Clinical Gastroenterology and Hepatology 2024;■:■–■

CLINICAL PRACTICE UPDATES

AGA Clinical Practice Update on Management of Inflammatory Bowel Disease in Patients with Malignancy: Commentary

Jordan E. Axelrad,[1] Jana G. Hashash,[2] and Steven H. Itzkowitz[3]

[1]*Inflammatory Bowel Disease Center at NYU Langone Health, Division of Gastroenterology, NYU Grossman School of Medicine, New York, New York;* [2]*Inflammatory Bowel Disease Center, Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, Florida; and* [3]*Division of Gastroenterology, the Icahn School of Medicine at Mount Sinai, New York, New York*

DESCRIPTION: **The purpose of this American Gastroenterological Association (AGA) Institute Clinical Practice Update (CPU) Commentary is to discuss the risks of various malignancies in patients with inflammatory bowel diseases (IBD) and the impact of the available medical therapies on these risks. The CPU will also guide the approach to the patient with IBD who develops a malignancy or the patient with a history of cancer in terms of IBD medication management.**

METHODS: **This CPU was commissioned and approved by the AGA Institute CPU committee and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership and underwent internal peer review by the CPU committee and external peer review through standard procedures of *Clinical Gastroenterology and Hepatology*. This communication incorporates important and recently published studies in the field, and it reflects the experiences of the authors who are experts in the diagnosis and management of IBD.**

Keywords: Thiopurines; Biologics; Small Molecules; Cancer; Lymphoma.

Chronic inflammation promotes the development of colorectal, intestinal, and some extraintestinal malignancies in patients with inflammatory bowel disease (IBD) (Figure 1).[1] Additionally, immunosuppressive medications used to treat IBD increase the risk of extraintestinal malignancies in this patient population (Figure 1). This clinical practice update is meant to help physicians understand the risk of cancer in patients with IBD and guide the management of patients with IBD who develop an active malignancy or have a history of cancer.

Cancer Risk Caused by Underlying Inflammatory Bowel Disease

Colorectal Cancer

Colorectal cancer (CRC) is one of the most common malignancies in patients with IBD and is a direct consequence of chronic colonic inflammation. Previously, the reported risk for developing CRC was 15% after 30 years of colonic inflammation.[2,3] In a recent meta-analysis of population-based cohort studies, rates of CRC were found to be declining among patients with IBD colitis: 1%, 2%, and 5% risk of CRC after 10, 20, and >20 years from an initial IBD diagnosis, respectively.[4,5] Incidence rates for early stage cancers have been increasing, likely caused by improved endoscopic technology, guidelines to regularly perform surveillance, and a shift in dysplasia management from colectomy to endoscopic resection.[6,7]

Chronic colonic inflammation increases the risk of multifocal dysplasia because of a field cancerization effect.[8] In a cohort of patients with ulcerative colitis diagnosed with CRC, more than one-third had synchronous CRC or dysplasia at a distant colonic site at the time of colectomy.[6] This emphasizes the importance of endoscopic mucosal healing and close dysplasia

Abbreviations used in this paper: **aHR, adjusted hazard ratio; CD, Crohn's disease; CI, confidence interval; CRC, colorectal cancer; IBD, inflammatory bowel diseases; ICI, immune checkpoint inhibitors; IRR, incidence rate ratio; NMSC, nonmelanoma skin cancers; PSC, primary sclerosing cholangitis; PY, person-year; TNF, tumor necrosis factor.**

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2024.03.032

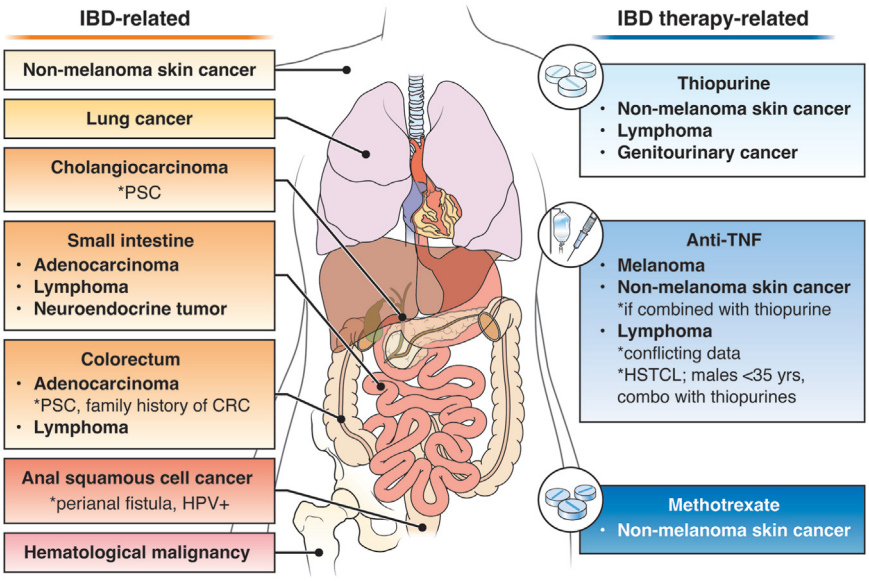

Figure 1. Risk of cancer related to IBD and risk of cancer related to IBD-related medications. HPV, human papillomavirus; HSTCL, hepatosplenic T-cell lymphoma.

surveillance, especially among high-risk patients.[9] Other than active colonic inflammation, risk factors for CRC in IBD include longer disease duration, greater extent of colonic involvement, family history of CRC, and concomitant primary sclerosing cholangitis (PSC).[1,10,11] PSC increases the odds for CRC and colorectal dysplasia by more than 3-fold compared with patients with IBD and no PSC.[12]

Small Bowel Cancers

Patients with Crohn's disease (CD) who have small bowel inflammation are at an increased risk for developing small bowel adenocarcinoma (adjusted hazard ratio [aHR], 15.8; 95% confidence interval [CI], 11.0–22.8) and neuroendocrine tumors (aHR, 5.5; 95% CI, 3.83–7.92), although, the absolute risk remains low (2.4/10,000 person-years [PY] in CD, 4.6/10,000 PY in ileal CD, compared with 0.28/10,000 PY in reference individuals).[13] Risk factors for small bowel adenocarcinoma include tobacco use, male sex, childhood onset CD, long-standing small bowel inflammation, penetrating or stricturing CD, and prior small bowel resection.[13,14]

Intestinal Lymphoma

Intestinal lymphoma is estimated to be 2- to 3-fold increased in individuals with IBD compared with the general population, although like other small bowel cancers, the absolute risk remains very low (1–4/10,000 PY in CD compared with 0.7/10,000 PY in reference individuals).[15,16] These intestinal lymphomas are predominantly B-cell non-Hodgkin lymphoma and are often associated with the presence of Epstein-Barr virus.[1,16] Intestinal lymphomas occur more often in males, those with ongoing intestinal inflammation, and in patients who have had CD for more than 8 years.[1]

Anal Cancer

As with small intestinal adenocarcinoma and intestinal lymphoma, the absolute risk of anal cancer among patients with CD remains low, but higher than the general population. The Cancers et Surrisque Associé aux Maladies Inflammatoires Intestinales En France (CESAME) cohort showed that the incidence of anal squamous cell carcinoma was 2.6/10,000 PY among patients with IBD with anal or perianal lesions, as compared with 0.8/10,000 PY among patients with IBD without anal or perianal fistula.[17] One risk factor for developing anal squamous cell carcinoma is the presence of human papillomavirus.[17] In addition to human papillomavirus, long-standing perianal fistulizing disease increases the risk of anal squamous cell carcinoma and adenocarcinoma, with a combined incidence of 3.8/10,000 PY.[18]

Extraintestinal Malignancies

Cholangiocarcinoma is 4-times more likely to occur in patients with IBD compared with patients without IBD, with an incidence of 7.6/100,000 PY among patients with IBD as compared with 1.9/100,000 PY among non-IBD control subjects.[19,20] This risk is predominantly driven by concomitant PSC, which increases the risk of cholangiocarcinoma by more than 150-fold compared with individuals without PSC, equating to a 5%–10% lifetime risk.[1,21]

Systematic review data suggest that patients with IBD demonstrated an increased risk of nonmelanoma skin cancers (NMSC; CD incidence rate ratio [IRR], 2.22 [95% CI, 1.41–3.48]; ulcerative colitis IRR, 1.38 [95% CI,

1.12–1.71]), hematologic malignancy (CD IRR, 2.40; 95% CI, 1.81–3.18), and lung cancer (CD IRR, 1.53; 95% CI, 1.23–1.91).[20] Melanoma, multiple myeloma, and non-Hodgkin lymphoma have been reported as possibly associated with IBD; however, these studies did not account for medication use.[22,23]

Cancer Risk Associated with Inflammatory Bowel Disease Therapies

Thiopurines

In patients with IBD who are treated with thiopurines, there is an increased risk of NMSC. In a study of 108,579 patients with IBD, thiopurine use was associated with an almost 2-fold increase in the development of NMSC,[24] and ongoing thiopurine use might increase the risk of recurrent NMSC. Furthermore, patients with prior basal cell carcinoma were more likely to have a recurrence of basal cell carcinoma in the setting of continued thiopurine use.[25] This risk of skin cancer is thought to persist, albeit to a lesser extent, after discontinuing thiopurines, emphasizing the importance of annual dermatologic examinations in patients with IBD, with current and prior thiopurine use.[26]

Nonintestinal lymphoma is another risk associated mainly with thiopurine use. In a recent meta-analysis, the standardized incidence ratio of lymphoma among patients with IBD treated with thiopurines ranged from 2.8 to 9.2 compared with those unexposed to thiopurines.[27] The absolute risk was highest among individuals older than age 50 (1/354 PY), whereas the highest relative risk was among individuals younger than 30 years (standardized incidence ratio, 7.0).[27] Although most IBD-related lymphomas are B-cell in origin, males younger than 35 years of age are also at risk for hepatosplenic T-cell lymphoma. Hepatosplenic T-cell lymphoma is associated with long-term thiopurines use, frequently with combination anti–tumor necrosis factor (TNF) therapy, and is often fatal.[28] There are also very limited data suggesting an association between current use of thiopurines with an increased risk of acute myeloid leukemia and myelodysplastic syndromes.[29]

Genitourinary cancer is also associated with thiopurine use in IBD. In both the CESAME and Danish cohorts, patients on thiopurines, particularly males, had a 2.8-times higher risk of urinary tract cancers compared with individuals with IBD not using thiopurines.[30,31] In a multicenter Dutch prospective cohort study, females with IBD had a 1.3-times higher risk of cervical high-grade dysplasia or cervical cancer compared with matched control subjects without IBD.[32] This risk was largely associated with cumulative exposure to immunomodulators and not biologic agents.[33]

Methotrexate

There are limited data on use of methotrexate monotherapy in IBD, but there may be a small increased risk of NMSC.[34]

Anti–Tumor Necrosis Factor Therapy

Data linking the use of anti-TNF therapy with lymphoma and melanoma are conflicting. In a retrospective analysis of insurance claims data, anti-TNF use was associated with a nearly 2-fold increased risk of melanoma compared with unexposed IBD control subjects.[24] In contrast, an analysis of Danish patients found no association between anti-TNF therapy and melanoma,[35] and a recent meta-analysis showed no difference in risk of melanoma among patients with IBD treated with biologics as compared with patients treated with nonbiologic therapies.[36]

Most, but not all, studies suggest no increased risk of lymphoma with anti-TNF monotherapy,[37–40] but there is a consistently increased risk of lymphoma when anti-TNF agents are combined with thiopurines.[28] This is particularly true in young Epstein-Barr virus unexposed patients. Most concerning is hepatosplenic T-cell lymphoma, although only a handful of cases in patients with IBD are reported each year.

Janus Kinase Inhibitors

Thus far, data have not suggested an increased risk of malignancy in patients with IBD treated with Janus kinase inhibitors. However, clinical trial data from patients older than 50 years with rheumatoid arthritis demonstrated an increased risk of any malignancy compared with anti-TNF, particularly NMSC, lung cancer, and lymphoma.[41] Furthermore, meta-analysis data of patients with inflammatory joint, skin, and bowel disease yielded a higher incidence of malignancy with Janus kinase inhibitor use as compared with anti-TNFs, but not placebo or methotrexate.[42] Conversely, a pooled analysis of clinical trial and long-term extension studies from patients with rheumatoid arthritis have not revealed a similar association between Janus kinase inhibitors and malignancy.[43]

Other Inflammatory Bowel Disease Therapies

Current evidence does not show an increased risk of malignancy in patients with IBD treated with vedolizumab, ustekinumab, risankizumab, mirikizumab, ozanimod, and etrasimod, although, long-term data are lacking. Furthermore, there are no data on cancer risk in patients combining biologic and small molecule therapies.

Table 1. What to do with IBD-related medications after a malignancy develops

Patient with IBD on	Develops	What to do with IBD drug	Comments
Thiopurine	Lymphoma	Stop thiopurine	Most are B-cell lymphomas Increased association with Epstein-Barr virus Risk reverses after stopping thiopurine
Anti-TNF		Consider alternative therapy	Risk not supported in all studies Black box warning
Anti-TNF + thiopurine		Stop thiopurine and consider alternative therapy for anti-TNF	Increased risk of hepatosplenic T-cell lymphoma
Anti-integrin		No change	Limited data
Anti-IL 12/23, Anti-IL 23		No change	Limited data
JAK inhibitor		No change	Limited data
S1P receptor modulator		No change	Limited data
Thiopurine	Other hematologic malignancy	Consider alternative therapy	Limited data
Anti-TNF		No change	
Anti-TNF + thiopurine		No change	
Anti-integrin		No change	Limited data
Anti-IL 12/23, Anti-IL 23		No change	Limited data
JAK inhibitor		No change	Limited data
S1P receptor modulator		No change	Limited data
Thiopurine	Melanoma	No change	
Anti-TNF		Stop anti-TNF	Risk not supported in all studies
Anti-TNF + thiopurine		Stop anti-TNF	Risk not supported in all studies
Anti-integrin		No change	Limited data
Anti-IL 12/23, Anti-IL 23		No change	Limited data
JAK inhibitor		No change	Limited data
S1P receptor modulator		No change	Limited data
Thiopurine	Non-melanoma skin cancer	Stop thiopurine	Stop thiopurine if recurrent and difficult to manage skin cancers
Anti-TNF		No change	
Anti-TNF + thiopurine		Stop thiopurine	Stop thiopurine if recurrent and difficult to manage skin cancers
Anti-integrin		No change	Limited data
Anti-IL 12/23, Anti-IL 23		No change	Limited data
JAK inhibitor		No change	Limited data
S1P receptor modulator		No change	Limited data
Thiopurine	Solid organ malignancy	Consider alternative therapy	Consider cessation if cervical or genitourinary cancer Risk not supported in all studies
Anti-TNF		No change	
Anti-TNF + thiopurine		No change	Limited data
Anti-integrin		No change	Limited data
Anti-IL 12/23, Anti-IL 23		No change	Limited data
JAK inhibitor		No change	Limited data
S1P receptor modulator		No change	Limited data

Management of Patients with Inflammatory Bowel Disease and Active or Recent Cancer

Impact of Inflammatory Bowel Disease Therapies on Active Cancer: What to Do with the Inflammatory Bowel Disease Medications?

Little is known about the possible impact of IBD therapies on patients who have an active cancer. In a retrospective, multicenter study evaluating the safety of IBD-directed immunosuppressive therapies in patients with any active and recent (within the past 5 years) cancers, there were similar rates of cancer progression in patients exposed to anti-TNF agents versus non-TNF biologics versus immunomodulator monotherapy.[44] Table 1 offers guidance about managing IBD medications in individuals with IBD who develop cancer. The greatest concern is with thiopurines and anti-TNFs; there are insufficient data to alter management of other IBD medications. Given the

increased risk of lymphoma and NMSC with thiopurines, if a patient on a thiopurine develops lymphoma, it should be discontinued. Consider stopping thiopurines for those who develop multiple or recurrent NMSC. As for anti-TNF agents, if melanoma develops while on an anti-TNF, it should be discontinued, and if lymphoma develops, consider stopping the anti-TNF.

Oncologists commonly defer to gastroenterologists regarding IBD-directed immunosuppressive therapy during cancer treatment. This underscores the importance of understanding the relationship between IBD disease activity and cancer treatments. Despite limited data, in patients with active cancers undergoing oncologic treatment, if IBD activity needs to be controlled, the use of IBD therapies, including most biologic agents, is warranted, with the caveat that there be close collaboration between the treating oncologist and gastroenterologist.

Immune checkpoint inhibitors (ICIs) targeting cytotoxic T-lymphocyte-associated protein 4, programmed cell death protein 1, or programmed death-ligand 1 are used to treat active cancers and are associated with improved outcomes for multiple malignancies. However, a common complication is a variant of colitis that may resemble IBD.[45–47] A meta-analysis evaluating the gastrointestinal toxicities associated with ICIs found that the relative risk of diarrhea and colitis was 1.64 (95% CI, 1.19–2.26) and 10.35 (95% CI, 5.78–18.53), respectively.[48] In general, ICI colitis is treated with steroids, and biologics for steroid refractoriness.[49] In patients with known underlying IBD, treatment with ICIs can increase the risk of IBD relapse. In a meta-analysis, treatment with ICIs led to IBD relapse in 40% of patients with at least one-third requiring biologics.[50] Cytotoxic T-lymphocyte-associated protein 4 inhibitors were associated with a higher risk of IBD relapse compared with programmed cell death protein 1 and programmed death-ligand 1 inhibitors.

Impact of Cancer Therapies on Inflammatory Bowel Disease: What to Do with Cancer Treatment?

Cancer treatment may impact the underlying course of IBD. Decisions regarding IBD-therapy in patients who develop cancer is nuanced, and should consider symptom burden and inadequacy of IBD treatment worsening quality of life, impacting tolerability of cancer-directed treatment. In a retrospective study of 84 patients with IBD who were diagnosed with any extraintestinal cancer, most patients with active IBD achieved remission if treated with cytotoxic chemotherapeutic agents, suggesting a beneficial effect on intestinal inflammation.[51] Furthermore, nearly all patients remained in IBD remission at 5 years after a cancer diagnosis indicating a durable benefit to cytotoxic chemotherapy. By contrast, hormonal deprivation therapy, whether used alone or in combination with cytotoxic chemotherapy, was associated with an increased risk of IBD relapse. The effect of hormonal deprivation therapy on the disease course of IBD was examined in a multicenter study of 447 patients with either breast or prostate cancer and IBD. Of 400 patients with inactive IBD, hormone deprivation therapy alone or in combination with cytotoxic chemotherapy was significantly associated with risk of IBD flare (hazard ratio [HR], 2.00 [95% CI, 1.21–3.29] and 1.86 [95% CI, 1.01–3.43], respectively).[52] Of those in remission, only 42% of patients receiving hormone deprivation monotherapy compared with 75% receiving cytotoxic chemotherapy alone remained in remission on follow-up (250 months). Although further evidence is needed to clarify the impact of hormonal deprivation therapy on the development and disease course of IBD, patients diagnosed with cancers that are commonly treated with hormone deprivation therapy may be at increased risk for IBD disease reactivation and should be closely followed by a gastroenterologist.

Management of Patients with Inflammatory Bowel Disease with Prior Cancers

Patients with prior cancers are not well-represented in IBD clinical trials. Thus, data on the impact of IBD medications on incident cancers (new or recurrent) are limited. Although there is concern that IBD treatments may increase the risk of incident cancer, given the known association between malignancies and immunosuppressants,[53] recent data have not corroborated any increased risk.[53–55]

In the CESAME cohort, although incident cancer risk was higher among 405 patients with any previous cancer (HR, 1.9; 95% CI, 1.2–3.0), there was no significant association between exposure to immunomodulators and risk of new or recurrent cancer.[56] Similar findings for immunomodulators were confirmed by the Spanish Estudio Nacional en Enfermedad Inflamatoria intestinal sobre Determinantes genéticos y Ambientales (ENEIDA) registry.[57] In a multicenter study from the New York Crohn's and Colitis Organization, of 333 patients with a history of any cancer, 90 (27%) patients developed an incident cancer, but there was no difference in the risk of incident or recurrent cancer based on anti-TNF versus antimetabolites versus combination therapy versus no treatment.[55] Likewise, two recent meta-analyses that included 11,700[58] and 24,328[59] persons with immune-mediated diseases and a history of cancer showed no significant difference in cancer recurrence in patients receiving anti-TNF therapy, immunomodulators, or no immunosuppression.[59] A second meta-analysis showed that the pooled IRR of new or recurrent cancers among patients with a history of cancer exposed to anti-TNFs was no greater than for patients unexposed to anti-TNF with immune-mediated diseases or IBD.[60]

Studies of vedolizumab and ustekinumab exposure in patients with IBD have also confirmed no apparent incident cancer signal. In a study of 463 patients with IBD who had a prior cancer, there was no increase in the risk of incident cancer in patients exposed to vedolizumab versus anti-TNF agents versus no therapy (aHR, 1.38 [95% CI, 0.38–1.36] vs aHR, 1.03 [95% CI, 0.65–1.64], respectively).[61] Likewise, in another study of 390 patients with IBD and previous cancer, there was no incident cancer increase in the patients exposed to vedolizumab (aHR, 1.36; 95% CI, 0.27–7.01) or ustekinumab (aHR, 0.96; 95% CI, 0.17–5.41).[54]

Prospective data are so far lending further reassurance that IBD medications are not associated with a significant increased risk of incident cancer in patients with IBD and a history of a cancer. Preliminary data from the ongoing Safety of Immunosuppression in a Prospective Cohort of Inflammatory Bowel Disease Patients with a HIstoRy of CancEr (SAPPHIRE) registry confirm these findings.[62] Among 305 patients with IBD and a prior cancer, 210 (69%) were exposed to subsequent immunosuppressive therapy. During a median follow-up of 4.8 years, 46 (15%) patients developed subsequent cancers (25 new, 21 recurrent). In a proportional hazards model adjusting for demographic and clinical factors, no significant association was found between receipt of immunosuppression and incident cancer (aHR, 1.41; 95% CI, 0.69–2.90), or with any of the major drug classes. Further evidence is pending in the ongoing IBD, Cancer, and Serious Infection in Europe (I-CARE) registry, of 298 patients with a history of cancer exposed to anti-TNF agents or vedolizumab.[63]

Summary and Future Directions

Similar to patients without IBD, those with IBD are at similar risk for sporadic cancers and age-appropriate screening guidelines should be followed. Patients with IBD are at an increased risk of cancer from long-standing intestinal inflammation and/or the use of immunosuppressive therapies to treat IBD. As the population of patients with IBD ages, there is an increasing risk of cancer development. Many of these patients will require cancer treatment and many will require further treatment for their IBD. Much remains unknown regarding the interaction between IBD, IBD medications, and cancer treatment, and the risk of cancer recurrence in patients with IBD and a personal history of cancer. It is hoped that with further research and real-world experience, cancer risks in patients with IBD will be further elucidated as they relate to specific cancer types and specific drugs used to treat IBD.

References

1. Beaugerie L, Itzkowitz SH. Cancers complicating inflammatory bowel disease. N Engl J Med 2015;372:1441–1452.
2. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut 2001;48:526–535.
3. Axelrad JE, Lichtiger S, Yajnik V. Inflammatory bowel disease and cancer: the role of inflammation, immunosuppression, and cancer treatment. World J Gastroenterol 2016;22:4794–4801.
4. Bernstein CN, Blanchard JF, Kliewer E, et al. Cancer risk in patients with inflammatory bowel disease: a population-based study. Cancer 2001;91:854–862.
5. Lutgens MWMD, Oijen MGH van, Heijden GJMG van der, et al. Declining risk of colorectal cancer in inflammatory bowel disease: an updated meta-analysis of population-based cohort studies. Inflamm Bowel Dis 2013;19:789–799.
6. Choi C-HR, Rutter MD, Askari A, et al. Forty-year analysis of colonoscopic surveillance program for neoplasia in ulcerative colitis: an updated overview. Am J Gastroenterol 2015; 110:1022–1034.
7. Murthy SK, Feuerstein JD, Nguyen GC, et al. AGA clinical practice update on endoscopic surveillance and management of colorectal dysplasia in inflammatory bowel diseases: expert review. Gastroenterology 2021;161:1043–1051.e4.
8. Zhou RW, Harpaz N, Itzkowitz SH, et al. Molecular mechanisms in colitis-associated colorectal cancer. Oncogenesis 2023; 12:48.
9. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: an update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative of the International Organization for the Study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. Gastroenterology 2021; 160:1570–1583.
10. Askling J, Dickman PW, Karlén P, et al. Family history as a risk factor for colorectal cancer in inflammatory bowel disease. Gastroenterology 2001;120:1356–1362.
11. Cleveland NK, Rubin DT. Cancer prevention in patients with inflammatory bowel disease. Pract Gastroenterol 2021; 45:12–28.
12. Zheng H-H, Jiang X-L. Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and inflammatory bowel disease: a meta-analysis of 16 observational studies. Eur J Gastroenterol Hepatol 2016;28:383–390.
13. Axelrad JE, Olén O, Sachs MC, et al. Inflammatory bowel disease and risk of small bowel cancer: a binational population-based cohort study from Denmark and Sweden. Gut 2021; 70:297–308.
14. Bojesen RD, Riis LB, Høgdall E, et al. Inflammatory bowel disease and small bowel cancer risk, clinical characteristics, and histopathology: a population-based study. Clin Gastroenterol Hepatol 2017;15:1900–1907.e2.
15. Scharl S, Barthel C, Rossel J-B, et al. Malignancies in inflammatory bowel disease: frequency, incidence and risk factors-results from the Swiss IBD Cohort Study. Am J Gastroenterol 2019;114:116–126.
16. Sokol H, Beaugerie L, Maynadié M, et al. Excess primary intestinal lymphoproliferative disorders in patients with inflammatory bowel disease. Inflamm Bowel Dis 2012; 18:2063–2071.
17. Beaugerie L, Carrat F, Nahon S, et al. High risk of anal and rectal cancer in patients with anal and/or perianal Crohn's disease. Clin Gastroenterol Hepatol 2018;16:892–899.e2.
18. Ruel J, Ko HM, Roda G, et al. Anal neoplasia in inflammatory bowel disease is associated with HPV and perianal disease. Clin Transl Gastroenterol 2016;7:e148.

19. Erichsen R, Jepsen P, Vilstrup H, et al. Incidence and prognosis of cholangiocarcinoma in Danish patients with and without inflammatory bowel disease: a national cohort study, 1978-2003. Eur J Epidemiol 2009;24:513–520.
20. Lo B, Zhao M, Vind I, et al. The risk of extraintestinal cancer in inflammatory bowel disease: a systematic review and meta-analysis of population-based cohort studies. Clin Gastroenterol Hepatol 2021;19:1117–1138.e19.
21. Singh S, Talwalkar JA. Primary sclerosing cholangitis: diagnosis, prognosis, and management. Clin Gastroenterol Hepatol 2013; 11:898–907.
22. Greuter T, Vavricka S, König AO, et al. Malignancies in inflammatory bowel disease. Digestion 2020;101(Suppl 1):136–145.
23. Kappelman MD, Farkas DK, Long MD, et al. Risk of cancer in patients with inflammatory bowel diseases: a nationwide population-based cohort study with 30 years of follow-up evaluation. Clin Gastroenterol Hepatol 2014;12:265–273.e1.
24. Long MD, Martin CF, Pipkin CA, et al. Risk of melanoma and nonmelanoma skin cancer among patients with inflammatory bowel disease. Gastroenterology 2012;143:390–399.e1.
25. Khan N, Patel D, Trivedi C, et al. Repeated occurrences of basal cell cancer in patients with inflammatory bowel disease treated with immunosuppressive medications. Am J Gastroenterol 2020;115:1246–1252.
26. 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; 141:1621–1628.e1.
27. 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 2015;13:847–858.e4; quiz e48.
28. 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;9:36–41.e1.
29. Khan N, Patel D, Trivedi C, et al. Incidence of acute myeloid leukemia and myelodysplastic syndrome in patients with inflammatory bowel disease and the impact of thiopurines on their risk. Am J Gastroenterol 2021;116:741–747.
30. Bourrier A, Carrat F, Colombel JF, et al. Excess risk of urinary tract cancers in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Aliment Pharmacol Ther 2016;43:252–261.
31. Pasternak B, Svanström H, Schmiegelow K, et al. Use of azathioprine and the risk of cancer in inflammatory bowel disease. Am J Epidemiol 2013;177:1296–1305.
32. Goetgebuer RL, Kreijne JE, Aitken CA, et al. Increased risk of high-grade cervical neoplasia in women with inflammatory bowel disease: a case-controlled cohort study. J Crohns Colitis 2021;15:1464–1473.
33. Kreijne JE, Goetgebuer RL, Erler NS, et al. Cumulative exposure to immunomodulators increases risk of cervical neoplasia in women with inflammatory bowel disease. Aliment Pharmacol Ther 2023;58:207–217.
34. Gordon H, Biancone L, Fiorino G, et al. ECCO guidelines on inflammatory bowel disease and malignancies. J Crohns Colitis 2023;17:827–854.
35. 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; 311:2406–2413.
36. Esse S, Mason KJ, Green AC, et al. Melanoma risk in patients treated with biologic therapy for common inflammatory diseases: a systematic review and meta-analysis. JAMA Dermatol 2020;156:787–794.
37. Lemaitre M, Kirchgesner J, Rudnichi A, et al. Association between use of thiopurines or tumor necrosis factor antagonists alone or in combination and risk of lymphoma in patients with inflammatory bowel disease. JAMA 2017;318: 1679–1686.
38. Yang C, Huang J, Huang X, et al. Risk of lymphoma in patients with inflammatory bowel disease treated with anti-tumour necrosis factor alpha agents: a systematic review and meta-analysis. J Crohns Colitis 2018;12:1042–1052.
39. Dahmus J, Rosario M, Clarke K. Risk of lymphoma associated with anti-TNF therapy in patients with inflammatory bowel disease: implications for therapy. Clin Exp Gastroenterol 2020; 13:339–350.
40. Osterman MT, Sandborn WJ, Colombel J-F, et al. Increased risk of malignancy with adalimumab combination therapy, compared with monotherapy, for Crohn's disease. Gastroenterology 2014; 146:941–949.
41. Ytterberg SR, Bhatt DL, Mikuls TR, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. N Engl J Med 2022;386:316–326.
42. Russell MD, Stovin C, Alveyn E, et al. JAK inhibitors and the risk of malignancy: a meta-analysis across disease indications. Ann Rheum Dis 2023;82:1059–1067.
43. Curtis JR, Lee EB, Kaplan IV, et al. Tofacitinib, an oral Janus kinase inhibitor: analysis of malignancies across the rheumatoid arthritis clinical development programme. Ann Rheum Dis 2016; 75:831–841.
44. Holmer AK, Luo J, Russ KB, et al. Comparative safety of biologic agents in patients with inflammatory bowel disease with active or recent malignancy: a multi-center cohort study. Clin Gastroenterol Hepatol 2023;21:1598–1606.e5.
45. Bellaguarda E, Hanauer S. Checkpoint inhibitor-induced colitis. Am J Gastroenterol 2020;115:202–210.
46. Ribas A, Hamid O, Daud A, et al. Association of pembrolizumab with tumor response and survival among patients with advanced melanoma. JAMA 2016;315:1600–1609.
47. Hashash JG, Francis FF, Farraye FA. Diagnosis and management of immune checkpoint inhibitor colitis. Gastroenterol Hepatol (NY) 2021;17:358–366.
48. Abdel-Rahman O, ElHalawani H, Fouad M. Risk of gastrointestinal complications in cancer patients treated with immune checkpoint inhibitors: a meta-analysis. Immunotherapy 2015; 7:1213–1227.
49. Dougan M, Wang Y, Rubio-Tapia A, et al. AGA clinical practice update on diagnosis and management of immune checkpoint inhibitor colitis and hepatitis: expert review. Gastroenterology 2021;160:1384–1393.
50. Meserve J, Facciorusso A, Holmer AK, et al. Systematic review with meta-analysis: safety and tolerability of immune checkpoint inhibitors in patients with pre-existing inflammatory bowel diseases. Aliment Pharmacol Ther 2021;53:374–382.
51. Axelrad JE, Fowler SA, Friedman S, et al. Effects of cancer treatment on inflammatory bowel disease remission and reactivation. Clin Gastroenterol Hepatol 2012;10:1021–1027.e1.

52. Axelrad JE, Bazarbashi A, Zhou J, et al. Hormone therapy for cancer is a risk factor for relapse of inflammatory bowel diseases. Clin Gastroenterol Hepatol 2020;18:872–880.e1.
53. Holmer A, Singh S. Overall and comparative safety of biologic and immunosuppressive therapy in inflammatory bowel diseases. Expert Rev Clin Immunol 2019;15:969–979.
54. Hong SJ, Zenger C, Pecoriello J, et al. Ustekinumab and vedolizumab are not associated with subsequent cancer in IBD patients with prior malignancy. Inflamm Bowel Dis 2022;28:1826–1832.
55. Axelrad J, Bernheim O, Colombel J-F, et al. Risk of new or recurrent cancer in patients with inflammatory bowel disease and previous cancer exposed to immunosuppressive and antitumor necrosis factor agents. Clin Gastroenterol Hepatol 2016;14:58–64.
56. Beaugerie L, Carrat F, Colombel J-F, et al. Risk of new or recurrent cancer under immunosuppressive therapy in patients with IBD and previous cancer. Gut 2014;63:1416–1423.
57. Mañosa M, Chaparro M, Juan A, et al. Immunomodulatory therapy does not increase the risk of cancer in persons with inflammatory bowel disease and a history of extracolonic cancers. Am J Gastroenterol 2019;114:771–776.
58. Gupta A, Peyrin-Biroulet L, Ananthakrishnan AN, et al. Risk of Cancer Recurrence in Patients With Immune-Mediated Diseases With Use of Immunosuppressive Therapies: An Updated Systematic Review and Meta-Analysis. Clin Gastroenterol Hepatol 2024;Mar22(3):499–512.e6.
59. Shelton E, Laharie D, Scott FI, et al. Cancer recurrence following immune-suppressive therapies in patients with immune-mediated diseases: a systematic review and meta-analysis. Gastroenterology 2016;151:97–109.e4.
60. Micic D, Komaki Y, Alavanja A, et al. Risk of cancer recurrence among individuals exposed to antitumor necrosis factor therapy: a systematic review and meta-analysis of observational studies. J Clin Gastroenterol 2019;53:e1–e11.
61. Vedamurthy A, Gangasani N, Ananthakrishnan AN. Vedolizumab or tumor necrosis factor antagonist use and risk of new or recurrent cancer in patients with inflammatory bowel disease with prior malignancy: a retrospective cohort study. Clin Gastroenterol Hepatol 2022;20:88–95.
62. Itzkowitz SH, Jiang Y, Villagra C, et al. Safety of immunosuppression in a prospective cohort of inflammatory bowel disease patients with a history of cancer: SAPPHIRE registry. Clin Gastroenterol Hepatol 2024. Article in Press.
63. Peyrin-Biroulet L, Rahier J-F, Kirchgesner J, et al. I-CARE, a European prospective cohort study assessing safety and effectiveness of biologics in inflammatory bowel disease. Clin Gastroenterol Hepatol 2023;21:771–788.e10.

Correspondence
Address correspondence to: Jordan E. Axelrad, MD, MPH, Inflammatory Bowel Disease Center at NYU Langone Health, 305 East 33rd Street, New York, New York 10016. e-mail: Jordan.Axelrad@nyulangone.org.

Conflicts of interest
The authors disclose the following: Jordan Axelrad has received research grants from BioFire Diagnostics and Genentech; and consultancy fees, advisory board member, or honorarium from BioFire Diagnostics, Adiso, Bristol-Myers Squibb, AbbVie, Pfizer, Fresnius, Ferring, and Janssen. Jana G. Hashash has served as a Consultant/Advisory Board Member for Bristol-Myers Squibb. Steven Itzkowitz has received research grants from Freenome and Exact Sciences Corporation; and consulting fees from Exact Sciences Corporation and Geneoscopy.

Funding
Jordan Axelrad has received support from the Crohn's and Colitis Foundation, the Judith Stewart Colton Center for Autoimmunity, and the NIH NIDDK Diseases K23DK124570. Steven Itzkowitz has received support from New York Crohn's and Colitis Organization.