

Current Treatment Strategies for Inflammatory Bowel Disease Patients at the Risk of Developing Cancer: A Comprehensive Review

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J Coloproctol 2023;43(3):e227–e234.

Abstract

Inflammatory bowel disease (IBD) is a chronic condition that affects the digestive tract and can lead to inflammation and damage to the intestinal lining. IBD patients with cancer encounter difficulties since cancer treatment weakens their immune systems. A multidisciplinary strategy that strikes a balance between the requirement to manage IBD symptoms and the potential effects of treatment on cancer is necessary for effective care of IBD in cancer patients. To reduce inflammation and avoid problems, IBD in cancer patients is often managed by closely monitoring IBD symptoms in conjunction with the necessary medication and surgical intervention. Anti-inflammatory medications, immunomodulators, and biologic therapies may be used for medical care, and surgical options may include resection of the diseased intestine or removal of the entire colon. The current study provides a paradigm for shared decision-making involving the patient, gastroenterologist, and oncologist while considering recent findings on the safety of IBD medicines, cancer, and recurrent cancer risk in individuals with IBD. We hope to summarize the pertinent research in this review and offer useful advice.

Keywords

- ▶ Inflammatory bowel disorder
- ▶ Cancer
- ▶ treatment
- ▶ malignancy
- ▶ Anti-TNF
- ▶ therapy
- ▶ risks
- ▶ inflammation
- ▶ immunosuppression

Introduction

Inflammatory Bowel Disorder is a chronic disorder which causes inflammation of the inner lining of our digestive tract. The disorder consists mainly of two conditions: Crohn's disease (CD) and Ulcerative colitis (UC).¹ However, the signs and symptoms of these two conditions are almost the same and the difference lies in their severity. Crohn's disease causes inflammation of any part of the gastrointestinal tract. The typical symptoms of patients diagnosed with CD include abdominal pain, diarrhea, bloating, nausea, vomiting and weight loss and if left undiagnosed with

time it can develop into fibrous fistulas. Malnourishment and growth retardation are the commonly observed symptoms in young patients of CD. Unlike CD, Ulcerative colitis causes severe inflammation of the mucosal and sub mucosal lining of colon and rectum and is restricted to that area only. Bloody stools, mild diarrhea 4 times a day which might increase up to 6 times with the progression in the severity of disease are the most observed symptoms of UC. Each condition has the potential to raise the risk of colorectal cancer.² In 2021, IBD affected more than 6 million people worldwide, with almost 1 in 4 of these patients living in the US. In the Middle East, Southeast Asia, and the Asia Pacific,

received

April 30, 2023

accepted after revision

June 21, 2023

DOI <https://doi.org/>

10.1055/s-0043-1772787.

ISSN 2237-9363.

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Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

the incidence of inflammatory bowel disease (IBD) is increasing annually due to changes in diet and environment, urbanization, and other factors. In Taiwan, India, and China, the prevalence of Crohn's disease increased from 0.6 per 100,000 to 3.9 per 100,000 between 2010 and 2020, while the prevalence of UC increased from 2.1 per 100,000 to 12.8 per 100,000 between 2007 and 2019.³

One in two people will develop some form of cancer during their lifetimes, making cancer the second biggest cause of mortality in the world (behind cardiovascular disorders). To preserve and improve quality of life and prevent the development of disease-related problems, such as cancer, IBD requires the best long-term treatment possible.⁴ The primary cause of morbidity and mortality associated with IBD is colorectal cancer, and colorectal cancer incidence is rising in developing nations as a result of their westernized lifestyles, which include insufficient physical activity, obesity, alcohol consumption, smoking, and consumption of red and processed meat.⁵ According to certain cohort and case control studies, some IBD-related malignancies are brought on by immunosuppressive medications such thiopurines or anti-TNF rather than by intestinal inflammation.⁶ The development of better treatment choices and surveillance measures has been linked to an increase in IBD-related cancer incidence and prevalence during the past few years (Jess et al., 2013). New biological medications have also been made available for clinical use, which has fundamentally altered how IBD is managed over the long term. Therefore, this review article focuses on the (1) Current IBD therapies which are associated with cancer risk (2) IBD related malignancies (3) Molecular pathophysiology of IBD related Colorectal cancer (4) Treatment decision for patient with prior history of cancer (5) Treatment decision for patients with active cancer. The development of better treatment choices and surveillance measures has been linked to an increase in IBD-related cancer incidence and prevalence during the past few years.

Current IBD Therapies Associated with Cancer Risk

Anti-TNF's

Most of the recent research focuses on cancer patients who have received anti-TNF treatment.⁷ TNF is a desirable therapeutic target in immune-mediated inflammatory diseases due to its crucial role in triggering the proinflammatory cascade.⁸ TNF can both promote and inhibit tumor growth, so it might be challenging to predict whether people who get anti-TNFs will develop cancer. Early research revealed a marginally elevated risk of lymphoma with anti-TNF use.⁹ However, a later systematic review discovered that with monotherapy, this was not the case. There is an elevated risk of lymphoma when combined with thiopurines.¹⁰ Patients with prior cancer who received anti-TNF therapy did not significantly increase their risk of developing new or recurrent cancer when compared to controls, according to a systematic review and meta-analysis of observational studies.¹¹

Methotrexate

Both as an antineoplastic agent and an anti-inflammatory, methotrexate is frequently utilized. In a study comparing the efficiency of various rheumatoid arthritis disease-modifying medications, methotrexate was found to have a higher risk of cancer than TNF antagonists, but a lower risk than thiopurines.¹² However, a second retrospective investigation found methotrexate to be a risk factor for lymphoproliferative diseases.¹³ Patients receiving methotrexate for psoriasis and rheumatoid arthritis have a slightly increased chance of developing melanoma and melanoma skin malignancies.¹⁴ However, this risk was not observed in methotrexate treated IBD patients.¹⁵

Thiopurines

Thiopurines demonstrate anti-inflammatory properties through T-cell inhibition (Monaco et al., 2015). They are mutagenic because they impede DNA repair mechanisms and cause somatic mutations.¹⁶ They disrupt the DNA repair process, cause somatic mutations, and are hence considered to be mutagenic.¹⁷ The tumor suppressor genes are also altered by them. Thiopurines were linked to a considerably higher incidence of non-lymphoma Hodgkin's and leukemia, according to a recent retrospective analysis.¹⁸ With an odds ratio (OR) of 3.22, a nested case control study from UK24 revealed a comparable low incidence of lymphoma in thiopurine-treated IBD patients.¹⁹ Thiopurines may increase a person's susceptibility to skin cancer by making DNA more sensitive to UV light.²⁰ In multiple cohort studies, thiopurine treatment in IBD patients has also been linked to an increased incidence of skin malignancies, notably non-melanoma skin cancer (NMSCs).^{21,22} All the malignancies associated with the usage of these drugs are depicted in ► Fig. 1.

IBD Related Malignancies

IBD related malignancies are classified into two types which is depicted in ► Fig. 2.

Immunosuppression Related Malignancies

By changing DNA, lowering immune monitoring of cancer or dysplastic cells, and affecting immune control of chronic infection by mutagenic viruses, immunosuppressive drugs have the potential to trigger tumor growth.^{16,17,23}

Cervical Cancer

Cervical cancer rates in women with IBD have been found to be higher in a small number of studies. HPV infection is frequently linked to cervical cancer. But it's still not clear whether this is because of an inherent danger or because of immunosuppression.⁶ Cervical cancer rates have generally been declining over the past few decades because of widespread adoption of screening techniques. Additionally, clinical practice has widely used HPV vaccination. All Swiss women between the ages of 11 and 14 are strongly advised to have this immunization. The vaccination of women up to the age of 26 is advised. As part of the cantonal vaccination

Cancer Drugs	Lymphoma	Melanoma	NMSC	Lung cancer	Breast cancer
Thiopurine	Potential risk	Potential risk	Very high risk	Potential risk	Potential risk
Methotrexate	Very low risk	Very low risk	Very low risk	Potential risk	Potential risk
Anti-TNFs	Very low risk	Very high risk	Potential risk	No risk	No risk



Fig. 1 Malignancy risk of drugs used for IBD. Sebastian S, Neilaj S. Practical guidance for the management of inflammatory bowel disease in patients with cancer. Which treatment? Therapeutic Advances in Gastroenterology. 2019 Jan; 12:1756284818817293.

program, all expenses are entirely reimbursed. Given the well-established and undeniable link between HPV infection and the onset of cervical cancer, women with IBD who fall into this age group should be especially encouraged to get vaccinated. Additionally, they should visit their gynecologist every one to two years. Men experience HPV-related infections less commonly than women do. However, male participants should be advised to get vaccinated against HPV.

Urinary Tract Cancer

Kidney and bladder cancer rates have been linked to the use of thiopurines in transplant patients.²⁴ Similar results in the IBD population have also been demonstrated, but the risk is almost exclusively limited to older guys, particularly smokers.²⁵ When anti-TNF was used, no such rise was noticed.²⁶ Thiopurines shouldn't be used in people who require immunosuppressive medication and have a history of urogenital

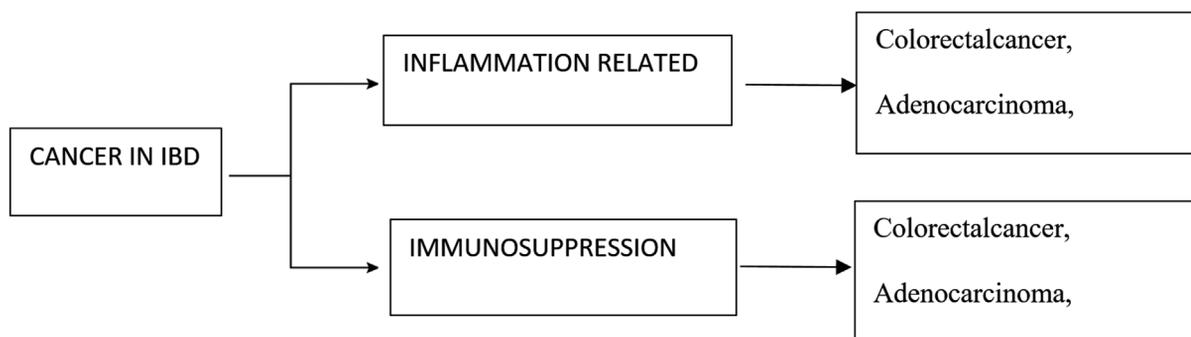


Fig. 2 Classification of IBD in cancer patients. Sebastian S, Neilaj S. Practical guidance for the management of inflammatory bowel disease in patients with cancer. Which treatment? Therapeutic Advances in Gastroenterology. 2019 Jan; 12:1756284818817293.

malignancy. It is yet unclear what function screening techniques, such as urine cytology and/or cystoscopy, play in individuals receiving thiopurine medication.

Inflammation-related Malignancies

Intestinal Lymphoma

IBD patients may experience lymphomas in the intestine at a frequency of up to 10-48.3 per 100,000 patient years, albeit they are often uncommon.^{27,28} In fact, compared to the overall population, IBD patients seem to have a 3-fold increase.²⁷ IBD-related lymphomas are typically B-cell non-Hodgkin subtypes and are present in intestinal lesions that are continuously inflamed.^{6,28} Intestinal lymphoma is predisposed to by three factors: (1) severe inflammation; (2) middle-aged men; and (3) protracted disease duration (>8 years).²⁸ Because EBV is frequently found in intestinal lymphoma cells and has been linked to other lymphoma subtypes, inflammation promoted EBV replication is believed to be a major factor in this form of malignancy.²⁹

Anal Carcinoma

The screening for anal malignancies by gastroenterologists can be reluctant. For the tumor to be found, a thorough rectal examination is necessary. Males who have sex with males, females with high grade cervical dysplasia, and the presence of fistula in patients with long-standing perianal CD are among the risk factors, despite the low incidence (0.01-0.02/1,000).^{6,30} The frequency rises to 0.38 per 1,000 patient years in the latter.⁶ Malignancies emerging from fistulas can be either adenocarcinoma or squamous cell carcinoma, whereas anal cancers are typically of squamous epithelial origin and associated with HPV infection.³¹ There is no connection between these malignancies and HPV infection. Anal carcinoma usually has a dismal prognosis.

Colorectal Cancer

The third most frequent cancer kind worldwide is colorectal cancer.³² The uncontrolled division and survival of aberrant cells in the colon or rectum is its defining features. Genetics, IBD, diabetes, insufficient exercise, obesity, alcohol use, smoking, and consumption of red and processed meat are the main risk factors for CRC. CRC typically starts as a slow-growing polyp, a noncancerous growth that appears on the inner surface of the colon or rectum and develops over the course of 10 to 20 years. The most typical kind is an adenoma, or adenomatous polyp. The glandular cells that create the mucus that lubricates the colorectum give birth to adenomas. One or more adenomas will eventually form in about one-third to one-half of the people. Less than 10% of adenomas are thought to evolve to invasive carcinoma, even though all of them have the potential to develop into cancer. The larger an adenoma, the greater the chance that it may develop into cancer. Adenocarcinoma, which makes up around 96% of all CRCs, is a type of cancer that develops from the lining of the colorectum. There are no indications of early CRC. As the tumor spreads, it may bleed or block the intestine, cause anemia, weakness, extreme exhaustion, and

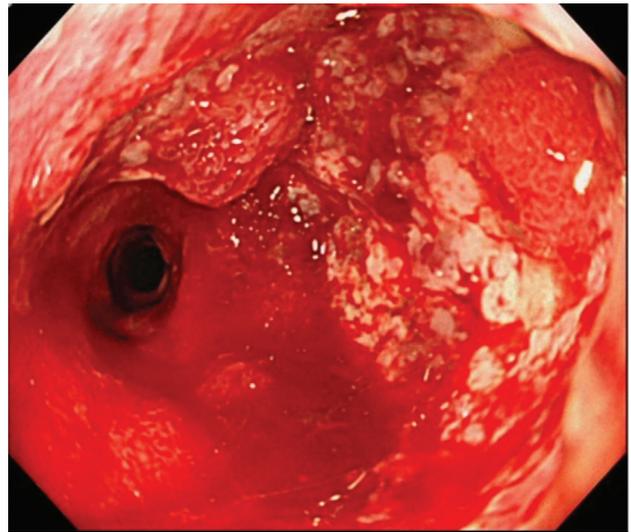


Fig. 3 53-year-old man diagnosed with tumor in the lower rectum. Wadehra A, Alkassis S, Rizwan A, Yazdanpanah O. Rectal invasion by metastatic prostate adenocarcinoma. *Cureus*. 2021 Jun 10;13(6).

occasionally shortness of breath. It may also cause bleeding from the rectum, blood in the stool or in the bathroom after having a bowel movement, dark or black stools, changes in bowel habits or the shape of the stool, cramping or discomfort in the lower abdomen, or the urge to urinate when the bowel is empty.³³ A photograph of typical tumor in the lower rectum diagnosed in 53-year-old man is depicted in **–Figs 3 and 4**.

Molecular Pathophysiology of IBD-CRC

The following is a summary of the causes of neoplastic alterations in IBD: oxidative stress, intestinal microbiota, mucosal inflammatory mediators as immunological responses, genetic instability, epigenetic modification, and immune response.^{34–36}

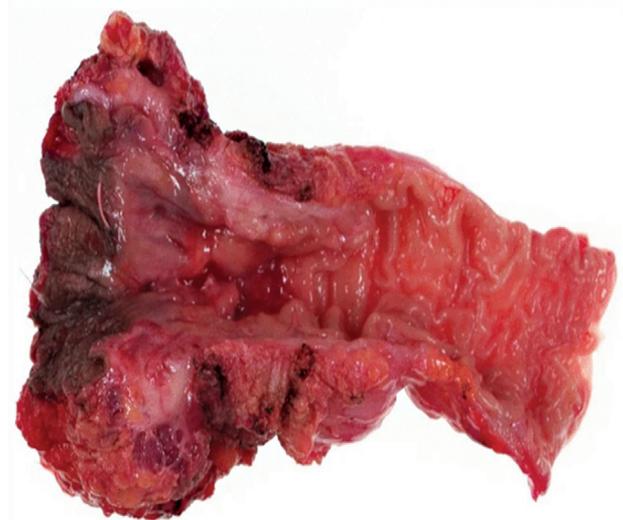


Fig. 4 Tumor of 20mm detected macroscopically in the lower rectum. Asfaw MH, Adidam S, Aduli F, Kibreab A, Asemota J.

Multifocal dysplasia frequently precedes the development of colitis mucosal cancer, demonstrating a “field change effect.”³⁷ Long-standing UC is associated with aneuploidy, a sign of genomic instability, which is found at 20%–50% in dysplastic lesions and 50%–90% in malignancies.^{38,39} Since aneuploidy is frequently more prevalent than dysplasia in IBD, significant genetic changes must take place in the colonic mucosa without affecting its appearance.³⁷

The two major types of genomic instability found in CRCs are chromosomal instability (CIN) and microsatellite instability (MSI).⁴⁰ The loss of P53 function is a critical stage in the development of cancer linked to colitis. MSI has been observed to develop in IBD-associated CRC at varying frequency due to poor DNA mismatch repair.^{41–43} The activation of cyclooxygenase (COX)-2, inflammatory cytokines, and chemokines are other crucial components in the development of CRC in IBD. According to some data, NSAIDs reduce the risk of CRC in IBD patients by 40%–50%.^{35,44} NSAIDs affect COX enzymes, which then has an effect. One of the three COX enzyme isoforms, COX-2, is stimulated by inflammation and activated by inflammatory mediators such as IL-1, IFN, and TNF.³⁵ Previous research has revealed that 85% of adenocarcinomas and approximately 50% of adenomas express higher levels of COX-2.^{45,46} According to reports, UC-associated neoplasia exhibits early overexpression of COX-2 messenger RNA and COX-2 protein. Activated macrophages and T cells release TNF-, which binds to the TNF-receptor (TNF-R) and has been shown to cause inflammation and colitis-related malignancies.³⁴

By damaging proteins and nucleic acids and causing denaturation and a number of changes, such as base modifications, double-base lesions, and strand breaks, oxidative stress also aids in the aetiology of colon cancer.⁴⁷ Increased expression of NOS and ROSs is seen in inflamed tissues from patients with active UC or CD.⁴⁷ ROSs can interact with key genes involved in carcinogenic pathways such as *P53* and DNA mismatch repair genes.⁴¹

The development of colitis-related cancer may be influenced by commensal or particular bacteria, according to several different mouse models of IBD. For instance, IBD (mainly colon and rectum) caused by *Enterococcus faecalis*, as well as rectal dysplasia and cancer, were seen in IL-10 knock-out animals.⁴⁸ All IL-10 gene knockout mice under pathogen-free settings developed colitis after 3 months of age, and CRC was seen in 25% and 60% of the mice after 3 and 6 months, respectively.⁴⁹ Colon cancer incidence and mucosal inflammatory activity were both decreased in IL-10 knockout mice with altered enteric flora caused by probiotic lactobacilli.⁵⁰

Making Treatment Decisions

Treatment Decision in Patients with Prior History of Cancer

When compared to people without a history of cancer, patients with IBD have a twofold greater chance of developing a new or recurring cancer, however this risk has been demonstrated to be unrelated to medicine use.⁶ Anti-TNF

medication and the newer biologics do not seem to be linked to an increased risk of new or recurring malignancy in IBD, according to recent data that appear to be generally supportive of this claim.⁵¹ Compared to conventional immunosuppression, anti-TNF, and no immunosuppression, patients receiving thiopurines experienced a rise in non-melanoma skin cancer, but no increased risk of cancer recurrence overall.⁵² Guidelines from the European Crohn's Colitis Organization (ECCO) suggested that it might be overly cautious, especially when considering the possibility of not treating IBD properly. The BSG 2019 IBD recommendation emphasizes that biologics shouldn't be disregarded in patients who have had past cancer and instead recommends making individualized selections.⁵³ According to observational studies, people with IBD who have had cancer in the past do not appear to have a noticeably higher risk of developing new or recurring cancer. Following a cancer diagnosis, IBD treatment decisions are difficult to make because they must consider the type of cancer, its natural history, the time between the cancer diagnosis and the end of treatment, the need for the IBD treatment decision, the severity and prognosis of the IBD, as well as any available alternatives to biologics and immunosuppressants. Immunosuppressants and anti-TNF treatment should typically be postponed for at least 2 years in patients with a history of cancer; the postponement should be increased to 5 years in patients with cancers with a high risk of recurrence, such as cancers of the urinary tract, endometrial cancer, melanoma, and lung cancer. In situations of past EBV-related lymphoma, human papillomavirus-related carcinoma, or urinary tract cancer, thiopurines should be avoided. For cancers with an intermediate or high risk of recurrence, such as those of the urinary system, the gastrointestinal tract, leukaemia, and multiple myeloma, the ECCO consensus guidance on this topic advises waiting 2 years before beginning immunosuppressive and maybe up to 5 years.

Treatment Decisions in Patients with Active Cancer

When a new malignancy is discovered, most doctors will change the way that IBD is managed, especially by stopping immunosuppressants and using anti-TNF medications less frequently.⁵⁴ However, more evidence suggests that patients with active IBD at the time of their cancer diagnosis may benefit from cytotoxic medication for the treatment of their disease and experience remission.^{55,56} Based on expert opinion statements and treatment guidelines reporting the theoretical concern about worsening cancer outcomes, amino salicylates (5ASAs) and steroids are considered as the first option if the IBD is not well controlled despite the chemotherapy for the active cancer, and anti TNFs are considered as second-line therapy in non-responders.^{13,57} IBD treatment may influence how malignancies develop. Immunosuppressants (azathioprine, methotrexate) and anti-TNFs have been discovered to negatively affect disease-free survival and overall survival in colorectal cancer.^{58,59} However, there is no link between the malignancies and lymphomas that develop after anti-TNF therapy and a worse diagnostic stage or worse prognosis. Withholding anti-TNFs in this

situation is advised by expert guidelines because several studies of individuals with active or recent myeloma found a risk of progression to invasive melanomas when anti-TNFs were used (Annese et al., 2015). It is unclear whether methotrexate has comparable problems with tumor prognosis or tumor progression. Methotrexate use did not appear to affect lymphoma-specific survival, but the prognosis was less favorable than for lymphoma in the general population. However, substantial dosages of methotrexate are currently utilized to treat some malignancies, such as breast and urinary tract tumors. Withholding thiopurines during active cancer treatment is totally fair given the potential hazards associated with DNA alterations and myelosuppression.¹³ Because of their impact on the tumor and symptoms associated with it, oncologists frequently opt to use corticosteroids as a first line treatment once an IBD flare has been diagnosed. However, there is some evidence that suggests that steroids may also increase tumor cells' resistance to apoptosis and decrease immune surveillance. Additionally, some population-based studies indicate a higher risk of nonmelanoma lymphomas in people on extended corticosteroids, but it's unclear whether this risk is connected to how severe the underlying IBD is.^{59,60} Despite this, corticosteroids are generally considered to be a safer alternative to immunosuppressants. Anti-TNFs may currently serve as a fallback option, notwithstanding the lack of comparable trials comparing steroids and anti-TNFs in the therapy of uncontrolled IBD in cancer patients receiving treatment. Following cancer therapy, 5ASAs and enteral nutrition may be possibilities for milder illness flare-ups.

Future Perspectives

For the prevention and early identification of cancer in the general population as well as IBD patients, tumor screening programs are crucial and effective tools. Data on their effectiveness, however, come from retrospective case-control studies and case series. There are still no randomized controlled trials demonstrating a definite advantage of colonoscopy in IBD. It has been shown that chromoendoscopy combined with focused biopsies increases the rate of dysplasia identification. Uncertainty surrounds the function of more recent technologies like endomicroscopy and narrow-band imaging. To determine their position in the screening algorithm, trials are necessary. More research is required to determine the best screening methods for cancers of the urinary tract, small bowel, and cholangiocarcinoma. It will be fascinating to determine whether IBD phenotypes are particularly at risk for cancer subtypes from the perspective of customized treatment. In the future, this will make it easier to individually adapt both screening recommendations and therapy approaches.

Summary and Conclusions

IBD is still linked to cancer formation because it causes persistent intestinal inflammation and the use of potentially carcinogenic medications, despite newer research and meta-analyses casting doubt on the excess rates of cancer in IBD

patients. Thiopurines and anti-TNF have been demonstrated to be particularly effective in the latter. Clinicians have historically been reluctant to start immunosuppressive and biological therapy in patients with current cancer or a history of cancer because clinical guidelines based on expert consensus frequently recommend significant restrictions in medications, such as immunosuppression and biologics. Patients should be informed of the elevated risk of cancer associated with IBD and IBD medications. They should also be made aware that most cancer subtypes may be avoided with the right screening methods. Concerns among patients receiving anti-TNFs or thiopurines are being further evaluated as part of the ongoing prospective IBD Cancer and Serious Infections in Europe project. We'll have to wait and see how many patients have had past malignancies. Long-term prospective trials with representative patients are ultimately required.

Sl no.	Abbreviation	Expansion
1	IBD	Inflammatory bowel disease
2	UC	Ulcerative colitis
3	CD	Crohn's disease
4	TNF	Tumor necrosis factor
5	NMSC	Non melanoma skin cancer
6	EBV	Epstein barr virus
7	CRC	Colorectal cancer
8	NOS	Nitric oxide synthetase
9	ROS	Reactive oxygen species

Conflict of Interest

The authors declare no conflict of interest.

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