagonists.[60]

Other Hematologic Cancers

In the long term, thiopurines may promote acute myeloid leukemia and severe myelodysplastic syndromes because of proliferation of blood cells with defective DNA-mismatch repair that escape the cytotoxic effect of drugs.[70] This proliferation results in an increased risk of acute myeloid leukemia and myelodysplastic syndromes in past users of thiopurines.[62]

SKIN CANCERS

Nonmelanoma skin cancers include basal-cell carcinomas and squamous-cell carcinomas. Nonmelanoma skin cancers are more frequent than all other cancers and are usually not life-threatening. Current exposure to thiopurines is associated with an increased risk of nonmelanoma skin cancers.[63,64] Whether the excess risk persists in former users of thiopurines is debated. The carcinogenic action of thiopurines could include an increased toxicity of ultraviolet A radiation on

epithelial skin cells[71] and a direct mutagenic effect on the gene encoding PTCH.[52] In patients with inflammatory bowel disease, no excess risk of nonmelanoma skin cancer attributable to TNF-α antagonists was found in a large cohort drawn from a health plan claims database, after adjustment for thiopurine therapy.[65]

Patients with inflammatory bowel disease may have a slight unexplained intrinsic higher risk of developing melanoma.[72] Treatment with thiopurines is not associated with an alteration of this background risk.[65,66] In contrast, the risk of melanoma in patients with inflammatory bowel disease who were exposed to TNF-α antagonists has been reported to be 1.5 to 2 times higher than that in patients who were not exposed,[60,65] which represents an incidence rate of 0.5 per 1000 patient-years.[60] Given the excess risks of skin cancers associated with both inflammatory bowel disease and the drugs used to treat it, specialists increasingly propose that all patients with inflammatory bowel disease practice sun protection and skin surveillance from the time of diagnosis. Methods of skin surveillance should be discussed with the patient's dermatologist.

HPV-Related Cervical Cancer

It is still unclear whether the risk of HPV-related cervical cancer is intrinsically increased in women with inflammatory bowel disease[73] or independently worsened by exposure to an immunosuppressant. However, vaccination against HPV and regular Papanicolaou tests are recommended in all women with inflammatory bowel disease.

Urinary-Tract Cancers

Transplant recipients receiving immunosuppressive regimens that include thiopurines are at increased risk for kidney and bladder cancer.[74] As compared with patients with inflammatory bowel disease who had never taken thiopurines, patients who were currently using azathioprine were reported in a Danish registry study to have a higher incidence of urinary-tract cancers, whereas former users of azathioprine did not.[36] No excess risk of urinary-tract cancer has been reported in patients with inflammatory bowel disease who have been exposed to TNF-α antagonists.[60]

Overall Risk and Prevention of Cancers Related to Drugs for Inflammatory Bowel Disease

After adjustment for confounders, current use of thiopurines for inflammatory bowel disease has been shown to be associated with an overall relative risk of cancer of 1.3 to 1.7 in adequately powered cohort studies.[36,67] This excess risk is reversible after thiopurine withdrawal.[36] There is no overall excess risk of cancer in patients treated with TNF-α antagonists for inflammatory bowel disease,[60] but a long-term excess risk due to accumulated doses cannot be yet ruled out because of the relatively recent use of biologics. The first guidelines for managing the risk of cancers related to inflammatory bowel disease drugs are being elaborated. Some key measures currently being discussed are listed in Table S3 in the Supplementary Appendix. Preventive tools include sun protection and skin surveillance for the prevention and detection of skin cancers.

CONCLUSIONS

Among the chronic inflammatory diseases that often require the prolonged use of immunosuppressants, inflammatory bowel disease is an intriguing model, because immunosuppressants may reduce the incidence of inflammation-related cancers through their antiinflammatory effects or promote immunosuppression-related cancers. In addition to cohorts in which the excess risk of cancers associated with the use of TNF-α antagonists and newer biologics can be assessed, we need cohorts in which general and inflammatory bowel disease–related risk factors for cancers, including inflammatory bowel disease activity, are prospectively recorded, to clarify whether healing of inflammatory lesions decreases the incidence of cancers related to inflammatory bowel disease and to grade the independent potential chemopreventive effects of drugs used to treat the condition.

The risks of cancers related to inflammatory bowel disease must be considered when assessing the risk–benefit ratios associated with long-term therapeutic strategies in inflammatory bowel disease. Given the large influence of age, sex, and inflammatory bowel disease phenotype on the extent of the risks of inflammatory bowel disease–related cancers, risk–benefit models should now be stratified for age,[75] sex, and inflammatory bowel disease phenotype to provide tailored quantification of risks for making individual therapeutic decisions.

Dr. Beaugerie reports receiving consulting fees from Abbott, lecture fees and travel support from Abbott, AbbVie, Ferring, and Merck, Sharp, and Dohme, and grant support from AbbVie, Biocodex, and Ferring; and Dr. Itzkowitz, grant support and fees for serving on a scientific advisory board from Exact Sciences.

No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Drs. Fabrice Carrat, Jean-Frédéric Colombel, James Lewis, Tine Jess, and Laurent Peyrin-Biroulet for their comments of an earlier version of the manuscript.

REFERENCES

1. 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.e42-54.e42.
2. Duricova D, Pedersen N, Elkjaer M, Gamborg M, Munkholm P, Jess T. Overall and cause-specific mortality in Crohn's disease: a meta-analysis of population-based studies. Inflamm Bowel Dis 2010; 16:347-53.
3. 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;11:43-8.
4. Jess T, Gamborg M, Munkholm P, Sørensen TI. Overall and cause-specific mortality in ulcerative colitis: meta-analysis of population-based inception cohort studies. Am J Gastroenterol 2007;102:609-17.
5. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136(5):E359-E386.
6. Ekbom A, Helmick C, Zack M, Adami HO. Ulcerative colitis and colorectal cancer: a population-based study. N Engl J Med 1990;323:1228-33.
7. Jess T, Simonsen J, Jorgensen KT, Pedersen BV, Nielsen NM, Frisch M. Decreasing risk of colorectal cancer in patients with inflammatory bowel disease over 30 years. Gastroenterology 2012;143(2):375.e1-81.e1.
8. Beaugerie L, Svrcek M, Seksik P, et al. Risk of colorectal high-grade dysplasia and cancer in a prospective observational cohort of patients with inflammatory bowel disease. Gastroenterology 2013; 145(1):166.e8-75.e8.
9. Rubin DT, Huo D, Kinnucan JA, et al. Inflammation is an independent risk factor for colonic neoplasia in patients with ulcerative colitis: a case-control study. Clin Gastroenterol Hepatol 2013;11(12): 1601.e4-8.e4.
10. Gupta RB, Harpaz N, Itzkowitz S, et al. Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. Gastroenterology 2007;133:1099-105.
11. Lutgens MW, Vleggaar FP, Schipper ME, et al. High frequency of early colorectal cancer in inflammatory bowel disease. Gut 2008;57:1246-51.
12. Lutgens MW, van Oijen MG, van der Heijden GJ, Vleggaar FP, Siersema PD, Oldenburg B. Declining risk of colorectal cancer in inflammatory bowel disease: an updated meta-analysis of population-based cohort studies. Inflamm Bowel Dis 2013;19:789-99.
13. Rutter M, Saunders B, Wilkinson K, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology 2004;126:451-9.
14. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut 2001;48:526-35.
15. Herrinton LJ, Liu L, Levin TR, Allison JE, Lewis JD, Velayos F. Incidence and mortality of colorectal adenocarcinoma in persons with inflammatory bowel disease from 1998 to 2010. Gastroenterology 2012;143:382-9.
16. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA Jr, Kinzler KW. Cancer genome landscapes. Science 2013;339:1546-58.
17. Ullman TA, Itzkowitz SH. Intestinal inflammation and cancer. Gastroenterology 2011;140:1807-16.
18. Itzkowitz SH, Yio X. Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. Am J Physiol Gastrointest Liver Physiol 2004;287:G7-G17.
19. Galandiuk S, Rodriguez-Justo M, Jeffery R, et al. Field cancerization in the intestinal epithelium of patients with Crohn's ileocolitis. Gastroenterology 2012;142(4): 855.e8-64.e8.
20. Risques RA, Lai LA, Himmetoglu C, et al. Ulcerative colitis-associated colorectal cancer arises in a field of short telomeres, senescence, and inflammation. Cancer Res 2011;71:1669-79.
21. Brentnall TA, Crispin DA, Rabinovitch PS, et al. Mutations in the p53 gene: an early marker of neoplastic progression in ulcerative colitis. Gastroenterology 1994; 107:369-78.
22. Scarpa M, Castagliuolo I, Castoro C, et al. Inflammatory colonic carcinogenesis: a review on pathogenesis and immunosurveillance mechanisms in ulcerative colitis. World J Gastroenterol 2014;20: 6774-85.
23. Abreu MT, Peek RM Jr Gastrointestinal malignancy and the microbiome. Gastroenterology 2014;146(6):1534.e3-46.e3.
24. Irrazábal T, Belcheva A, Girardin SE, Martin A, Philpott DJ. The multifaceted role of the intestinal microbiota in colon cancer. Mol Cell 2014;54:309-20.
25. Itzkowitz SH, Harpaz N. Diagnosis and management of dysplasia in patients with inflammatory bowel diseases. Gastroenterology 2004;126:1634-48.
26. Rubin DT, Rothe JA, Hetzel JT, Cohen RD, Hanauer SB. Are dysplasia and colorectal cancer endoscopically visible in patients with ulcerative colitis? Gastrointest Endosc 2007;65:998-1004.
27. Annese V, Daperno M, Rutter MD, et al. European evidence based consensus for endoscopy in inflammatory bowel disease. J Crohns Colitis 2013;7:982-1018.
28. Laine L, Kaltenbach T, Barkun A, et al. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. Gastroenterology 2015;148:639-51.
29. Farraye FA, Odze RD, Eaden J, Itzkowitz SH. AGA technical review on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. Gastroenterology 2010;138:746-74.
30. Cairns SR, Scholefield JH, Steele RJ, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut 2010;59:666-89.
31. Wanders LK, Dekker E, Pullens B, Bassett P, Travis SP, East JE. Cancer risk after resection of polypoid dysplasia in patients with longstanding ulcerative colitis: a meta-analysis. Clin Gastroenterol Hepatol 2014;12:756-64.
32. Lyakhovich A, Gasche C. Systematic review: molecular chemoprevention of colorectal malignancy by mesalazine. Aliment Pharmacol Ther 2010;31:202-9.
33. Velayos FS, Terdiman JP, Walsh JM. Effect of 5-aminosalicylate use on colorectal cancer and dysplasia risk: a systematic review and metaanalysis of observational studies. Am J Gastroenterol 2005; 100:1345-53.
34. Nguyen GC, Gulamhusein A, Bernstein CN. 5-Aminosalicylic acid is not protective against colorectal cancer in inflammatory bowel disease: a meta-analysis of non-referral populations. Am J Gastroenterol 2012;107:1298-304.
35. van Schaik FD, van Oijen MG, Smeets HM, van der Heijden GJ, Siersema PD, Oldenburg B. Thiopurines prevent advanced colorectal neoplasia in patients with inflammatory bowel disease. Gut 2012;61:235-40.
36. Pasternak B, Svanström H, Schmiegelow K, Jess T, Hviid A. Use of azathioprine and the risk of cancer in inflammatory bowel disease. Am J Epidemiol 2013; 177:1296-305.
37. Gong J, Zhu L, Guo Z, et al. Use of thiopurines and risk of colorectal neoplasia in patients with inflammatory bowel diseases: a meta-analysis. PLoS One 2013; 8(11):e81487.
38. Jess T, Lopez A, Andersson M, Beaugerie L, Peyrin-Biroulet L. Thiopurines and risk of colorectal neoplasia in

patients with inflammatory bowel disease: a meta-analysis. Clin Gastroenterol Hepatol 2014;12(11):1793.e1-1800.e1.
39. Van Assche G, Dignass A, Bokemeyer B, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 3: special situations. J Crohns Colitis 2013;7:1-33.
40. Jess T, Gamborg M, Matzen P, Munkholm P, Sørensen TI. Increased risk of intestinal cancer in Crohn's disease: a meta-analysis of population-based cohort studies. Am J Gastroenterol 2005;100:2724-9.
41. Svrcek M, Piton G, Cosnes J, et al. Small bowel adenocarcinomas complicating Crohn's disease are associated with dysplasia: a pathological and molecular study. Inflamm Bowel Dis 2014;20:1584-92.
42. Elriz K, Carrat F, Carbonnel F, Marthey L, Bouvier AM, Beaugerie L. Incidence, presentation, and prognosis of small bowel adenocarcinoma in patients with small bowel Crohn's disease: a prospective observational study. Inflamm Bowel Dis 2013;19:1823-6.
43. Weber NK, Fletcher JG, Fidler JL, et al. Clinical characteristics and imaging features of small bowel adenocarcinomas in Crohn's disease. Abdom Imaging 2014 April 24 (Epub ahead of print).
44. Piton G, Cosnes J, Monnet E, et al. Risk factors associated with small bowel adenocarcinoma in Crohn's disease: a case-control study. Am J Gastroenterol 2008;103:1730-6.
45. Sokol H, Beaugerie L, Maynadié M, et al. Excess primary intestinal lymphoproliferative disorders in patients with inflammatory bowel disease. Inflamm Bowel Dis 2012;18:2063-71.
46. Wong NA, Herbst H, Herrmann K, et al. Epstein-Barr virus infection in colorectal neoplasms associated with inflammatory bowel disease: detection of the virus in lymphomas but not in adenocarcinomas. J Pathol 2003;201:312-8.
47. Slesser AA, Bhangu A, Bower M, Goldin R, Tekkis PP. A systematic review of anal squamous cell carcinoma in inflammatory bowel disease. Surg Oncol 2013;22:230-7.
48. Laukoetter MG, Mennigen R, Hannig CM, et al. Intestinal cancer risk in Crohn's disease: a meta-analysis. J Gastrointest Surg 2011;15:576-83.
49. Erichsen R, Jepsen P, Vilstrup H, Ekbom A, Sørensen HT. Incidence and prognosis of cholangiocarcinoma in Danish patients with and without inflammatory bowel disease: a national cohort study, 1978-2003. Eur J Epidemiol 2009;24:513-20.
50. Chang JS, Tsai CR, Chen LT. Medical risk factors associated with cholangiocarcinoma in Taiwan: a population-based case-control study. PLoS One 2013;8(7):e69981.
51. Singh S, Talwalkar JA. Primary sclerosing cholangitis: diagnosis, prognosis, and management. Clin Gastroenterol Hepatol 2013;11:898-907.
52. Harwood CA, Attard NR, O'Donovan P, et al. PTCH mutations in basal cell carcinomas from azathioprine-treated organ transplant recipients. Br J Cancer 2008;99:1276-84.
53. Münz C, Moormann A. Immune escape by Epstein-Barr virus associated malignancies. Semin Cancer Biol 2008;18:381-7.
54. Zitvogel L, Tesniere A, Kroemer G. Cancer despite immunosurveillance: immunoselection and immunosubversion. Nat Rev Immunol 2006;6:715-27.
55. Lewis JD, Bilker WB, Brensinger C, Deren JJ, Vaughn DJ, Strom BL. Inflammatory bowel disease is not associated with an increased risk of lymphoma. Gastroenterology 2001;121:1080-7.
56. Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Lancet 2009;374:1617-25.
57. Kandiel A, Fraser AG, Korelitz BI, Brensinger C, Lewis JD. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. Gut 2005;54:1121-5.
58. Pietersma F, Piriou E, van Baarle D. Immune surveillance of EBV-infected B cells and the development of non-Hodgkin lymphomas in immunocompromised patients. Leuk Lymphoma 2008;49:1028-41.
59. Kotlyar DS, Osterman MT, Diamond RH, et al. A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2011;9(1):36.e1-41.e1.
60. Nyboe Andersen N, Pasternak B, Basit S, et al. Association between tumor necrosis factor-α antagonists and risk of cancer in patients with inflammatory bowel disease. JAMA 2014;311:2406-13.
61. Kotlyar DS, Lewis JD, Beaugerie L, et al. Risk of lymphoma in patients with inflammatory bowel disease treated with azathioprine and 6-mercaptopurine: a meta-analysis. Clin Gastroenterol Hepatol 2014 May 28 (Epub ahead of print).
62. Lopez A, Mounier M, Bouvier AM, et al. Increased risk of acute myeloid leukemias and myelodysplastic syndromes in patients who received thiopurine treatment for inflammatory bowel disease. Clin Gastroenterol Hepatol 2014;12:1324-9.
63. Peyrin-Biroulet L, Khosrotehrani K, Carrat F, et al. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. Gastroenterology 2011;141:1621-8.
64. Ariyaratnam J, Subramanian V. Association between thiopurine use and nonmelanoma skin cancers in patients with inflammatory bowel disease: a meta-analysis. Am J Gastroenterol 2014;109:163-9.
65. Long MD, Martin CF, Pipkin CA, Herfarth HH, Sandler RS, Kappelman MD. Risk of melanoma and nonmelanoma skin cancer among patients with inflammatory bowel disease. Gastroenterology 2012;143(2):390.e1-9.e1.
66. Peyrin-Biroulet L, Chevaux JB, Bouvier AM, Carrat F, Beaugerie L. Risk of melanoma in patients who receive thiopurines for inflammatory bowel disease is not increased. Am J Gastroenterol 2012;107:1443-4.
67. Beaugerie L, Carrat F, Colombel JF, et al. Risk of new or recurrent cancer under immunosuppressive therapy in patients with IBD and previous cancer. Gut 2014;63:1416-23.
68. Mariette X, Cazals-Hatem D, Warszawki J, Liote F, Balandraud N, Sibilia J. Lymphomas in rheumatoid arthritis patients treated with methotrexate: a 3-year prospective study in France. Blood 2002;99:3909-15.
69. Siegel CA, Marden SM, Persing SM, Larson RJ, Sands BE. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. Clin Gastroenterol Hepatol 2009;7:874-81.
70. Offman J, Opelz G, Doehler B, et al. Defective DNA mismatch repair in acute myeloid leukemia/myelodysplastic syndrome after organ transplantation. Blood 2004;104:822-8.
71. O'Donovan P, Perrett CM, Zhang X, et al. Azathioprine and UVA light generate mutagenic oxidative DNA damage. Science 2005;309:1871-4.
72. Singh S, Nagpal SJ, Murad MH, et al. Inflammatory bowel disease is associated with an increased risk of melanoma: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2014;12:210-8.
73. Rungoe C, Simonsen J, Riis L, Frisch M, Langholz E, Jess T. Inflammatory bowel disease and cervical neoplasia: a population-based nationwide cohort study. Clin Gastroenterol Hepatol 2015;13(4):693.e1-700.e1.
74. Gutierrez-Dalmau A, Campistol JM. Immunosuppressive therapy and malignancy in organ transplant recipients: a systematic review. Drugs 2007;67:1167-98.
75. Scott FI, Vajravelu RK, Bewtra M, et al. The benefit-to-risk balance of combining infliximab with azathioprine varies with age: a Markov model. Clin Gastroenterol Hepatol 2015;13(2):302.e11-9.e11.