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Managing inflammatory bowel disease in patients receiving cancer-associated chemotherapy and beyond

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Abstract

Managing patients with inflammatory bowel disease (IBD) and a current or previous history of cancer is becoming increasingly common. This scoping review aims to provide an up-to-date overview of the available literature on the management of IBD in cancer patients, including those in remission and those undergoing active cancer treatment. This scoping review was conducted, using PubMed, EMBASE and Scopus, to identify studies on IBD management in adult patients with active or prior malignancy, published between January 2019 and July 2024. Search terms included "inflammatory bowel disease" and "malignancy". Thirty-three studies met the criteria for inclusion; most were retrospective cohort studies. Seventeen studies analyzed incident risk of new or recurrent malignancy after starting IBD medications in patients with prior cancer. Most of these studies suggest a limited risk of cancer recurrence after restarting IBD medications. The remaining studies looked at IBD patients receiving active cancer therapy, assessing the risk of IBD relapse and/or the side effects of cancer therapy in IBD patients. Most IBD patients treated with cytotoxic chemotherapy did not experience relapse of IBD activity during therapy. However, those on either hormonal chemotherapies or immune checkpoint inhibitors were more likely to experience IBD relapse, although the data are inconsistent. This review highlights the limited cancer recurrence risk associated with IBD therapies in cancer patients. Individualized, multidisciplinary approaches are essential for managing IBD in patients with a history of cancer. Future research should prioritize large-scale prospective studies to guide IBD and cancer management.

Keywords Inflammatory bowel disease, neoplasms, chemotherapy, biological products, scoping review

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Introduction

Managing inflammatory bowel disease (IBD) in patients with active or prior cancer is particularly challenging, given the limited availability of safety and efficacy data for this population. Patients with malignancy are often excluded from clinical trials, and available safety and efficacy data for therapies in this population are frequently derived from small observational studies conducted years after market entry. These limited studies [1,2] suggest that the immunosuppressive effects of cytotoxic chemotherapy improve IBD activity and highlight the higher risks of IBD flare in those IBD patients on hormonal cancer therapies. However, these studies have large confidence intervals (CI) due to their small size, resulting in uncertainty surrounding their conclusions.

In regard to IBD medications in those with a prior history of cancer, one of the first guidelines on the topic, published by the European Crohn's and Colitis Organisation (ECCO) in 2015 [3], and a subsequent review article [4], recommended delaying immunosuppressant and anti-tumor necrosis factor (TNF) agents for at least 2 years after cancer diagnosis, and up to 5 years for high-recurrence cancers. This recommendation was mostly based on a study by Penn [5], which showed that immunosuppressed renal transplant patients with a prior diagnosis of cancer had the highest recurrence (54%) in the 2 years following completion of chemotherapy, decreasing progressively thereafter (33% at 2-5 years and 13% after

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5 years). Although Penn's study was limited by its retrospective design, and its population did not include IBD patients, its findings influenced early guideline recommendations. The extensive range of biologics, especially gut-selective therapies, adds further complexity to extrapolating Penn's conclusions to IBD patients. The most recent ECCO 2023 guidelines [6] no longer recommended a 5-year delay in restarting IBD therapy post-cancer, reflecting the distinct cancer risk factors of the IBD population compared to renal transplant recipients.

This review provides a comprehensive analysis of current evidence to help manage IBD in patients with a previous or current history of cancer. While a systematic review answers a focused question through critical appraisal, a scoping review maps the breadth of the existing literature, allowing identification of knowledge gaps and guidance of future research. A scoping review was also considered the most appropriate methodology, given the heterogeneity of studies, and the range of malignancies, treatments and outcomes measured.

Materials and methods

This scoping review was conducted in line with the JBI Evidence Synthesis recommendations and is reported according to Preferred Reporting Items for Systematic Reviews and Meta- Analyses for Scoping Reviews (PRISMA-ScR) standards.

Selection criteria

Inclusion criteria: (a) conducted on adult humans; (b) published as abstracts or full articles in peer-reviewed journals; (c) focused on IBD management in patients with active or prior malignancy; and (d) observational studies, systematic reviews or meta-analyses.

Exclusion criteria: (a) literature reviews, consensus guidelines, animal or *in vitro* studies; (b) organ transplant-focused outcomes; (c) surgical or radiation-only treatment modalities; (d) case reports or studies with fewer than 20 IBD patients; (e) insufficiently reported results; and (f) duplicate or outdated publications (only the most up to date were retained).

Search strategy

We conducted a comprehensive systematic search of PubMed, Embase and Scopus from January 1, 2019, to July 31, 2024, using both free-text terms and Medical Subject Headings (MeSH). The search period was intentionally limited to this period to focus on the most relevant studies, given the recent advancements in treatment modalities for IBD. To ensure inclusion of relevant studies, we used key terms such as "inflammatory bowel disease", "malignancy", and "tumor necrosis factor inhibitors", as further detailed in Supplementary Table 1.

Additionally, a manual search was conducted by scanning the reference lists of included studies and relevant reviews. Studies were included based on the relevance of their content, without bias towards the author or journal. Two authors (ST and CRF) independently screened all studies by title and abstracts to exclude studies that did not meet the selection criteria. Articles deemed potentially eligible for inclusion were then reviewed in full text by RP and CRF, with any disagreements resolved by consensus or through consultation with a third reviewer (HV).

Data extraction

Studies that met the criteria after full text review were manually extracted to a standardized excel template by CRF and ST to include author, year, study design, aim of the study, number of IBD patients with concurrent malignancy, types of cancer, types of IBD treatments studied, and if applicable, time from index cancer to the use of immunosuppression. The tables were subsequently independently reviewed by RP and finally by HV to ensure accuracy.

Results

Search and study selection

The PRISMA flow diagram in Fig. 1 summarizes the identification, screening and exclusion of studies. The literature search yielded 3380 citations, including 2373 unique entries. Of these, 2307 were excluded during abstract screening for not meeting eligibility criteria. Sixty-six citations underwent full text review, resulting in the exclusion of 34 studies for the following reasons: wrong study design (n=12), updates or duplicate studies (n=14), observational studies with fewer than 20 patients (n=4), studies with only surgery or radiation as a treatment modality (n=1), studies of the wrong population (n=2), and insufficiently reported results (n=1). An additional study was identified from reference review, and a full paper that was initially found as a poster was also included [7]. Ultimately, 33 studies met the inclusion criteria and were included in the final analysis: 17 studies that evaluated the incident risk of new or recurrent malignancy, 10 studies that examined the use of immune checkpoint inhibitors (ICIs) among patients with prior IBD, and 7 studies that examined IBD patients with active cancer on therapy. One study by Holmer *et al* [8] evaluated both the risk of cancer recurrence in those with prior malignancies and the safety of IBD medications in those with active cancer.

Initiating IBD medications post-malignancy: studies of incident cancer risk

Among the 17 studies [7-23] evaluating the incident risk of new or recurrent malignancies in IBD patients

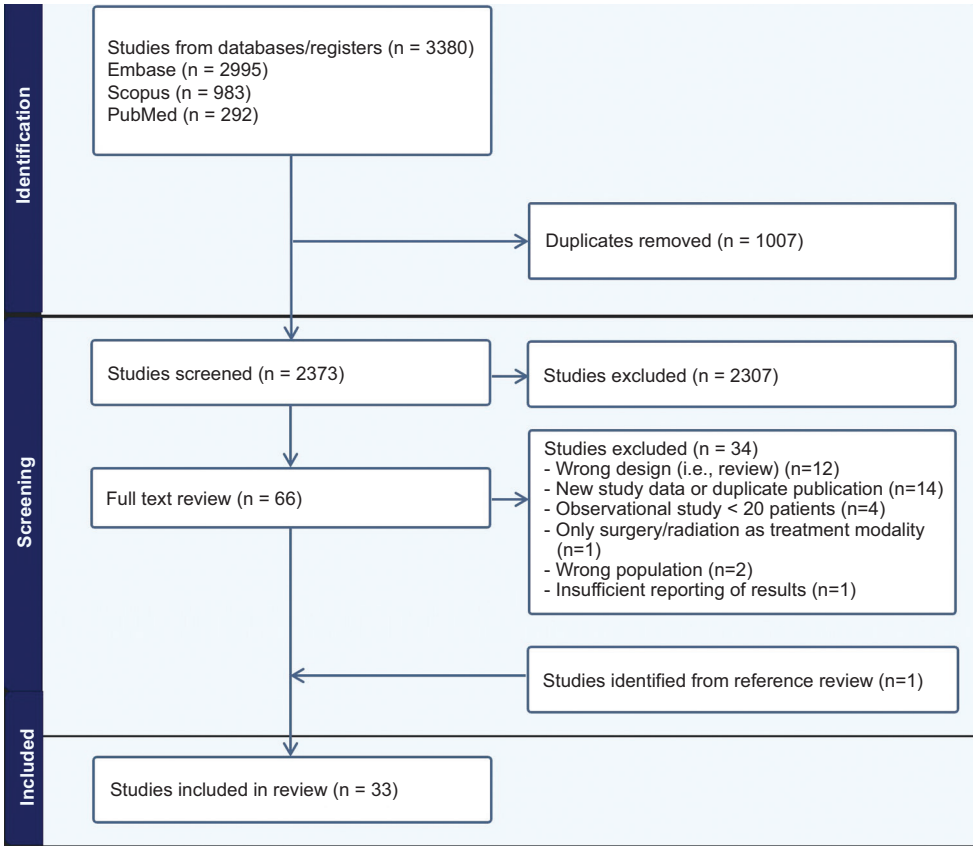

Figure 1 PRISMA flow diagram

with prior cancers (Table 1), multiple retrospective cohort studies [7-10,12-14,16,17,19], 2 meta-analyses [21,22] and an ongoing prospective study [23] found no increased risk of cancer with IBD medications. However, there were some notable exceptions [15,18]. Khan *et al* reported a higher risk of basal cell carcinoma (BCC) recurrence with thiopurine use (hazard ratio [HR] 1.65, 95%CI 1.24-2.19; P=0.0005) but no increased risk with anti-TNF or combination therapies [15]. Shani *et al* found that infliximab monotherapy was associated with a higher risk of non-melanoma skin cancer (NMSC) recurrence (odds ratio [OR] 9.85, 95%CI 2.3-51.7; P=0.003) [18].

One study created a risk prediction model to attempt to identify risk factors for the development of new or recurrent cancers in IBD patients with a history of malignancy [11]. Predictors included starting immunosuppressive therapy within 2 years after the diagnosis of index cancer (univariate OR 2.58, 95%CI 1.51-4.39), requiring chemotherapy for index cancer (univariate OR 1.39, 95%CI 0.82-2.31), older age at index cancer diagnosis (univariate OR 2.37, 95%CI 1.24-4.49), and a diagnosis of NMSC (univariate OR 2.45, 95%CI 1.58-3.79) [11].

Conversely, Manosa *et al* analyzed the ENEIDA registry of 520 IBD patients with extracolonic cancer and found that those treated with anti-TNF or thiopurines had no higher risk of new or recurrent cancers compared to non-exposed patients (16% vs. 18%, P=0.53) [9]. A supplementary analysis of the meta-analysis by Gupta *et al*, which included 6642 IBD patients with prior cancer, found comparable incident cancer rates among patients not on immunosuppression (39/1000 person-years, 95%CI 25-53), those on anti-TNF (43/1000 person-years, 95%CI 26-60), immunomodulators (60/1000 person-years, 95%CI 25-87), and combination immunosuppression (60/1000 person-years, 95%CI 20-100) [21]. A study by Poullenot *et al*, which included 538 IBD patients with prior non-digestive cancer [13], evaluated therapy with vedolizumab and came to a similar conclusion. After comparing those on immunomodulators (thiopurines and methotrexate), anti-TNF or vedolizumab, and those not on therapy, they found no significant difference in incident cancer between the treatment groups [13].

Other studies also included evaluation of anti-interleukins. Pang *et al*'s analysis of a large cohort of 5062 IBD patients with prior cancer found that patients exposed to vedolizumab (59 patients) or ustekinumab (18 patients) did not have a higher risk of new or recurrent cancer compared to historical cancer risk data in patients treated with anti-TNFs, immunomodulators, or without immunosuppressive therapy following cancer diagnosis [16]. Hasan *et al*'s multicenter retrospective study (341 IBD patients with a history of cancer) found no greater risk of incident cancer in patients receiving post malignancy treatment with ustekinumab (HR 0.88, 95%CI 0.25-3.03), vedolizumab (HR 0.18, 95%CI 0.03-1.35), or anti-TNF (HR 0.47, 95%CI 0.20-1.12) [14].

Studies also evaluated the timing of IBD treatments in relation to the cancer diagnosis. Holmer *et al* studied a cohort

Table 1 Studies examining the risk of new or recurrent malignancies in IBD patients with a history of cancer

Author [ref.] year	Study design	Questions addressed by the study	Number of IBD patients with cancer history	Types of Cancer	Treatment							Findings
					Anti-TNF	Anti TNF+ IMM	IMM	Anti-integrin	Anti IL 12/23	JAKi	S1PR	
Manosa *et al* [9] 2019	Multi-center retrospective cohort study	Risk of new and recurrent cancers in treatment naïve IBD patients with a history of extracolonic cancer after exposure to immunosuppression	520	Extracolonic	√	√	√					1) Patients exposed to anti-TNF and thiopurines after cancer diagnosis did not have a greater risk of new or recurrent cancers (incident cancers: 16% exposed vs.18% non-exposed; P=0.53). 2) Cancer-free survival was higher in exposed patients (99%, 98%, and 97% at 1, 2, and 5 years) compared to non-exposed patients (97%, 96%, and 92% at 1, 2, and 5 years; P=0.03)
Micic *et al* [22] 2019	Systematic review & meta-analysis	Risk of new and recurrent cancers among patients with immune-mediated disorders treated with TNF inhibitors	1046	Breast; solid; GI; dermatologic	√		√					The pooled incidence rate ratio of new or recurrent cancer among individuals with a history of cancer exposed to anti-TNF therapy was not significantly different compared with control therapies (incidence rate ratio 0.90, 95%CI 0.59-1.37 for all patients and 0.68, 95%CI 0.40-1.16 for IBD patients)
Pang *et al* [16] 2019	Single-center retrospective cohort study	Risk of new and recurrent cancers in IBD patients with a prior history of cancer subsequently being exposed to VDZ or USK	77	Solid, dermatologic, hematologic, GI				√	√			Exposure to VDZ or USK in IBD patients with a history of cancer was not associated with a greater risk of subsequent cancer compared to historical data of exposure to anti-TNF,

(Contd...)

Table 1 *(Continued)*

Author [ref.] year	Study design	Questions addressed by the study	Number of IBD patients with cancer history	Types of Cancer	Treatment							Findings
					Anti-TNF	Anti TNF+ IMM	IMM	Anti-integrin	Anti IL 12/23	JAKi	S1PR	
												immunomodulators or no immunosuppression following a diagnosis of cancer
Khan *et al* [15] 2020	Multi-center retrospective cohort study (VAHS)	Risk of repeated BCC occurrence among IBD patients with prior BCC continued on IBD medications	518	BCC	√	√	√					Active thiopurine use after BCC diagnosis was associated with a higher risk of repeated occurrence of BCC (aHR 1.65, 95%CI 1.24-2.19; P=0.0005) compared to no immunosuppressive medications. This risk was no longer present 6 months after discontinuation of thiopurines
Rouvroye *et al* [10] 2020	Multi-center retrospective cohort study	Risk of premalignant and malignant vulvar and vaginal lesions in IBD patients on immunosuppressive drugs	55	Vulvar and vaginal neoplasia	√		√	√				The use of immunosuppressive therapy did not influence the rate of recurrence of vulvovaginal malignancy
Waljee *et al* [12] 2020	Multi-center retrospective cohort study	Risk of incident and recurrent cancers in patients with IBD, RA, or PsO who received anti-TNF after initial cancer diagnosis	1641	Breast, lung; hematologic, CRC, other GI, dermatologic; others not specified	√							1) The incidence rate of incident cancer per 1000 person-years of patients who received anti-TNF therapy (30.3 cases, 95%CI 24-38.2) was similar to those who did not receive anti-TNF (34.4 cases, 95%CI 31.7-37.3). 2) There was no difference in the group who started anti-TNF within 2 years of cancer diagnosis

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Table 1 *(Continued)*

Author [ref.] year	Study design	Questions addressed by the study	Number of IBD patients with cancer history	Types of Cancer	Treatment							Findings
					Anti-TNF	Anti TNF+ IMM	IMM	Anti-integrin	Anti IL 12/23	JAKi	S1PR	
												compared to those who were initiated on treatment 2 years after cancer diagnosis
Gangasani *et al* [11] 2021	Multi-center retrospective cohort study	Risk of incident and recurrent cancers in IBD patients with a history of malignancy	435	Hematologic, solid, GI, dermatologic	√		√	√				Predictors in the risk model for the development of new or recurrent cancer were: time-period within 2 years after the diagnosis of index cancer (OR 2.58, 95%CI 1.51-4.39), requiring chemotherapy for index cancer (OR 1.39, 95%CI 0.82-2.31), age at index cancer (OR 2.37, 95%CI 1.24-4.49) and a diagnosis of non-melanoma skin cancer (OR 2.45, 95%CI 1.58-3.79)
Hasan *et al* [14] 2022	Multi-center retrospective cohort study	Risk of incident cancer in IBD patients with prior malignancy who were subsequently treated with USK, VDZ, or anti-TNF	341	Hematologic, solid organ, GI, dermatologic	√			√	√			There was no greater risk of incident cancer in patients receiving post-malignancy treatment with biologics, including USK (HR 0.88, 95%CI 0.25-3.03), VDZ (HR 0.18, 95%CI 0.03-1.35), or anti-TNF (HR 0.47, 95%CI 0.20-1.12)
Hong *et al* [19] 2022	Single-center retrospective cohort study	Risk of developing subsequent cancer in IBD patients with a history of cancer exposed to VDZ or UST compared with patients who received immunomodulators,	390	Hematologic, solid, GI, dermatologic	√	√	√	√	√			In a multivariable Cox model, adjusting for age, IBD subtype, smoking, cancer recurrence risk, and cancer stage, there was no increase in subsequent cancer with VDZ (aHR 1.36, 95%CI 0.27-7.01) or USK (aHR 0.96, 95%CI

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Table 1 *(Continued)*

Author [ref.] year	Study design	Questions addressed by the study	Number of IBD patients with cancer history	Types of Cancer	Treatment							Findings
					Anti-TNF	Anti TNF+ IMM	IMM	Anti-integrin	Anti IL 12/23	JAKi	S1PR	
		anti-TNF, or no immunosuppression										0.17-5.41). Patients with >1 biologic exposure did not have a greater risk of subsequent cancer
Poullenot *et al* [13] 2022	Multi-center retrospective cohort study	Evaluate the rate of incident cancer in patients with IBD and prior malignancy according to different type of IBD therapies	538	Breast, lymphoma, dermatologic	√		√	√	√			There was no difference in cancer incidence in IBD patients with prior non-digestive malignancy treated with VDZ compared to TNF. Incidence rate was not different between the groups on no immunomodulators, anti-TNF or VDZ. Patients on USK were excluded from the analysis because of low numbers
Vedamurthy *et al* [17] 2022	Single-center retrospective cohort study	Risk of incident and recurrent cancers in IBD patients following an index cancer diagnosis treated with VDZ versus anti-TNF therapy	463	Hematologic, solid, GI, dermatologic	√			√				1) In an adjusted multivariable Cox model, neither VDZ (HR 0.72, 95%CI 0.38-1.36) nor anti-TNF therapy (HR 1.03, 95%CI 0.65-1.64) were associated with a higher risk of cancer recurrence or new cancer development. 2) Restricting the analysis to biologic initiation within the first 5 years after cancer diagnosis showed no association between anti-TNF (HR 0.68, 95%CI 0.37-1.22) or VDZ use

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Table 1 *(Continued)*

Author [ref.] year	Study design	Questions addressed by the study	Number of IBD patients with cancer history	Types of Cancer	Treatment							Findings
					Anti-TNF	Anti TNF+ IMM	IMM	Anti-integrin	Anti IL 12/23	JAKi	S1PR	
												(HR 1.10, 95%CI 0.57-2.12) and risk of new or recurrent cancers
Holmer *et al* [8] 2023	Multi-center retrospective cohort study	Risk of incident cancer or cancer recurrence among IBD patients with recent malignancy (within 5 years) who were on anti-TNF vs. non-TNF biologic therapies	170	Hematologic, solid, dermatologic	√	√	√	√	√			Among IBD patients with a history of prior recent cancer, the risk of recurrence-free survival was similar between patients who received anti-TNF and non-TNF biologics (HR 0.94, 95%CI 0.24-3.77)
Shani *et al* [18] 2023	Single-center retrospective cohort study	Risk of incident and recurrent cancers in IBD patients with prior malignancy treated with advanced therapies	86	Lymphoma, other hematologic, solid, dermatologic	√	√	√	√	√	√		Treatment with infliximab was found to be significantly associated with recurrence of NMSC (P=0.003)
LeCosquer *et al* [7] 2024	Multi-center retrospective cohort study	Risk of incident cancer among IBD patients with prior breast cancer who initiated IBD therapies 7-64 months after cancer diagnosis	207	Breast	√		√	√	√			After accounting for established breast-cancer prognostic factors, there was a borderline non-statistically significant difference in incident cancer risk in IBD patients with prior breast cancer subsequently exposed to immunosuppressives vs. unexposed (adjusted incidence rates 28.9 vs. 10.2 per 1000 person-years; P=0.052)
Gupta *et al* [21] 2024	Systematic review & meta-analysis	Risk of incident and recurrent cancers among patients on immunosuppressive	6642	Breast, prostate, lymphoma, other hematologic, solid organ, GI	√	√	√	√	√			1) Rates of cancer recurrence were similar among patients who received

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Table 1 *(Continued)*

Author [ref.] year	Study design	Questions addressed by the study	Number of IBD patients with cancer history	Types of Cancer	Treatment							Findings
					Anti-TNF	Anti TNF+ IMM	IMM	Anti-integrin	Anti IL 12/23	JAKi	S1PR	
		therapies (for IBD, RA, PsO, AS) and a prior history of malignancy										immunosuppressive therapy for their immune-mediated disease, compared to those not on those therapies. 2) Stratification of studies by timing of immunosuppression initiation did not reveal a medication effect based on early (<5 years) or delayed treatment initiation
Itzkowitz *et al* [23] 2024	Prospective registry study	Risk of incident and recurrent cancers in IBD patients with prior history of cancer who are exposed to IBD therapies within 5-10 years of cancer diagnosis	305	Solid, dermatologic, GI, hematologic, other	√	√	√	√	√	√	√	No association between IBD therapy (IMM, TNF, combination, vedolizumab, ustekinumab, risankizumab, tofacitinib, upadacitinib, ozanimod), and risk of developing new or recurrent cancer
Mancone *et al* [20] 2024	Retrospective	Risk of incident and recurrent cancers in IBD patients treated with IBD therapies after cancer	41	Dermatologic, solid, GI	√	√	√	√	√			After a median follow up of 91 months after initial cancer diagnosis, 2 IBD patients (4.8%) developed new or recurrent cancer after IMM/biologics use. No cancer-related deaths occurred in any IBD patients

aHR, adjusted hazard ratio; BCC, basal cell cancer; CI, confidence interval; GI, gastrointestinal cancers; HR, hazard ratio; IBD, inflammatory bowel disease; IMM, immunomodulator; JAKi, Janus kinase inhibitor; NMSC, non-melanoma skin cancers; OR, odds ratio; PsO, psoriasis; RA, rheumatoid arthritis; S1PR, sphingosine 1-phosphate receptor; TNF, tumor necrosis factor; USK, ustekinumab; VAHS, Veterans Affairs Healthcare System; VDZ, vedolizumab

of 170 patients who had recent prior cancer (within 5 years) treated with biologics and immunomodulators, but excluding those on oral small molecule medications, and found the risk of recurrence-free survival was similar between patients who received TNF and non-TNF biologics (HR 0.94, 95%CI 0.24-3.77) [8]. Another cohort study of 463 IBD patients with prior cancer diagnosis found that neither vedolizumab (HR 1.38, 95%CI 0.38-1.36) nor anti-TNF therapy (HR 1.03, 95%CI 0.65-1.64) was associated with a higher risk of cancer recurrence or new cancer development [17]. The median time before the initiation of anti-TNF therapy in this study was 1.3 years, and the above conclusion continued to hold true even when the analysis was restricted to biologic initiation within the first 5 years after cancer diagnosis. A final retrospective cohort study of 390 IBD patients with prior cancer, which used a multivariable Cox model, adjusting for age, IBD subtype, smoking, cancer recurrence risk and cancer stage, found no greater incidence of new or subsequent cancer associated with vedolizumab (adjusted HR 1.36, 95%CI 0.27-7.01) or ustekinumab (adjusted HR 0.96, 95%CI 0.17-5.41), despite the median time to starting treatment with ustekinumab after cancer diagnosis being 5 months [19]. Interestingly, even patients who were exposed to more than 1 biologic did not have a greater risk of subsequent cancer.

Meta-analyses by Micic *et al* and Waljee *et al* examined the risk of recurrent or new primary malignancy in larger populations, which included patients with rheumatoid arthritis, psoriasis and IBD. Micic *et al* (1046 IBD patients) reported no greater cancer risk with anti-TNF (incidence rate ratio 0.68, 95%CI 0.40-1.16) [22]. Waljee *et al* (25,738 patients, including 1641 with IBD) found similar cancer incidence rates between anti-TNF (30.3 cases/1000 person-years) and control groups (34.4 cases/1000 person-years) [12]. Sensitivity analysis showed no difference in cancer risk between individuals treated with anti-TNF within 2 years of their initial cancer diagnosis and those who started treatment more than 2 years after cancer diagnosis.

The SAPPHIRE registry [23] is investigating the risk of new cancer or cancer recurrence in patients with IBD who are exposed to immunosuppression within 5-10 years of cancer diagnosis, compared to those not exposed to immunosuppression. This study is one of the few studies to include Janus kinase (JAK) inhibitors and ozanimod in the analysis, in addition to immunomodulators, anti-TNFs, vedolizumab and ustekinumab. This study followed 305 patients: 51 were exposed to immunomodulators, 199 to biologics and 16 to small molecules, while 95 patients did not have exposure to these therapies. Some patients were exposed to more than 1 agent. Data from these 305 patients showed that exposure to the above immunosuppressive IBD monotherapies was not associated with a statistically significant risk of new or recurrent cancers compared to no therapy [23].

Managing IBD patients with current active malignancy

Seven cohort studies evaluated outcomes in IBD patients with active cancer receiving cancer therapies, including cytotoxic chemotherapy, hormonal therapy and targeted therapies (Table 2) [8,24-29].

Use of IBD medications in patients with active cancer

Guerra Marina's retrospective study looked at IBD medications in lymphoma patients and found that 58% of patients had changes made to their IBD medications after cancer diagnosis, although the investigators noted no difference in mortality or lymphoma recurrence related to the use of biologics or thiopurines [27]. Holmer *et al* performed a multicenter retrospective cohort study of 125 IBD patients with active cancer who were treated with biologics (anti-TNF, vedolizumab, ustekinumab), immunomodulators or combination therapy after their cancer diagnosis [8]. Interestingly, there was no difference in the risk of progression-free survival between patients who were treated with anti-TNFs and those treated with non-TNF biologics, including vedolizumab and ustekinumab [8]. Of those treated with anti-TNFs, 18% (incidence rate [IR] 4.4 per 100 person-years) had progression of their cancer, compared to 23% (IR 10.4 per 100 person-years) in the vedolizumab/ustekinumab group, and therefore the study surmised that anti-TNFs, vedolizumab and ustekinumab have comparable safety in active cancer [8].

Types of chemotherapy and their impact on IBD activity

Cytotoxic chemotherapy: Severyns et a*l* (52 patients with lymphoma) found no IBD relapses during cancer treatment with cytotoxic chemotherapy, despite discontinuation of IBD treatments such as thiopurines, anti-TNFs and vedolizumab [25]. Similarly, Hammoudi *et al* (49 patients with colorectal cancer receiving adjuvant chemotherapy) reported a low IBD relapse rate (4%), despite discontinuation of IBD therapies, with relapses effectively managed using 5-aminosalicylic acid (5-ASA) medications [28]. This study also noted no significantly greater level of chemotherapy-related toxicity in IBD patients [28]. A larger study by Perez-Galindo *et al* (a multi-center cohort of 180 IBD patients with extraintestinal malignancy), again showed a lower risk of IBD relapse among patients receiving cytotoxic chemotherapy [26].

Hormonal therapy: In contrast, Axelrad *et al* studied 400 patients with quiescent IBD at the time of breast or prostate cancer diagnosis and found a higher risk of IBD flare with hormonal therapy, either alone (HR 2, 95%CI 1.21-3.29) or combined with cytotoxic chemotherapy (HR 1.86, 95%CI 1.01-3.43) [24]. Notably, patients receiving cytotoxic chemotherapy alone had higher IBD remission rates (75%) compared to those on hormonal therapy alone (42%) at 250 months [24]. The authors recommended close monitoring and a lower threshold for escalation of IBD therapies for patients on hormonal regimens [24].

Targeted chemotherapies: For targeted treatments, Herrera-Gomez *et al* found that the use of bevacizumab while on chemotherapy among solid tumor patients (n=27) was generally safe in patients with moderately active or quiescent

Table 2 Studies of IBD patients with active cancer receiving cancer therapies

Author [ref.] year	Study design	Questions addressed by the study	Number of IBD patients with cancer	Types of cancer	Findings
Axelrad *et al* [24] 2020	Multi-center retrospective cohort study	Risk of IBD relapse in patients receiving cancer treatment (cytotoxic, hormonal, or combination)	447	Breast, prostate	1) At long term follow up, 75% of patients receiving cytotoxic chemotherapy remained in remission from IBD compared to 42% who received hormone monotherapy. 2) Hormone monotherapy and combination cytotoxic with hormone therapy were associated with IBD relapse (HR 2.00, 95%CI 1.21-3.29 and HR 1.86, 95%CI 1.01-3.43, respectively). 3) Patients with active IBD at cancer diagnosis were significantly more likely to require hospitalization for a complication of IBD or cancer treatment compared to patients with inactive IBD (41% vs. 18%; P=0.001)
Severyns *et al* [25] 2020	Multi-center retrospective cohort study	Risk of IBD relapse in patients receiving cytotoxic chemotherapy for lymphoma	52	Lymphoma	Patients who received cytotoxic chemotherapy did not experience a relapse of IBD during chemotherapy and had a low risk of IBD relapse (23%) at 3 years after chemotherapy, despite antiTNF, azathioprine and ustekinumab being held for all patients at lymphoma diagnosis
Herrera-Gomez *et al* [29] 2022	Single-center retrospective cohort study	Safety profile of bevacizumab in cancer patients with a history of IBD treated with bevacizumab and chemotherapy	27	Solid (colorectal, small bowel, breast, NSCLC)	1) No IBD flares were diagnosed in patients with moderately active or quiescent IBD on bevacizumab combined with chemotherapy. 2) One patient with pancolonic Crohn's disease and metastatic colorectal cancer experienced perforation due to mesenteric ischemia after cancer treatment. Otherwise, this cancer treatment for IBD patients was deemed feasible and with an acceptable safety profile
Guerra Marina *et al* [27] 2023	Multi-center retrospective cohort study	Assess if medications for IBD were altered after diagnosis of lymphoma	52	Lymphoma	IBD treatments were changed after lymphoma diagnosis in 58% of patients but neither lymphoma recurrence nor mortality of lymphoma was related to the use or duration of thiopurines or biologic therapies
Hammoudi *et al* [28] 2023	Single-center retrospective cohort study	1) Risk of IBD relapse in patients receiving cancer treatment for CRC after stopping IBD medications. 2) Side-effects from chemotherapy in IBD patients being treated for CRC	49	CRC	1) The IBD relapse rate was 4% despite discontinuation of biologics or thiopurines at cancer diagnosis, and both relapses were managed with 5-ASA medications. 2) No unexpected chemotherapy side-effect was observed, including no significant increase in grade 3-4 chemotherapy toxicity

(Contd...)

Table 2 *(Continued)*

Author [ref.] year	Study design	Questions addressed by the study	Number of IBD patients with cancer	Types of cancer	Findings
Holmer *et al* [8] 2023	Multi-center retrospective cohort study	Risk of cancer progression, mortality, and serious infections in IBD patients with active malignancy on TNF vs. nonTNF therapy	125	Hematologic, solid, dermatologic (melanoma)	There was no difference in the risk of progression-free survival between TNF inhibitors and nonTNF biologics (vedolizumab and ustekinumab) in patients with active cancer (HR 0.76, 95%CI 0.25-2.30; P=0.62)
Perez Galindo *et al* [26] 2023	Multi-center retrospective cohort study	Risk of IBD relapse in patients receiving cancer treatment (cytotoxic chemotherapy, hormonal therapy, targeted therapy, or immunotherapy)	180	Extraintestinal malignancy	1) 33% experienced relapse of IBD after cancer treatment initiation. IBD treatment was discontinued in 40.6% of patients at cancer diagnosis (77.1% of patients on thiopurines and 79.2% on anti-TNF) 2) Patients who received chemotherapy were at a lower risk of IBD relapse. Older patients were at a lower risk of IBD relapse. Active IBD at baseline was associated with a higher risk of IBD relapse

ASA, aminosalicylates; CRC, colorectal cancer; CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; NSCLC, non-small cell lung cancer; TNF, tumor necrosis factor

IBD [29]. No IBD flares were observed, although 1 patient experienced perforation due to mesenteric ischemia.

Studies on ICIs in IBD patients

Ten studies examined the use of ICIs in patients with IBD [30-39]. Three studies were single-center retrospective cohort studies [30-32], 3 were multi-center cohort studies [33-35] and 4 were systematic reviews with meta-analyses [36-39]. In a retrospective study of 102 patients, 41% of IBD patients receiving ICIs experienced gastrointestinal (GI) adverse events, including a 4% perforation rate, compared to 11% of GI adverse events in non-IBD patients (P<0.001) [33]. Smaller studies similarly showed GI symptoms, such as diarrhea or rectal bleeding, in 36.8% of IBD patients [30], IBD flare rates of 32-50% [32,34,36] and colitis in 19% IBD patients on ICIs [31,36]. Meta-analyses reported a pooled IBD flare rate of 33-40% among IBD patients treated with ICIs [37-39], particularly with cytotoxic T lymphocyte-associated protein 4 inhibitors as compared to program death ligand 1 or program cell death protein 1 inhibitors [33,39]. In a meta-analysis by Meserve *et al*, 37% of those with an IBD flare required initiation of biologics; overall, 35% of IBD patients had to discontinue the ICI chemotherapy [39].

Discussion

The therapeutic options available for managing patients with IBD are ever-expanding, including new anti-interleukins and small molecules. With the emergence of new treatment options, safety data from both randomized controlled studies and real-world data must be considered. This was recently summarized by Bhat *et al* 2024 [40]. Examples include the elevated risks of infections, venous thromboembolism and dyslipidemia with JAK inhibitors, and the side-effects of bradycardia and liver enzyme elevations with sphingosine 1-phosphate (S1P) receptor modulators.

Unfortunately, most randomized controlled trials do not include data on patients with IBD with active or prior cancer; therefore, managing these patients remains a clinical challenge, given the limited high-quality data. Most evidence to inform decisions in this patient population comes from retrospective observational studies or meta-analyses consisting of such data, limiting generalizability because of potential factors that include selection bias and unmeasured confounding factors. Prospective data, such as those from the SAPPHIRE registry in the US, remain rare, and tend to include patients managed at specialized centers.

Previous recommendations to delay IBD therapy for 5 years after cancer diagnosis were largely based on post-transplant literature. However, more recent studies [12,17,19,21] have challenged this paradigm, with biologics being initiated earlier, often within months of cancer diagnosis. Reflecting this shift, the 2023 ECCO guidelines no longer recommend a 5-year delay in restarting IBD therapy post-cancer, instead advocating for case-by-case decision making [6]. Our review found that most IBD therapies can be safely continued or initiated in patients with prior malignancy (Table 3). Notable exceptions were thiopurines in patients with IBD with prior BCC [15] and infliximab in patients with IBD with prior NMSC [18], where initiation of these medications led to

Table 3 Recommendations for IBD-related medications in patients with active or prior cancer

Drug class	ECCO 2023 recommendations	AGA 2024 CPU position [41]	Current scoping review	Therapeutic implications
Thiopurines	Hold in patients with active cancer (exception non-aggressive BCC and preneoplastic lesion on the cervix with close monitoring). May be initiated with caution in patients with prior cancer. However, acknowledge that data is limited, and may be skewed by patients with cancers at overall low risk of recurrence, who initiated treatment >5 years since cancer resolution	Hold in patients with active lymphoma. Consider stopping for other hematologic malignancy, NMSC (especially recurrent or difficult to manage skin cancers) and cervical/genitourinary cancers	One prospective registry study [23], 1 meta-analysis [21] and a retrospective cohort study [9] showed no statistically significantly increased cancer risk in patients with prior cancer on thiopurines. In 1 study of patients with BCC the cancer recurrence risk was higher in those patients actively taking azathioprine [15]	Consider holding thiopurines in active cancer (especially lymphoma). Can consider using thiopurines with caution in patients with prior cancer in low-risk cases, implementing skin and lymphoproliferative surveillance. Can consider avoiding thiopurines in patients with prior BCC (limited evidence)
Anti-TNF agents	Permitted even in recent/ active cancer; no clear increase in recurrence. Decisions individualized with oncology input with consideration of IBD activity and the alternative treatment options	Hold in active melanoma. Consider alternative therapy in patients with active lymphoma (risk increases when combined with thiopurine); consider HSTCL risks	One retrospective cohort study showed TNF had comparable safety to vedolizumab and ustekinumab in active cancer [8]. No statistically significant increased risk of incident cancer in patients with prior cancer in 1 prospective registry study [23], 2 meta-analyses [21,22] and multiple retrospective studies [8,9,12-14,17], apart from 1 study [18] with higher risk of NMSC recurrence	Avoid in active melanoma or lymphoma. Can be an effective post-cancer option with skin/hematologic monitoring and oncology coordination. May be a signal to avoid in those with NMSC, but more data needed (small patient numbers in retrospective study)
Vedolizumab (anti-integrin)	Insufficient data in active cancer; decisions made case by case. Considered safe in patients with prior malignancy with no signal for increased recurrence	Insufficient data to alter treatment in active cancer. Advised no change in treatment during active cancer. Studies have identified no apparent incident cancer signal when started in patients with prior malignancy	No statistically significant increased risk of incident cancer in patients with prior cancer in 1 prospective registry study [23], 1 meta-analysis [21] and several retrospective cohort studies [13,14,16,17,19]	Insufficient data to alter treatment in active cancer. One of the preferred first-line IBD treatments after cancer; no mandatory delay; monitor clinical response (slower onset) and coordinate with oncology
Ustekinumab (anti-IL-12/23)	Insufficient data in active cancer; decisions made case by case. Considered safe in patients with prior malignancy with no signal for increased recurrence	Insufficient data to alter treatment in active cancer. Advised no change in treatment during active cancer. Studies have identified no apparent incident cancer signal when started in patients with prior malignancy	No statistically significant increased risk of incident cancer in patients with prior cancer in 1 prospective registry study [23], 1 meta-analysis [21] and several retrospective cohort studies [14,16,19]	Insufficient data to alter treatment in active cancer. Favorable safety in post-cancer patients (no increased cancer recurrence). Option for anti-TNF-refractory patients or those with comorbidities; no mandatory delay; and coordinate with oncology
JAK inhibitors (tofacitinib, upadacitinib)	Insufficient evidence in active or prior malignancy	Insufficient data to alter treatment in active cancer	No statistically significant increased risk of incident cancer in patients with prior cancer in 1 prospective registry study (SAPPHIRE) [23], but small numbers (13 patients)	Remains unclear about use in active cancer. Elevated risks (including non-cancer risks: infections, VTE, dyslipidemia). Limited data post-cancer. Reserve for refractory disease and implement close malignancy surveillance

(Contd...)

Table 3 *(Continued)*

Drug class	ECCO 2023 recommendations	AGA 2024 CPU position [41]	Current scoping review	Therapeutic implications
S1PR modulators (ozanimod)	Not specifically addressed; very limited data; caution advised	Insufficient data to alter treatment in active cancer	No increased cancer risk in patients with prior cancer in 1 prospective registry study (SAPPHIRE) [23], but minimal patients (4 patients)	Remains unclear about use in active cancer and patients with prior cancer. Consider later-line therapies; stay alert to emerging long-term safety data

AGA, American Gastroenterological Association; BCC, basal cell cancer; ECCO, European Crohn's and Colitis Organisation; HSTCL, hepatosplenic T-cell lymphoma; IBD, inflammatory bowel disease; IL, interleukin; JAK, Janus kinase; NMSC, non-melanoma skin cancers; S1PR, sphingosine 1-phosphate receptor; TNF, tumor necrosis factor; VTE, venous thromboembolism

an increased risk of cancer recurrence. This is echoed in the recent American Gastroenterological Association (AGA) clinical practice update [41], which advises one should consider holding thiopurines in patients who develop multiple or recurrent NMSC (such as BCC), non-lymphoma hematological malignancy or cervical/genitourinary cancers. For active lymphoma, this AGA clinical practice update made a stronger recommendation that thiopurines should be held. This AGA practice update also advises stopping anti-TNF therapy in patients with melanoma and considering holding it in patients with lymphoma [41].

Our review also examined the management of IBD in patients with active cancer. Diagnosing an IBD flare during cancer treatment is challenging because of the overlapping symptoms of IBD, infections, and side-effects of cancer therapies [42,43]. Therefore, a comprehensive diagnostic workup, including endoscopic evaluation to rule out infection, is essential prior to initiating treatment for an IBD flare [42]. Although corticosteroids remain the first-line treatment for flares, their potential impact on tumor immunosurveillance should prompt multidisciplinary discussions with oncologists [42,44]. Biologics, such as anti-TNFs, vedolizumab and ustekinumab, are effective second-line options, with early studies suggesting comparable safety profiles [42,44]. Mild flares can often be managed with 5-ASA in ulcerative colitis, and enteral nutrition can be considered in Crohn's [42]. Coordinating IBD care in cancer patients requires close collaboration between oncologists and gastroenterologists to balance IBD control and cancer management. Treatment decisions should consider both IBD factors (disease activity, severity and flare risk) and malignancy characteristics (cancer type, stage, prognosis and treatment-related immunosuppression), with oncological management often taking precedence [45].

Our review suggests that cytotoxic chemotherapy has a dual role in managing cancer and suppressing IBD activity, as suggested by studies showing lower rates of IBD relapse during treatment. In contrast, hormonal therapies are associated with a greater risk of IBD flare-ups. As ICI therapies are increasingly used across various cancers, IBD flares should be expected, with a pooled estimate of 33-40%. Currently, no data or consensus support treating high-risk IBD patients proactively before starting ICIs, though this remains an area for future study. Targeted therapies, such as bevacizumab, appear to be generally safe in patients with quiescent or moderately active IBD, although rare complications, such as mesenteric ischemia, have been reported.

Despite some uncertainty, our scoping review aligns with the current ECCO 2023 guidelines [6] and the recent AGA clinical practice update [41], which state that, with a few exceptions, most IBD-related medications can generally be continued or initiated in patients with active or prior cancer (Table 3).

The ECCO guidelines state that thiopurines should preferably be withdrawn in patients with active cancer. The AGA practice update suggests stopping azathioprine in patients with lymphoma, other hematological cancers, NMSC or cervical/genitourinary cancers, but suggests that azathioprine can be continued in patients with melanoma.

For patients with a history of cancer, the ECCO guidelines suggest that thiopurines can be initiated with caution. Our scoping review concurs with this conclusion.

The ECCO guidelines recommend the use of anti-TNFs in patients with IBD with active or previous history of cancer; however, the AGA practice update suggests stopping anti-TNF therapy in patients with active melanoma and considering alternatives in patients with active lymphoma.

Data on vedolizumab and ustekinumab in active cancer remain limited, but the AGA practice update supports no change in therapy for patients taking vedolizumab or ustekinumab, whereas the ECCO recommends that decisions be made on a case-by-case basis.

The ECCO guidelines concur with our scoping review, showing that neither vedolizumab nor ustekinumab appears to increase the risk of cancer recurrence in patients with prior malignancy.

There is insufficient evidence on JAK inhibitors or S1P receptor modulators in patients with current or prior malignancy, and this is stated in the ECCO guidelines. The AGA practice update, however, supports no change in therapy in those with active cancer. Our scoping review, mainly influenced by the SAPPHIRE registry, showed no increased cancer risk with JAK inhibitors or ozanimod in prior cancer patients, though sample sizes are small.

Given the uncertainty concerning optimal IBD management for patients with active or prior malignancy, treatment decisions should be collaborative, involving patients, gastroenterologists, and oncologists. As new therapies emerge, prospective registries will be crucial for guiding evidence-based care.

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Supplementary material

Supplementary Table 1 Search strategies for PubMed (n=292), Scopus (n=983), and Embase (n=2995) from January 1, 2019, to July 31, 2024, on inflammatory bowel disease, malignancy, and related treatments, excluding non-original research

PubMed (292)	(((management [tw] OR treatment [tw] OR intervention [tw] OR drug therapy [tw] OR therapy [tw] OR best practice [tw] OR strategies [tw]) AND (Azathioprine [tw] OR Methotrexate [tw] OR Mercaptopurine [tw] OR Tumor Necrosis Factor Inhibitors [tw] OR Infliximab [tw] OR Adalimumab [tw] OR Golimumab [tw] OR Certolizumab [tw] OR Ustekinumab [tw] OR Risankizumab [tw] OR Mirikizumab [tw] OR Anti-interleukin [tw] OR Anti Integrin [tw] OR Vedolizumab [tw] OR Natalizumab [tw] OR Jaki [tw] OR Upadacitinib [tw] OR Tofacitinib [tw] OR S1PR modulator [tw] OR Ozanimod [tw] OR Etrasimod [tw])) AND ((cancer [tw] OR malignancy [tw] OR malignant neoplasm [tw] OR neoplasms [tw])) AND ((inflammatory bowel disease [tw] OR IBD [tw] OR Crohn's disease [tw] OR ulcerative colitis [tw] OR indeterminate colitis inflammatory bowel disease [tw])) NOT (("animals"[mesh] NOT "humans"[mesh])) AND (2019:2024[pdat])) NOT ((letters OR editorials OR commentary OR "in-vitro studies" OR "book chapters" OR surveys))
Scopus (983)	(TITLE-ABS-KEY ((management OR treatment OR intervention OR therapy OR "best practices" OR strategies)) AND TITLE-ABS-KEY ((azathioprine OR methotrexate OR mercaptopurine OR "Tumor Necrosis Factor Inhibitors" OR infliximab OR adalimumab OR golimumab OR certolizumab OR ustekinumab OR risankizumab OR mirikizumab OR anti-interleukin OR "Anti Integrin" OR vedolizumab OR natalizumab OR jaki OR upadacitinib OR tofacitinib OR "S1PR modulator" OR ozanimod OR etrasimod)) AND TITLE-ABS-KEY ((cancer OR malignancy OR "malignant neoplasm" OR neoplasms)) AND TITLE-ABS-KEY (("inflammatory bowel disease" OR ibd OR "Crohn's disease" OR "ulcerative colitis" OR "indeterminate colitis inflammatory bowel disease")) AND NOT ALL (letters OR editorials OR commentary OR "in-vitro studies" OR "book chapters" OR surveys)) AND PUBYEAR > 2019 AND PUBYEAR < 2025
Embase (2995)	('management'/exp OR 'management' OR 'treatment' OR 'treatment'/exp OR treatment OR 'intervention' OR 'intervention'/exp OR 'interventional therapy'/exp OR 'drug therapy' OR 'therapy' OR 'therapy'/exp OR therapy OR 'best practices' OR strategies) AND ('azathioprine' OR 'methotrexate' OR 'mercaptopurine' OR 'tumor necrosis factor inhibitor' OR 'infliximab' OR 'adalimumab' OR 'golimumab' OR 'certolizumab' OR 'ustekinumab' OR 'risankizumab' OR 'mirikizumab' OR 'anti interleukin' OR 'anti integrin' OR 'vedolizumab' OR 'natalizumab' OR 'jaki' OR 'upadacitinib' OR 'tofacitinib' OR 's1pr modulator' OR 'ozanimod' OR 'etrasimod') AND cancer OR 'neoplasm' OR 'malignant neoplasm' OR 'malignancy' AND 'inflammatory bowel disease' OR 'Crohn disease' OR 'ulcerative colitis' OR 'indeterminate colitis inflammatory bowel disease' NOT ('letter' OR survey OR 'book chapter' OR 'in-vitro studies' OR commentary OR 'editorial') AND (2019:py OR 2020:py OR 2021:py OR 2022:py OR 2023:py OR 2024:py)