

Extraintestinal malignancies in inflammatory bowel disease – deciphering hazardous relationships: A literature review

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Abstract

Inflammatory bowel disease (IBD) is a chronic, systemic disease with complex and unclear pathogenesis, primarily affecting the gastrointestinal tract. Inflammatory bowel disease is associated with a wide spectrum of extraintestinal complications, among which cancer is of particular importance. It is well known that IBD is associated with a higher risk of colorectal cancer (CRC). Yet, the incidence of CRC in this group of patients has decreased due to the development of surveillance techniques and therapy. In contrast, the relationship between IBD and extraintestinal malignancies (EMs) remains unclear, and it is taking on new significance in light of the rise in the incidence of malignant tumors, both in IBD patients and in the general population. Based on the literature review, it can be stated that the available studies suggest a possible association between IBD and oral, pancreatic and hepatobiliary malignancies. However, the dynamic epidemiological situation, combined with the methodological limitations of many existing studies, underscores the need for further research to better understand the relationship between IBD and cancer. In this group of patients, special oncological vigilance, the employment of the available prevention methods (e.g., vaccination), patient education, and, when recommended, screening tests are required. A clinical challenge involving a multidisciplinary approach is the treatment of IBD in cancer patients, especially during disease exacerbation, as well as cancer therapy in IBD patients.

Keywords: inflammation, neoplasms, inflammatory bowel disease, immunosuppression therapy

Cite as

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Highlights

- Inflammatory bowel disease (IBD) significantly increases the risk of colorectal cancer (CRC), although modern surveillance strategies and advanced therapies have reduced the overall CRC incidence in IBD patients.
- The relationship between IBD and extraintestinal malignancies (EMs) remains uncertain; however, it is gaining importance as the global cancer rates continue to rise.
- Current evidence from our literature review suggests a potential association between IBD and several extraintestinal cancers, including oral, pancreatic and hepatobiliary malignancies.

Introduction

Inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), is a chronic disease of complex and unclear etiology. It is assumed that in genetically predisposed individuals, environmental factors, such as impaired intestinal permeability and dysbiosis, lead to the dysregulation of the immune system and chronic intestinal inflammation. Inflammation can affect other organs, leading to extraintestinal manifestations in IBD patients.¹

Currently, nearly 3.9 million females and 3.0 million males are living with IBD worldwide, and a considerable rise in both incidence and prevalence of IBD has been observed. Inflammatory bowel disease is an incurable disease with a difficult-to-predict course, and cancer is the second most common cause of death for IBD patients after cardiovascular disease.^{2,3}

Many researchers are striving to elucidate the molecular mechanisms underlying cancer development in patients with IBD, which are gradually becoming better understood. Most scientific studies focus on colorectal cancer (CRC). In their recent study, Hisamatsu et al. found that chronic inflammation in IBD promotes tumor development by activating several key pathways, including NF- κ B, JAK/STAT and Wnt/ β -catenin, which drive cell proliferation and survival.⁴ In addition to neoplastic transformation via DNA damage, the oxidative stress caused by chronic inflammation is also an important factor inducing the mutations and chromosomal instability required for cancer progression. Advances in epigenetics, in turn, have shown that CpG island hypermethylation and mismatch repair defects contribute to early carcinogenesis in colitis-induced cancer.⁴ Chronic inflammation due to IBD results in systemic immune activation and epithelial damage, which may promote carcinogenesis not only in the colon, but also across many organ systems. Immunosuppressive therapies predispose to immune deregulation, leading to an enhanced risk for virus-related malignancies (e.g., lymphoma) and skin cancers. Additionally, continuous inflammatory signals and cytokine imbalance may lead to the formation of an in vivo microenvironment for malignancies beyond the gut mucosa,

contributing to an increased incidence of cholangiocarcinoma (CCA)/urothelial carcinoma. This seems to imply that a set of both iatrogenic and intrinsic immune pathologies can be postulated as drivers of a systemic cancer risk in IBD patients.⁵

Another relevant factor is the influence of gut microbiota disorders on the process of carcinogenesis. Minervini et al. in their review showed that gut dysbiosis, or the imbalance of gut microbiota, promotes the process of carcinogenesis due to the production of toxins that have a harmful effect on the genome, the induction of inflammation and the disruption of the host immune response.⁶ Bacteria that exert a harmful effect include *Fusobacterium nucleatum*, *Escherichia coli* and *Bacteroides fragilis*. These microorganisms, by weakening the host immune response, may allow cancer cells to evade elimination by the immune system.⁶

Banthia et al. in their review indicate that there is an association between periodontal disease and an increased risk of cancer, especially in the case of head and neck, esophageal, lung, and gastrointestinal cancers.⁷ However, the researchers present no evidence of an association between periodontal disease and the risk of metastasis in already diagnosed cancers. It is important to remember that chronic inflammation and the changes in the oral microbiome involving specific pathogens may promote cancer development.⁷

Patients with IBD are at significantly increased risk of CRC, mainly due to the pro-neoplastic effects of chronic intestinal inflammation. The most important risk factors for CRC in IBD patients are the duration of the disease, its extent and severity, the presence of post-inflammatory pseudopolyps, the coexistence of primary sclerosing cholangitis (PSC), and a family history of CRC.^{8–10} The worldwide incidence rate of CRC in CD is estimated to be between 19.5 and 344.9/100,000 per year, and between 54.5 and 543.5/100,000 per year in patients with UC.¹¹ It is estimated that in the cases of long-standing UC and Crohn's colitis (except for proctitis), there is a 2–3-fold increased risk of CRC as compared to the general population. Nevertheless, the available studies indicate that the rates of CRC in IBD are decreasing over time, likely due to improved medical therapies and endoscopic surveillance.

In contrast, the link between IBD and extraintestinal malignancies (EMs) remains unclear. In general, the incidence of malignant tumors is on the rise, both in the general population and in patients with IBD. The treatment of patients with IBD has advanced with the introduction of novel therapies. However, it is important to note the increased risk of cancer associated with immunosuppressive treatment.

Our review is innovative, since it is one of the few that focus on the association between IBD and the risk of less frequently discussed EMs. The review aims to summarize the available data and identify potential pathophysiological mechanisms that may link chronic inflammation to the development of malignancies at sites remote from the gut. Analyses such as ours may contribute to better identification of risk groups and the development of more effective cancer surveillance strategies in patients with IBD. The present review explores the relationship between IBD and EMs, including their characteristics and risk factors. Understanding these associations may help inform clinical decision-making and improve cancer surveillance in patients with IBD.

Material and methods

The literature search was performed in the Embase and PubMed databases, using the combinations of the following keywords: (“cancer*” OR “malignancy*” OR “tumor*” AND “Crohn’s disease” OR “ulcerative colitis” OR “inflammatory bowel disease*” OR “IBD”). The search was limited to the articles published between January 2015 and August 2024. The asterisks allowed us to retrieve records where the query words appeared with suffixes. The exclusion criteria were as follows: experimental studies (including animal studies and in vitro research); non-IBD studies; studies solely on CRC; non-original articles; non-English language; abstracts; and posters. The evidence-based medicine (EBM) pyramid was used to assess the quality of the studies.¹² This narrative review followed the Scale for the quality Assessment of Narrative Review Articles (SANRA) criteria and the SANRA score for the review is presented in Fig. 1.¹³

Results

We found 39 studies that examined the link between EMs and IBD, along with 20 studies on the connection between EMs and IBD treatment, that met the inclusion criteria.

We systematized the search results according to the location of the tumor: oral, head and neck cancers; thyroid cancer (TC); lung cancer (LC); breast cancer (BC); pancreatic cancer (PC); hepatobiliary cancer; urinary tract cancer; prostate cancer (PCa); reproductive system

cancers; central nervous system malignancies; hematological malignancies; and skin cancers.

Scale for the quality Assessment of Narrative Review Articles – SANRA

1. Justification of the article's importance for the readership
 - The importance is not justified. 0
 - The importance is alluded to, but not explicitly justified. 1
 - The importance is explicitly justified. 2
2. Statement of concrete aims or formulation of questions
 - No aims or questions are formulated. 0
 - Aims are formulated generally, but not concretely or in terms of clear questions. 1
 - One or more concrete aims or questions are formulated. 2
3. Description of the literature search
 - The search strategy is not presented. 0
 - The literature search is described briefly. 1
 - The literature search is described in detail, including the search terms and the inclusion criteria. 2
4. Referencing
 - Key statements are not supported by references. 0
 - The referencing of key statements is inconsistent. 1
 - Key statements are supported by references. 2
5. Scientific reasoning (e.g., the incorporation of appropriate evidence, such as RCTs in clinical medicine)
 - The article's point is not based on appropriate arguments. 0
 - Appropriate evidence is introduced selectively. 1
 - Appropriate evidence is generally present. 2
6. Appropriate presentation of data (e.g., absolute vs. relative risk, effect sizes without confidence intervals)
 - Data is presented inadequately. 0
 - Data is often not presented in the most appropriate way. 1
 - Relevant outcome data is generally presented appropriately. 2

SUMSCORE: 11

Fig. 1. Scale for the quality Assessment of Narrative Review Articles (SANRA)

Inflammatory bowel diseases and oral, head and neck cancers

Most head and neck cancers (HNC) originate from the mucosal epithelium of the oral cavity, pharynx and larynx, and are known as head and neck squamous cell carcinoma (HNSCC). Cancers of the oral cavity and larynx are generally linked to tobacco consumption, alcohol abuse, or both, while pharynx cancers are increasingly associated with human papillomavirus (HPV) infection, primarily HPV-16.¹⁴

The relationship between IBD and an increased risk of oral cancer has been the subject of many studies. In IBD, disturbances occur not only in the gut microbiome, but also in the oral microbiome.^{15,16} The resulting dysbiosis contributes to an increase in pro-inflammatory cytokines, leading to the development of periodontitis.^{17,18} The presence of chronic inflammation promotes oxidative stress and DNA damage, which increases the risk of the neoplastic transformation of oral epithelial cells. It should also be noted that patients with IBD undergoing immunosuppressive therapy are at increased risk of de-

veloping dysplastic lesions in the oral cavity. Immunosuppression weakens the body's natural immune defense mechanisms, reducing the ability to eliminate cells with tumorigenic potential, while simultaneously increasing susceptibility to HPV infection, a key risk factor for the development of oral cancer.^{19–21}

We identified 6 studies examining the association between IBD and cancers of the oral cavity, head and neck (Table 1).^{20,22–26} The results of all the studies, including a recently published Mendelian randomization study, were consistent and suggested an increased risk of oral cancer in IBD patients. In the study by Katsanos et al., it was demonstrated that patients with IBD had an elevated risk of malignant tumors in the oral cavity, particularly tongue cancer.²⁰ Immunosuppression, dysbiosis, a weakened immune system, and HPV infection are key risk factors. In light of these findings, the importance of regular dental examinations, patient education and preventive HPV vaccination in patients with IBD should be emphasized. Omitting HPV vaccination in patients with IBD is acknowledged as a significant vaccination oversight.²⁷ Studies showing no association between HPV vaccination and the IBD risk are also relevant.²⁸

Thyroid cancer

Thyroid cancer includes papillary TC, follicular cancer, medullary cancer, and poorly or undifferentiated cancer. Thyroid cancer stands as the most prevalent form of endocrine cancer, with papillary cancer comprising over 80% of all cases.²⁹ It predominantly affects women and is more prevalent in white individuals than in African Americans.³⁰ In our review, we identified 5 studies that evaluated the risk of TC in patients with IBD (Table 2).^{22,31–34} The results of the abovementioned studies are inconclusive. So et al. demonstrated that the risk of TC was not significantly higher in IBD patients as compared to the healthy population.²² In 2 studies, the risk of TC was higher only in patients with CD.^{31,32} On the other hand, other studies indicate an elevated risk of this cancer only in patients with UC.^{33,34}

Lung cancer

Lung cancer (LC) is the most commonly diagnosed cancer and the leading cause of cancer-related deaths, with an estimated 1.8 million deaths worldwide.³⁵ The available studies are inconclusive in assessing the relationship between IBD and LC (Table 3).^{33,36–40} Jung et al. showed that the risk of LC in IBD patients was similar to that in the general population.³³ In turn, other studies suggest a link between CD and an increased risk of LC, which is not confirmed in UC, even indicating a reduced risk of lung cancer in this group of patients.³⁶ Yet, the meta-analysis published in 2021 by Lo et al. suggests an increased risk of LC in IBD patients.⁴⁰

Breast cancer

Breast cancer is the most prevalent cancer in women, with an estimated 2.3 million new cases diagnosed globally each year.⁴¹ The known risk factors for BC are increasing age, prolonged estrogen exposure, obesity in postmenopausal women, reproductive and genetic factors, western lifestyle, as well as smoking and alcohol consumption.⁴¹ It seems that IBD patients have a shorter period of estrogen exposure as compared to the general population. This is due to a later onset of menarche and earlier menopause, which could be linked to a reduced risk of BC.⁴² In our review, only Van den Heuvel et al. noted a decreased risk of BC in female patients with IBD.⁴³ Three out of the 5 studies showed an increased risk of BC in IBD patients, while the rest reported a risk similar to that in the general population (Table 4).^{37,39,43–45}

Pancreatic cancer

The findings are consistent and indicate a higher risk of PC in patients with IBD (Table 5).^{33,46–51} A recently published meta-analysis of 11 cohort studies unequivocally showed a moderate increase in the PC risk in patients with IBD.⁵¹ Moreover, the study demonstrated a significantly higher PC risk in men with IBD as compared to women.⁵¹ The incidence of PC has been increasing worldwide yearly. The link between PC and IBD is primarily attributed to the chronic systemic inflammation caused by the disease. Kimchy et al. suggests that this increasing trend observed in the IBD population parallels the increase in the incidence of PC reported among the general population, but at a much greater rate.⁴⁹ In their study, Jung et al. observed an increased risk of PC, specifically in women with CD.³³ On the other hand, Burish et al. noted an increased risk of this cancer in patients with UC.⁴⁸ A particular factor that increases the risk of PC in patients with IBD is the presence of PSC. In a recently published systematic review and meta-analysis of cohort studies, the summary relative risk (*RR*) (95% confidence interval (*CI*)) comparing persons with PSC to persons without PSC was 7.56 (2.42–23.62; $I^2 = 0\%$, $n = 3$) for PC.⁵²

Hepatobiliary cancer

The available studies suggest that in patients with IBD there is a higher risk of hepatobiliary tumors (Table 6).^{33,37,53} The risk is especially high in patients with PSC. Concomitant IBD is reported in up to 60–80% of PSC patients.⁵⁴ There are strong positive associations between PSC and several tumors. For instance, in a recently published systematic review and meta-analysis of cohort studies, the summary *RR* (95% *CI*) comparing persons with PSC to persons without PSC was 584.37 (269.42–1,267.51; $I^2 = 89\%$; $n = 4$) for cholangiocarcinoma, 155.54 (125.34–193.02; $I^2 = 0\%$; $n = 3$) for hepatobiliary cancer and 30.22 (11.99–76.17; $I^2 = 0\%$; $n = 2$) for liver cancer.⁵²

Table 1. Inflammatory bowel disease (IBD) and oral, head and neck cancers

Study, year, country	Study design/ quality level*	Number of participants (n)/ type of cancer	Age [years] and gender of the participants	Inclusion criteria	Exclusion criteria	Findings
Katsanos et al. ²⁰ 2016 USA	retrospective study *C	7,294 IBD patients 11 OCC (7 CD, 4 UC); squamous cell cancer of the tongue and palate (n = 6); tonsillar, buccal and mandibular sarcomas (n = 3)	41–81 3,509 M 3,785 F	the IBD diagnosis	oral neoplastic lesions diagnosed before the IBD diagnosis	and increased risk of oral cancer in IBD patients (SIR: 9.77; 95% CI: 5.14–16.98), particularly in women
So et al. ²² 2017 China	population-based cohort study *C	2,621 IBD patients 1,603 UC 1,018 CD	all age categories 1,559 M 1,062 F	the IBD diagnosis	patients with IBD diagnosed before 1990 and whose dates of the IBD diagnosis were unknown	an increased risk of HNC in CD (SIR: 5.08; 95% CI: 1.64–15.76)
Nissen et al. ²³ 2018 the Netherlands	retrospective case– control study *D	66 IBD patients and 2,141 controls with OCC 31 IBD patients and 1,552 controls with PxC	all age categories	IBD patients with primary OCC and PxC	OCC and PxC in situ; lymphoma; the IBD diagnosis > 3 months after the OCC or PxC diagnosis; the OCC or PxC diagnosis before 1993 or after 2012; no confirmed IBD diagnosis	an older age at the IBD diagnosis was a risk factor for both OCC and PxC development; CD (OR: 1.04; 95% CI: 1.02–1.07) and UC (OR: 1.03; 95% CI: 1.01–1.06) were risk factors for OCC development; the proximal disease localization in CD was a risk factor for OCC development (OR: 1.103; 95% CI: 1.040–1.170; p = 0.028)
Van de Ven et al. ²⁴ 2020 Denmark	retrospective case– control study *D	1,855 IBD patients 1,004 UC 796 CD 55 LxC	NA 863 M 992 F	the IBD diagnosis	LxC in situ; the IBD diagnosis > 3 months after the LxC diagnosis; no confirmed diagnosis of IBD or LxC; the diagnosis before 1993 or after 2012; laryngeal lymphoma	the male sex was a risk factor for LxC in IBD patients; an older age at the IBD diagnosis was a risk factor for LxC development in UC; tobacco use, stricturing and penetrating disease were risk factors for LxC development in CD; IBD was not associated with impaired LxC survival
Gao et al. ²⁵ 2023 European countries	Mendelian randomization study *B	12,882 IBD patients 6,968 UC 5,956 CD	NA	the IBD diagnosis	NA	IBD, UC and CD have potential causal associations with OCC (IBD – OR: 1.180; 95% CI: 1.059–1.316; p = 0.003; UC – OR: 1.158; 95% CI: 1.041–1.288; p = 0.007; CD – OR: 1.112; 95% CI: 1.008–1.227; p = 0.034)
Harjunen et al. ²⁶ 2023 Finland	retrospective study *C	70,567 IBD patients 50,873 UC 19,694 CD 89 HNSCC	18–91 35,885 M 34,682 F	the IBD diagnosis; age ≥ 18 years	HNC diagnosed before the IBD diagnosis	the incidence of HNSCC was increased in IBD patients as compared to the estimates for the Finnish population in general (SIR: 1.300; 95% CI: 1.065–1.614; p = 0.062); only individuals with CD had a statistically significantly increased incidence of HNSCC (SIR: 1.715; 95% CI: 1.156–2.431; p = 0.034); the incidence was increased for men with CD (SIR: 1.951; 95% CI: 1.216–2.935; p = 0.025), but not for women (SIR: 1.317; 95% CI: 0.602–2.451; p = 0.873)

* B – randomized-controlled study; C – cohort study; D – case-controlled study; OCC – oral cavity cancer; CD – Crohn's disease; UC – ulcerative colitis; PxC – pharyngeal cancer; LxC – laryngeal cancer; HNSCC – head and neck squamous cell carcinoma; HNC – head and neck cancer; M – male; F – female; SIR – standardized incidence ratio; CI – confidence interval; OR – odds ratio; NA – not applicable.

Table 2. Inflammatory bowel disease (IBD) and thyroid cancer (TC)

Study, year, country	Study design/ quality level*	Number of participants (n)/ type of cancer	Age [years] and gender of the participants	Inclusion criteria	Exclusion criteria	Findings
So et al. ²² 2017 China	population-based cohort study *C	2,621 IBD patients 1,603 UC 1,018 CD	all age categories 1,559 M 1,062 F	the IBD diagnosis	patients with IBD diagnosed before 1990 and whose dates of the IBD diagnosis were unknown	the risk of TC was not significantly higher in IBD patients as compared to the healthy population
Wadhwa et al. ³¹ 2016 USA	case-control study *D	289,935 IBD patients 315,145 with diverticulitis	≥18	the IBD diagnosis	NA	CD, not UC, is associated with a higher risk of TC
Taborelli et al. ³² 2020 Italy	population-based cohort study *C	3,664 IBD patients 2,358 UC 1,306 CD	18–84 1,911 M 1,753 F	the IBD diagnosis	<5 years of residence in the Friuli-Venezia Giulia region preceding the IBD diagnosis; follow-up <90 days; codes for both UC and CD	a higher risk of TC only in CD (SIR: 5.58; 95% CI: 2.41–11.00)
Jung et al. ³³ 2017 South Korea	retrospective study *C	10,049 UC 5,595 CD	all age categories 9,743 M 5,548 F	the IBD diagnosis	previous cancer recognition	an increased risk of TC (SIR: 2.2; 95% CI: 1.1–3.9) in men with UC
Cao ³⁴ 2018 China	case-control study and meta-analysis *D/A	case-control study: 1,392 IBD patients 1,022 UC 370 CD control group: 1,392 patients with diverticulitis meta-analysis: 334,015 IBD patients	≥18	the IBD diagnosis	NA	in the case-control study, TC was more common in IBD patients than in controls ($p = 0.032$); in the meta-analysis, IBD patients showed an increased risk of TC; assessing UC and CD separately, the risk of TC was increased only in UC

* A – meta-analysis; B – randomized-controlled study; C – cohort study; D – case-controlled study; NA – not applicable.

Table 3. Inflammatory bowel disease (IBD) and lung cancer (LC)

Study; year, country	Study design/ quality level*	Number of participants (n)/ type of cancer	Age [years] and gender of the participants	Inclusion criteria	Exclusion criteria	Findings
Jung et al. ³³ 2017 South Korea	retrospective study *C	10,049 UC 5,595 CD	all age categories 9,743 M 5,548 F	the IBD diagnosis	previous cancer recognition	the risk of LC in UC (SIR: 1.25; 95% CI: 0.62–2.23) and CD (SIR: 1.66; 95% CI: 0.34–4.85) was comparable to that in the general population
Wilson et al. ³⁶ 2016 Switzerland	nested case–control study *D	39,294 IBD patients 1,603 UC 1,108 CD	NA	the IBD diagnosis	NA	an increased risk of trachea/ lungs cancer in CD (SIR: 2.91) and a reduced risk of LC in UC (SIR: 0.79)
Hovde et al. ³⁷ 2017 Norway	prospective population- based study *B	756 IBD patients 519 UC 237 CD	4–89 370 F	the IBD diagnosis	NA	in CD, an increased risk for trachea/lungs cancer as compared to controls
Biancone et al. ³⁸ 2020 Italy	prospective case–control study *B	204 CD 199 UC 29 LC 806 IBD controls	≥17 214 M 189 F	the CD or UC diagnosis; IBD diagnosis >3 months after the LC diagnosis; regular clinical assessments (≥2 visits/year)	previous malignancies; age <17 years	an increased risk of LC in both CD and UC
Loo et al. ³⁹ 2019 Canada	population-based study *C	35,985 IBD patients 20,644 CD 14,000 UC 1,341 IBD-U 225 ECs	≥18 16,563 M 19,422 F	the IBD diagnosis; age ≥18 years	prevalent IBD; less than 1 day of follow-up	an increased risk of respiratory cancers (SIR: 1.16)
Lo et al. ⁴⁰ 2021 multi-national study	meta-analysis of population- based cohort studies *A	NA	NA	the IBD diagnosis	NA	CD patients had an increased risk of LC (IRR: 1.53; 95% CI: 1.23–1.91), while UC patients had a borderline significantly lower risk

* A – meta-analysis; B – randomized-controlled study; C – cohort study; D – case-controlled study; IBD-U – inflammatory bowel disease unclassified; EC – extracolonic cancers; IRR – incidence rate ratio; NA – not applicable.

Table 4. Inflammatory bowel disease (IBD) and breast cancer (BC)

Study, year, country	Study design/ quality level*	Number of participants (n)/ type of cancer	Age [years] and gender of the participants	Inclusion criteria	Exclusion criteria	Findings
Hovde et al. ³⁷ 2017 Norway	prospective population- based study *B	756 IBD patients 519 UC 237 CD	4–89 370 F	the IBD diagnosis	NA	BC was observed more often in both, UC and DC
Loo et al. ³⁹ 2019 Canada	population-based study *C	35,985 IBD patients 20,644 CD 14,000 UC 1,341 IBD-U 225 ECs	≥18 16,563 M 19,422 F	the IBD diagnosis; age ≥18 years	prevalent IBD; less than 1 day of follow-up	an increased risk of BC (<i>SIR</i> : 1.13) was noted
Van den Heuvel et al. ⁴³ 2016 Denmark	population-based cohort study *C	2,325 IBD patients 1,515 UC 810 CD	≥18	the IBD diagnosis	NA	a decreased risk of BC in IBD patients (<i>SIR</i> : 0.11)
Tsai et al. ⁴⁴ 2015 Taiwan	population-based cohort study *C	4,856 women with IBD 19,424 control female patients	≥18 only F	the IBD diagnosis	NA	the incidence of BC was similar in the IBD and control cohorts (1.31 vs. 1.25 per 1,000 person-years); the <i>aHR</i> of BC was 0.95 (95% <i>CI</i> : 0.66–1.36) for IBD patients
Mansoor et al. ⁴⁵ 2020 USA	retrospective population- based study *C	306,390 IBD patients 165,750 CD 140,640 UC 6,500 BC	≥18	IBD female patients	NA	the prevalence of BC in individuals without IBD was 1.1%; the prevalence of BC was increased at 1.9% in CD (<i>OR</i> : 1.79; 95% <i>CI</i> : 1.73–1.85; <i>p</i> < 0.0001) and at 2.3% in UC (<i>OR</i> : 2.24; 95% <i>CI</i> : 2.17–2.32; <i>p</i> < 0.0001)

* B – randomized-controlled study; C – cohort study; *aHR* – adjusted hazard ratio; NA – not applicable.

Table 5. Inflammatory bowel disease (IBD) and pancreatic cancer (PC)

Study, year, country	Study design/quality level*	Number of participants (n)/type of cancer	Age [years] and gender of the participants	Inclusion criteria	Exclusion criteria	Findings
Jung et al. ³³ 2017 South Korea	retrospective study *C	10,049 UC 5,595 CD	all age categories 9,743 M 5,548 F	the IBD diagnosis	previous cancer recognition	there was a significantly increased risk of PC (RR: 1.0–3.1.0) in female CD patients
Mosher et al. ⁴⁶ 2018 USA	case–control study *D	2,080 IBD patients	NA	the IBD diagnosis	a history of heritable cancer syndromes	IBD patients were at significantly elevated risk of PC (RR: 4.23; 95% CI: 1.35–13.29)
Everhov et al. ⁴⁷ 2020 Denmark, Sweden	retrospective register-based cohort study *C	161,926 IBD patients/442 PC 97,514 UC 47,402 CD 17,010 IBD-U 1,599,024 control group/3,386 PC	all age categories 79,898 M 82,028 F	the IBD diagnosis	NA	the HR for PC was increased overall: 1.43 (1.30–1.58) in subtypes (UC: 1.35 (1.19–1.53); CD: 1.44 (1.18–1.74); IBD-U: 1.99 (1.50–2.64)), and especially in IBD patients with PSC: 7.55 (4.94–11.5)
Burisch et al. ⁴⁸ 2022 Denmark	retrospective study *C	1,161 UC	2–88	the UC diagnosis	NA	an increased risk of PC in patients with UC
Kimchy et al. ⁴⁹ 2023 USA	retrospective study analysis of hospitalizations of patients with IBD associated with PC *C	2,235,413 CD; 3,590 (0.16%) were found to be related to PC among the hospitalizations 1,324,746 UC; 2,878 (0.22%) were found to be related to PC among the hospitalizations	≥18	the IBD diagnosis; the PC diagnosis	NA	increased prevalence of PC in hospitalized IBD patients
Coward et al. ⁵⁰ 2023 Canada	retrospective population-based study *C	35,763 IBD patients 289,212 controls	all age categories	the IBD diagnosis	NA	IBD patients had a higher risk of PC (7.79; 5.53–10.97)
Zamani et al. ⁵¹ 2024	meta-analysis *A	11 cohort studies	NA	studies: (1) involving ≥100 adult subjects (aged ≥18 years) without a preexisting diagnosis of PC at the enrollment; (2) diagnosing IBD through endoscopy/colonoscopy or histological examinations; (3) reporting new cases of incident PC after the IBD diagnosis; (4) providing any statistical measures of association (compared with healthy populations) adjusted for potential confounding factors with their corresponding 95% CIs	(1) reviews, case reports, editorials, or letters to the editor; studies: (2) being published as duplicates or appraising the same population; (3) conducted on children; (4) lacking a clear presentation of the information concerning their methodology or the findings related to the study outcomes	the risk of PC increased by 79% in IBD patients (RR: 1.79; 95% CI: 1.16–2.75; $I^2 = 95.7\%$); patients either with CD (RR: 1.42; 95% CI: 1.24–1.63) or UC (RR: 1.50; 95% CI: 1.17–1.92) had an increased risk (p for interaction = 0.72); the annual incidence of PC potentially attributable to IBD increased by 55 cases (95% CI: 17–103) per million

* A – meta-analysis; C – cohort study; D – case-controlled study; RR – relative risk; HR – hazard ratio; PSC – primary sclerosing cholangitis; NA – not applicable.

Table 6. Inflammatory bowel disease (IBD) and hepatobiliary cancer

Study, year, country	Study design/ quality level*	Number of participants (n)/ type of cancer	Age [years] and gender of the participants	Inclusion criteria	Exclusion criteria	Findings
Jung et al. ³³ 2017 South Korea	retrospective study *C	10,049 UC 5,595 CD	all age categories 9,743 M 5,548 F	the IBD diagnosis	previous cancer recognition	an increased risk of liver cancers for women in UC (SIR: 4.4) and CD (SIR: 15.3)
Hovde et al. ³⁷ 2017 Norway	prospective population- based study *B	756 IBD patients 519 UC 237 CD	4–89 370 F	the IBD diagnosis	NA	an increased risk of liver/ biliary cancer in UC (SIR: 2.85)
Madanchi et al. ³³ 2016 Switzerland	retrospective study *C	1,026 IBD patients	19–102	the IBD diagnosis	NA	the observed incidence of CC (10.8/100,000) was higher than expected and known from the general population

* B – randomized-controlled study; C – cohort study; CCa – cholangiocarcinoma; NA – not applicable.

Urinary tract cancer

Urinary tract cancers comprise urinary bladder cancer (UBC), which tends to develop in older males, particularly those who smoke or have chronic inflammation, and renal cell carcinoma (RCC), which is associated with smoking, obesity and hypertension.^{55,56} In the early stages of RCC, elevated levels of tumor necrosis factor (TNF), a crucial mediator of cancer-related inflammation, have been observed.⁵⁷ Also in the case of urinary tract cancers, the results of the studies included in our review are ambiguous (Table 7).^{22,32,33,46,53,58–60} Importantly, an association between urinary tract cancer and thiopurines was suggested. In a French study, the incidence rates of urinary tract cancer were 0.48/1,000 patient-years in patients receiving thiopurines (95% CI: 0.21–0.95), 0.10/1,000 patient-years in patients who discontinued thiopurines (95% CI: 0.00–0.56) and 0.30/1,000 patient-years in patients never treated with thiopurines (95% CI: 0.12–0.62) at entry.⁶⁰ In turn, in another study, IBD patients had a significantly lower age at the RCC diagnosis, lower N-stage and lower M-stage, underwent more frequent surgical treatment for RCC as compared to the general population, and had a better survival independent of immunosuppression.⁵⁹

Prostate cancer

In men, prostate cancer (PCa) ranks as the most frequently diagnosed cancer in 118 countries.⁶¹ Men with IBD demonstrated a shorter time to develop PCa. An increasing adjusted hazard ratio (*aHR*) across years since the IBD diagnosis was observed (≤ 20 years, *aHR*: 1.22; > 20 years, *aHR*: 1.49; *p*-trend = 0.018).⁶² Men with IBD had higher rates of clinically significant PCa when compared with age- and race-matched controls.⁶³ In the majority of the analyzed studies, an increased risk of PCa was observed in patients with UC (Table 8).^{22,33,36,43,46,62–67}

Reproductive system cancers

The available studies regarding the association between IBD and reproductive cancers are inconclusive (Table 9).^{32,33,68–71} Rungoe et al. investigated the association between the occurrence of precancerous cervical lesions, finding that both CD and UC patients had an increased risk of low-grade and high-grade squamous intraepithelial lesion (SIL) as compared to the control group.⁶⁸ However, the risk of cervical cancer (CC) was elevated only in patients with CD.⁶⁸ Goetgebuer et al. also observed an increased risk of precancerous cervical lesions of cervical intraepithelial neoplasia (CIN) 2+ grade in patients with IBD.⁷⁰ The 2023 study by Hamid et al. reported a higher annual incidence of cervical, ovarian, endometrial, and vulvar cancers in female patients with IBD as compared to the general population.⁷¹ On the other hand, Kim et al. did not confirm an association between CC and IBD.⁶⁹

Table 7. Inflammatory bowel disease (IBD) and urinary tract cancers

Study, year, country	Study design/ quality level*	Number of participants (n)/ type of cancer	Age [years] and gender of the participants	Inclusion criteria	Exclusion criteria	Findings
So et al. ²² 2017 China	population-based cohort *C	2,621 IBD patients 1,603 UC 1,018 CD	all age categories 1,559 M 1,062 F	the IBD diagnosis	patients with IBD diagnosed before 1990 and whose dates of the IBD diagnosis were unknown	an increased risk of RCC in CD (SIR: 6.89)
Taborelli et al. ³² 2020 Italy	population-based cohort *C	3,664 IBD patients 2,358 UC 1,306 CD	18–84 1,911 M 1,753 F	the IBD diagnosis	<5 years of residence in the Friuli-Venezia Giulia region preceding the IBD diagnosis; follow-up <90 days; codes for both UC and CD	an increased risk of KC in UC (SIR: 2.06)
Jung et al. ³³ 2017 South Korea	retrospective study *C	10,049 UC 5,595 CD	all age categories 9,743 M 5,548 F	the IBD diagnosis	previous cancer recognition	in male and female patients with UC and CD, the risk of UBC and KC were comparable with that in the general population
Mosher et al. ⁴⁶ 2018 USA	case-control study *D	2,080 IBD patients	NA	the IBD diagnosis	a history of heritable cancer syndromes	IBD patients were at significantly elevated risk for KC (RR: 2.90; 95% CI: 1.46–5.84)
Madanchi et al. ⁵³ 2016 Switzerland	retrospective study *C	1,026 IBD patients	19–102	the IBD diagnosis	NA	the observed incidence of UBC (21.7/100,000), was higher than expected and known from the general population
Algaba et al. ⁵⁸ 2015 Spain	retrospective cohort study *C	9,100 IBD patients 4,550 CD 4,326 UC 224 IBD-U 5 UBC in CD 3 UBC in UC 6 KC in CD 4 KC in UC	all age categories	the IBD diagnosis	NA	there was no statistically significantly increased risk of UBC and KC in IBD patients (UBC IBD – 1.83 (0.28–1.11); UBC CD – 2.00 (0.29–1.63); UBC UC – 1.41 (0.14–1.30); KC IBD – 1.83 (0.90–3.19); KC CD – 2.00 (0.90–4.48); KC UC – 1.41 (0.53–3.74))
Derikx et al. ⁵⁹ 2015 Denmark	case-control study *D	NA	all age categories	NA	NA	pancolitis (OR: 1.8–2.5), penetrating CD (OR: 2.8), IBD-related surgery (OR: 3.7–4.5); male gender (OR: 3.2–5.0), and an older age at the IBD onset (OR: 1.0–1.1) were identified as independent risk factors for RCC
Bourrier et al. ⁶⁰ 2016 France	prospective observational cohort study *C	19,486 IBD patients 11,759 CD 7,727 UC or IBD-U	all age categories	the IBD diagnosis	NA	an increased risk of urinary tract cancers (HR: 2.82; 95% CI: 1.04–7.68; $p = 0.04$)

* C – cohort study; D – case-controlled study; UBC – urinary bladder cancer; KC – kidney cancer; RCC – renal cell carcinoma; NA – not applicable.

Table 8. Inflammatory bowel disease (IBD) and prostate cancer (PCa)

Study, year, country	Study design/ quality level*	Number of participants (n)/ type of cancer	Age [years] and gender of the participants	Inclusion criteria	Exclusion criteria	Findings
So et al. ²² 2017 China	population-based cohort study *C	2,621 IBD patients 1,603 UC 1,018 CD	all age categories 1,559 M 1,062 F	the IBD diagnosis	patients with IBD diagnosed before 1990 and whose dates of the IBD diagnosis were unknown	an increased risk of PCa in UC (SIR: 2.47; 95% CI: 1.24–4.95)
Jung et al. ³³ 2017 South Korea	retrospective study *C	10,049 UC 5,595 CD	all age categories 9,743 M 5,548 F	the IBD diagnosis	previous cancer recognition	an increased risk of PCa in UC (SIR: 3.47; 95% CI: 2.06–5.48)
Wilson et al. ³⁶ 2016 Switzerland	nested case-control study *D	39,294 IBD patients 1,603 UC 1,108 CD	NA	the IBD diagnosis	NA	a reduced risk of PCa in IBD patients taking aminosalicylates
Van den Heuvel et al. ⁴³ 2016 Denmark	population-based cohort study *C	2,325 IBD patients 1,515 UC 810 CD	≥18	the IBD diagnosis	NA	UC patients were not at increased risk of cancer overall (SIR: 1.12; 95% CI: 0.97–1.28) despite an increased risk of PCa (SIR: 1.82; 95% CI: 1.17–2.71)
Mosher et al. ⁴⁶ 2018 USA	case-control study *D	2,080 IBD patients	NA	the IBD diagnosis	a history of heritable cancer syndromes	IBD patients were at significantly elevated risk of PCa (RR: 1.70; 95% CI: 1.28–2.27)
Meyers et al. ⁶² 2020 UK	prospective population-based study *B	2,311 men with IBD 1,488 UC 643 CD 215,773 men without IBD (control group) 4,681 new cases of PCa in men without IBD and 66 in men with IBD (after a median follow-up of 78 months)	40–69 only M 21,084	IBD male patients	a prior history of a malignant cancer (any site) or the timing of the malignant cancer diagnosis relative to baseline could not be determined; the surgical removal of the prostate; earlier recorded death date; individuals whose genetically inferred sex was female	the association with PCa was only among men with UC (aHR: 1.47; 95% CI: 1.11–1.95; p = 0.007), and not CD (aHR: 1.06; 95% CI: 0.63–1.80; p = 0.820)
Burns et al. ⁶³ 2019 USA	retrospective matched-cohort study *C	1,033 male patients with IBD 9,306 men without IBD (control group) 715 PCa	only M 10,339	IBD male patients	female patients	the incidence of PCa at 10 years was 4.40% among men with IBD and 0.65% among controls
Khan et al. ⁶⁴ 2017 USA	retrospective cohort study *C	59,916 IBD 35,437 UC 28,332 CD 204 PCa	≥18	the IBD diagnosis	a diagnosis of rheumatoid arthritis or psoriasis; biological treatment; immuno- modulator or corticosteroids; age <18 years	the elderly with IBD have a higher risk of malignancy, specifically PCa, when compared with younger IBD patients and the general age-matched population
Ge et al. ⁶⁵ 2020	meta-analysis *A	NA	NA	the IBD diagnosis	NA	the risk of PCa was higher in UC (pooled SIR: 1.58; 95% CI: 1.08–2.30), but not in patients with CD (pooled SIR: 1.12; 95% CI: 0.97–1.31)
Na et al. ⁶⁶ 2022 South Korea	retrospective population-based cohort study *C	14,761 IBD patients 59,044 non-IBD patients	≥40 only M	IBD male patients	follow-up loss; any cancer development before the index date; follow-up <1 year from the index date; age <40 years; the female sex	the IBD status was not associated with the risk of PCa as compared to non-IBD (aHR: 0.93; 95% CI: 0.80–1.08; p = 0.320)
Zhou et al. ⁶⁷ 2023	meta-analysis of cohort studies *A	592,853 participants	NA	the IBD diagnosis	NA	IBD was linked to an elevated risk of incident PCa (HR: 1.20; 95% CI: 1.06–1.37; p = 0.004); UC was associated with an increased risk of incident PCa (HR: 1.20; 95% CI: 1.06–1.38; p = 0.006), while CD was not significantly linked to a higher risk of PCa (HR: 1.03, 95% CI: 0.91–1.17; p = 0.650)

* A – meta-analysis; B – randomized-controlled study; C – cohort study; D – case-controlled study; NA – not applicable.

Table 9. Inflammatory bowel disease (IBD) and reproductive system cancers

Study, year, country	Study design/ quality level*	Number of participants (n)/ type of cancer	Age [years] and gender of the participants	Inclusion criteria	Exclusion criteria	Findings
Taborelli et al. ³² 2020 Italy	population-based cohort study *C	3,664 IBD patients 2,358 UC 1,306 CD	18–84 1,911 M 1,753 F	the IBD diagnosis	<5 years of residence in the Friuli-Venezia Giulia region preceding the IBD diagnosis; follow-up <90 days; codes for both UC and CD	there was an increased risk of corpus uteri cancer in UC (SIR: 2.67)
Jung et al. ³³ 2017 South Korea	retrospective study *C	10,049 UC 5,595 CD	all age categories 9,743 M 5,548 F	the IBD diagnosis	previous cancer recognition	there was an increased risk of CC in UC (SIR: 5.7)
Rungoe et al. ⁶⁸ 2015 Denmark	population-based cohort study *C	27,398 female patients with IBD 18,681 UC 8,717 CD 1,508,334 women (control group)	NA	the IBD diagnosis	NA	patients with UC had an increased risk of low-grade (RR: 1.15; 95% CI: 1.00–1.32) and high-grade (RR: 1.12; 95% CI: 1.01–1.25) SIL, whereas patients with CD had an increased risk of low-grade (RR: 1.26; 95% CI: 1.07–1.48) and high-grade (RR: 1.28; 95% CI: 1.13–1.45) SIL, and CC as compared to controls (RR: 1.53; 95% CI: 1.04–2.27)
Kim et al. ⁶⁹ 2015 USA	population-based study *C	133,333 female patients with systemic inflammatory diseases 25,176 IBD	only F	a diagnosis of systemic inflammatory disease	NA	no association between IBD and CC
Goetgebuuer et al. ⁷⁰ 2021 Denmark	case–control cohort study *D	2,098 female patients with IBD	only F	the IBD diagnosis	no cytological or histological results during the study period	the CIN2+ detection rate was higher in the IBD cohort than in the matched cohort (SDR: 1.27; 95% CI: 1.05–1.52); women with IBD had an increased risk of CIN2+ (RR: 1.66; 95% CI: 1.21–2.25), and persistent or recurrent CIN during follow-up (OR: 1.89; 95% CI: 1.06–3.38)
Hamid et al. ⁷¹ 2023 USA	population-based control study *C	264,984 female patients with IBD 4,563 (1.7%) developed gynecological cancer 1,225 IBD and CC 1,395 IBD and ovarian cancer 1,567 IBD and endometrial cancer 376 IBD and vulvar cancer	all age categories only F	IBD female patients	a history of gynecological cancers prior to the IBD diagnosis	comparing the IBD population to the non-IBD general population, higher incidence proportion per year and prevalence of all 4 types of gynecological cancers were observed: for CC, the annual incidence proportion was 0.033% among women with IBD, while it was 0.014% in non-IBD patients; in ovarian cancer, the annual incidence proportion was 0.042% in the IBD group as compared to 0.021% in non-IBD patients; endometrial cancer showed an annual incidence proportion of 0.047% in women with IBD as compared to 0.028% in non-IBD patients, and vulvar cancer had an annual incidence proportion of 0.012% in IBD patients as compared to 0.004% in non-IBD patients

* C – cohort study; D – case–controlled study; CC – cervical cancer; SIL – squamous intraepithelial lesion; CIN – cervical intraepithelial neoplasia; CIN2+ – high-grade dysplasia and cervical cancer; SDR – standardized detection ratio; NA – not applicable.

Central nervous system malignancies

The number of studies assessing the risk of central nervous system tumors in patients with IBD is limited (Table 10).²⁵ In 2023, a large, multicenter, prospective study was published, which included 12,882 patients with IBD; it was found that there was a relationship between IBD, CD and brain malignancies.²⁵ More population studies are required to validate this correlation.

Hematological malignancies

The relationship between hematological malignancies and IBD is of great interest. Two large meta-analyses focusing on this relationship have been published recently.^{51,67} They have shed new light on the not always consistent results of single studies.^{32,53} Although further research work is needed, the abovementioned studies organize current knowledge, and provide a practical signpost for gastroenterologists and oncologists.

Zhou et al. demonstrated that the incidence of hematologic malignancies in the IBD cohort, both CD and UC patients, was higher than in non-IBD individuals.⁶⁷ Furthermore, the incidence of specific malignancies – non-Hodgkin’s lymphoma, Hodgkin’s lymphoma and leukemia – was also higher in IBD patients.⁶⁷

Zamani et al. published a systematic review and meta-analysis of population-based cohort studies that evaluated the risk of lymphoma in patients with IBD in comparison with those without IBD.⁵¹ The research demonstrated that the risk was moderately increased in patients with IBD, with CD having a slightly higher risk than UC. Considering the strengths of the study, especially the type of studies included and a very high number of participants, the significance of the findings showing a 30% higher risk of lymphoma in patients with IBD should be highlighted. Furthermore, based on the meta-regression and sensitivity analysis, Zamani et al. concluded that the overall increased risk of lymphoma in IBD was probably independent of the effects of medications. This is another important finding of the study considering the association between drugs, especially biologics and immunomodulators, and the risk of lymphoma.⁵¹ All the mentioned studies are presented in Table 11.^{32,51,53,67}

Skin cancers

There are well-recognized associations between IBD and skin cancers, which are most frequently linked to specific therapies (Table 12).^{22,39,43,46,72} The risk of basal cell carcinoma (BCC) and melanoma was increased in thiopurine and anti-TNF users, and the risk of squamous cell carcinoma (SCC) was increased only in thiopurine users.⁷²

Table 10. Inflammatory bowel disease (IBD) and central nervous system malignancies

Study, year, country	Study design/ quality level*	Number of participants (n)/ type of cancer	Age [years] and gender of the participants	Inclusion criteria	Exclusion criteria	Findings
Gao et al. ²⁵ 2023 European countries	Mendelian randomization study *B	12,882 IBD patients 6,968 UC 5,956 CD	NA	the IBD diagnosis	NA	there is a link between IBD and brain cancer (OR: 1.104; 95% CI: 1.003–1.216; $p = 0.043$); a relationship between CD and brain cancer was found (OR: 1.105; 95% CI: 1.013–1.205; $p = 0.024$)

* B – randomized-controlled study; NA – not applicable.

Table 11. Inflammatory bowel disease (IBD) and hematological malignancies

Study, year, country	Study design/ quality level*	Number of participants (n)/ type of cancer	Age [years] and gender of the participants	Inclusion criteria	Exclusion criteria	Findings
Taborelli et al. ³² 2020 Italy	population-based cohort study *C	3,664 IBD patients 2,358 UC 1,306 CD	18–84 1,911 M 1,753 F	the IBD diagnosis	<5 years of residence in the Friuli-Venezia Giulia region preceding the IBD diagnosis; follow-up <90 days; codes for both UC and CD	there was no increased risk of hematological malignancies in IBD patients
Zamani et al. ⁵¹ 2024	meta-analysis *A	23 studies 2,078 lymphoma events in 656,731 IBD patients	NA	studies: (1) involving adult subjects without a preexisting diagnosis of lymphoma at the enrollment; (2) diagnosing IBD through histological or radiological examinations; (3) reporting new cases of lymphoma after the IBD diagnosis; (4) providing any statistical measures of association (compared with healthy populations)	(1) reviews, case reports, editorials, or letters to the editor; studies: (2) being published as duplicates or appraising the same population; (3) conducted on children; (4) specifically dealing with cutaneous lymphoma (5) lacking a clear presentation of the information concerning their methodology or the findings related to the study outcomes	patients with IBD had 30% higher odds of lymphoma (RR: 1.30; 95% CI: 1.21–1.40); the risk of developing both NHL (RR: 1.31; 95% CI: 1.20–1.42) and HL (RR: 1.29; 95% CI: 1.06–1.53) was increased in patients with IBD (p for interaction = 0.881); an increased risk of lymphoma was observed in both CD (RR: 1.54; 95% CI: 1.27–1.80) and UC (RR: 1.22; 95% CI: 1.09–1.35; p for interaction = 0.026)
Madanchi et al. ⁵³ 2016 Switzerland	retrospective study *C	1,026 IBD patients	19–102	the IBD diagnosis	NA	the observed incidence of lymphoma (32.5/100,000) was higher than expected and known from the general population
Zhou et al. ⁶⁷ 2023	meta-analysis *A	20 cohort studies 756,377 participants	NA	(1) population: people without hematologic malignancies or related high-risk factors; (2) exposure: patients diagnosed with IBD; (3) control: people who did not suffer from IBD; (4) outcome: the incidence of hematological malignancies (5) cohort studies	(1) full text not available; (2) articles published before 2000; (3) articles not in English; (4) the patients had developed hematological malignancies before the IBD diagnosis; (5) different articles with the same source of the cohort data; more comprehensive or newer, updated studies were included	in comparison with the non-IBD cohort, the incidence of hematological malignancies in IBD patients was higher (SIR: 3.05; $p < 0.001$); in comparison with the non-IBD cohort, the incidence of hematological malignancies in CD (SIR: 3.56; $p = 0.005$) and UC (SIR: 2.29; $p = 0.005$) was higher; the incidence of NHL (SIR: 1.70; $p = 0.010$), HL (SIR: = 3.47; $p = 0.002$) and leukemia (SIR: 3.69; $p < 0.001$) was higher in the IBD cohort

* A – meta-analysis; C – cohort study; NHL – non-Hodgkin's lymphoma; HL – Hodgkin's lymphoma; NA – not applicable.

Table 12. Inflammatory bowel disease (IBD) and skin cancers

Study, year, country	Study design/ quality level*	Number of participants (n)/ type of cancer	Age [years] and gender of the participants	Inclusion criteria	Exclusion criteria	Findings
So et al. ²² 2017 China	population-based cohort study *C	2,621 IBD patients 1,603 UC 1,018 CD	all age categories 1,559 M 1,062 F	the IBD diagnosis	a previous history of cancer before IBD; cancer diagnosed within 6 months of the IBD diagnosis	an increased risk of NMSC in UC (SIR: 9.05) and CD (SIR: 13.88)
Loo et al. ³⁹ 2019 Canada	population-based study *C	35,985 IBD patients 20,644 CD 14,000 UC 1,341 IBD-U 225 ECs	≥ 18 16,563 M 19,422 F	the IBD diagnosis; age ≥ 18 years	prevalent IBD; less than 1 day of follow-up	an increased risk of NMSC (SIR: 22.62)
Van den Heuvel et al. ⁴³ 2016 Denmark	population-based cohort study *C	2,325 IBD patients 1,515 UC 810 CD	≥ 18	the IBD diagnosis	NA	an increased risk of skin cancer in CD (SIR: 1.55)
Mosher et al. ⁴⁶ 2018 USA	case-control study *D	2,080 IBD patients	NA	the IBD diagnosis	a history of heritable cancer syndromes	an increased risk of NMSC (RR: 2.38) and MSC (RR: 2.85) in IBD patients
Narous et al. ⁷² 2023 Canada	retrospective study *C	11,228 IBD patients 5,839 UC 5,389 CD BCC 647 SCC 169 other NMSCs 22 MSC 56	5,227 M 6,001 F	the IBD diagnosis	NA	patients with UC were more likely to have BCC predating their UC diagnosis (OR: 1.32; 95% CI: 1.08–1.60); for the post-IBD diagnosis, the risk of BCC (HR: 1.53; 95% CI: 1.37–1.70) and SCC (HR: 1.61; 95% CI: 1.29–2.01) were significantly increased across all IBD groups, except for SCC in UC; there was no significant association between melanoma and IBD post-IBD diagnosis

* C – cohort study; D – case-controlled study; BCC – basal cell carcinoma; SCC – squamous cell carcinoma; NMSC – non-melanoma skin cancer; MSC – melanoma skin cancer; NA – not applicable.

Effect of the use of thiopurines on the risk of developing extraintestinal malignancies

Despite the development of molecularly oriented therapeutic strategies, thiopurines, such as azathioprine and 6-mercaptopurine, still play an important role in treating IBD. Yet, the treatment with thiopurines in IBD patients is associated with an increased risk of developing hematological malignancies, non-melanoma skin cancer (NMSC), urinary tract cancers, and CC. However, the latter association is uncertain.

Hematological malignancies

Several studies have found that the use of immunosuppressive treatment with thiopurines may increase the risk of hematological malignancies in patients with IBD. A prospective observational study involving 19,486 IBD patients included in the Cancer et Sur-risque Associé aux Maladies Inflammatoires Intestinales en France (CESAME) showed that IBD patients who were currently treated with thiopurines and those who had never received the drugs showed no increased overall risk of lymphoproliferative neoplasms, including acute myeloid leukemia and myelodysplastic syndrome.⁷³ In contrast, patients who had been exposed to thiopurines in the past had a 7-fold increased risk of developing lymphoproliferative neoplasms.⁷³ Kotlyar et al. in a meta-analysis proved that the incidence of lymphoma during thiopurine use was almost 6 times higher, but this risk did not persist after thiopurines were discontinued.⁷⁴ Selected studies on the association between thiopurine therapy in IBD and hematological malignancies are presented in Table 13.^{67,74–76}

Urinary tract cancers

Studies on thiopurines and the urinary tract cancer risk present conflicting results. A cohort study involving 1,986 IBD patients, 30.1% of whom were receiving thiopurines, found that patients treated with thiopurines were at increased risk of developing urinary tract cancer.⁶⁰ In contrast, in a retrospective study, Caviglia et al. found no clinically significant association between thiopurines use and urothelial carcinoma.⁷⁷ The analyzed studies are presented in Table 14.^{60,75,77}

Cervical cancer

The effect of immunosuppressive drugs on the development of dysplasia and CC in IBD has been addressed many times and is still controversial.

A meta-analysis published in 2015 found an increased overall risk of cervical dysplasia and CC in IBD patients with current or prior treatment with immunosuppressive drugs as compared to the general population.⁷⁸ However,

Table 13. Thiopurines and hematological malignancies

Study, year, country	Study design/quality level*	Number of participants (n)/type of cancer	Age [years] and gender of the participants	Inclusion criteria	Exclusion criteria	Findings
Zhou et al. ⁶⁷ 2023	meta-analysis *A	20 cohort studies 756,377 participants 4 studies reported the percentage of TP patients with IBD	NA	the IBD diagnosis	patients developed hematological malignancies before being diagnosed with IBD	for patients with IBD who used TP – SIR: 3.80; 95% CI: 2.46–5.87; <i>p</i> = 0.001; the type of hematological malignancy was not specified
Kotlyar et al. ⁷⁴ 2015 USA	meta-analysis *A	24,029 IBD patients	NA	the IBD diagnosis; AZA or 6-MP treatment	anti-TNF treatment	current TP treatment – SIR: 5.71; 95% CI: 3.72–10.1; past TP treatment – SIR: 1.42; 95% CI: 0.86–2.34
Ardabili et al. ⁷⁵ 2022 the Netherlands	retrospective cohort study *C	1,016 IBD patients 643 CD 373 UC 653 patients used TP in monotherapy for at least 12 months	≥18	the IBD diagnosis; monotherapy with TP (AZA, 6-MP, 6-TG)	UC patients with a history of colectomy; patients starting combination therapy or using other immuno-suppressive drugs	the incidence rate of lymphoma was 1.04 (95% CI: 0.38–2.31) per 1,000 person-years
Lemaitre et al. ⁷⁶ 2017 France	cohort study *C	189,289 IBD patients 50,405 were exposed to TP monotherapy lymphoma (70 patients exposed to thiopurine monotherapy)	≥18	the IBD diagnosis	HIV infection; organ transplant recipients; cancer before inclusion or cancer <3 months after the IBD diagnosis; an uncertain IBD diagnosis	the risk of lymphoma was found to be higher in patients exposed to TP monotherapy (aHR: 2.60; 95% CI: 1.96–3.44; <i>p</i> < 0.001), anti-TNF monotherapy (aHR: 2.41; 95% CI: 1.60–3.64; <i>p</i> < 0.001), or combination therapy (aHR: 6.11; 95% CI: 3.46–10.8; <i>p</i> < 0.001)

* A – meta-analysis; C – cohort study; TP – thiopurine; AZA – azathioprine; 6-MP – 6-mercaptopurine; 6-TG – 6-thioguanine; TNF – tumor necrosis factor; HIV – human immunodeficiency virus; NA – not applicable.

Table 14. Thiopurines and urinary tract cancers

Study, year, country	Study design/quality level*	Number of participants (n)/type of cancer	Age [years] and gender of the participants	Inclusion criteria	Exclusion criteria	Findings
Bourrier et al. ⁶⁰ 2016 France	prospective observational cohort study *C	1,986 IBD patients 456 patients used TP in monotherapy UBC 6 KC 10	≥18	the IBD diagnosis	NA	an increased risk of urinary tract cancers (HR: 2.82; 95% CI: 1.04–7.68; <i>p</i> = 0.04)
Ardabili et al. ⁷⁵ 2022 the Netherlands	retrospective cohort study *C	1,016 IBD patients 643 CD 373 UC 653 patients used TP in monotherapy for at least 12 months	≥18	the IBD diagnosis; monotherapy with TP	UC patients with a history of colectomy; patients starting combination therapy or using other immuno-suppressive drugs	no increased risk of urinary tract cancers during TP treatment
Caviglia et al. ⁷⁷ 2021 Italy	retrospective cohort study *C	5,739 IBD patients	≥16	the IBD diagnosis	a lack of data on the presence of tumor comorbidities	treatment with TP was not a risk factor for urinary tract cancers (OR: 0.57; 95% CI: 0.19–1.69)

* C – cohort study; NA – not applicable.

this study has a limitation, as it did not take into account the effect of specific immunosuppressive drugs, the actual or cumulative dose, or the duration of therapy.⁷⁸ Of a different opinion are Mann et al., who in their meta-analysis did not confirm an increased risk of CC for patients using thiopurines.⁷⁹ In turn, Goetgebuer et al. found an increase in the risk of CIN2+ due to exposure to immunosuppressants.⁷⁰ A detailed overview of the studies under analysis is provided in Table 15.^{70,78,79}

Biological treatment and extraintestinal malignancies

The invention of biological drugs, and consequently their incorporation into the treatment standards for individuals with IBD, has significantly changed the approach to patient management. In addition to the obvious benefits of better control of the underlying disease, several challenges have also emerged that need to be addressed. Biological drugs have various mechanisms of action, but their common feature is the suppression of the immune system. The biologics used in IBD include: TNF- α inhibitors (infliximab, adalimumab, certolizumab, and golimumab); anti-integrin drugs (vedolizumab – a humanized immunoglobulin G1 (IgG1) monoclonal antibody that blocks the binding of integrin $\alpha 4\beta 7$ to MAdCAM-1, preventing lymphocyte migration to the intestines); drugs targeting the interleukin (IL) IL-12/IL-23 pathway (ustekinumab – a human monoclonal antibody targeting the p40 subunit of IL-12 and IL-23, inhibiting the binding of IL-12 and IL-23 to their respective receptors on the surface of T and NK cells, others – mirikizumab, rizankizumab).^{80,81}

TNF- α inhibitors and the risk of extraintestinal malignancies

Several studies have addressed the issue of the impact of using anti-TNF inhibitors in the treatment of IBD on the development of extraintestinal cancers (Table 16).^{76,82–84} Lemaitre et al., based on data from a cohort study involving 189,289 patients with IBD, concluded that there was a small, but statistically significant increase in the risk of lymphoma associated with the use of TNF-alpha inhibitors.⁷⁶ The risk of cancer was even higher when TNF-alpha inhibitors and thiopurines were used concurrently.⁷⁶ Chaparro et al., in their observational cohort study involving 11,011 patients from the Spanish ENEIDA registry, did not observe an association between the use of immunosuppressants (mainly thiopurines) nor anti-TNF drugs and an increased risk of EMs in individuals with IBD.⁸³ The study considered lymphomas, leukemia, NMSC, and melanoma skin cancer (MSC).⁸³ Similarly, D'Haens et al.⁸² and Kopylov et al.⁸⁴ did not describe an association between the use of anti-TNF inhibitors and an increased risk of EMs.

Anti-integrin drugs (vedolizumab) and the risk of extraintestinal malignancies

Colombel et al. in their meta-analysis found no significant association between the use of vedolizumab and an increased risk of EMs.⁸⁵ Furthermore, all patients exposed to vedolizumab who were diagnosed with skin cancer had a history of azathioprine therapy, and 2 continued to use azathioprine in the study.⁸⁵ Card et al., based on data from the GEMINI long-term safety (LTS) study, found that the number of malignancies occurring in patients using vedolizumab was similar to the expected number of malignancies in a population of IBD patients not using vedolizumab.⁸⁶ Singh et al. demonstrated that the use of vedolizumab did not increase the risk of malignancy as compared to infliximab.⁸⁷ In a meta-analysis conducted by Cohen et al. on a very large number of patients, we can find information that among EMs in patients with CD, there was UBC and KC, and then skin cancer, and among patients with UC – lymphomas and respiratory malignancies.⁸⁸ The study did not note any new safety concerns. The incidence of adverse events, such as malignancies, was low enough considering the patient-years of exposure to confirm the favorable safety profile of vedolizumab.⁸⁸ Additionally, a recent multicenter cohort study demonstrated no difference in cancer incidence in the IBD patients with prior non-digestive malignancy, treated with vedolizumab or anti-TNF.⁸⁹ The studies included in the analysis are listed in Table 17.^{85–88}

Drugs targeting the IL-12/IL-23 pathway (ustekinumab) and the risk of extraintestinal malignancies

In their study, Hong et al. showed that there was no association between the use of ustekinumab and the occurrence of malignancy in patients with prior malignancy.⁹⁰ Sandborn et al. showed in their meta-analysis that taking ustekinumab did not increase the risk of malignancy as compared to placebo.⁹¹ Table 18 provides a summary of the study results.^{90,91}

Small-molecule drugs and extraintestinal malignancies

There are 2 basic groups of small-molecule drugs: Janus-activated kinase (JAK) inhibitors (including tofacitinib, filgotinib, upadacitinib); and sphingosine-1-phosphate receptor modulators (including ozanimod), increasingly used to treat IBD.⁹² Chen et al. in their meta-analysis did not show any association between the use of small-molecule drugs and the occurrence of malignancy.⁹³ Goessens et al., in their observational study of IBD patients receiving combination therapy consisting of biologics and small-molecule

Table 15. Thiopurines and cervical cancer (CC)

Study, year, country	Study design/quality level*	Number of participants (n)/type of cancer	Age [years] and gender of the participants	Inclusion criteria	Exclusion criteria	Findings
Goettebauer et al. ⁷⁰ 2021 Denmark	case-control cohort study *D	2,098 female patients with IBD 1,382 CD 716 UC 1,030 using immuno-suppressants	≥18 only F	the IBD diagnosis	no cytological or histological results during the study period	the CIN2+ detection rate was higher in the IBD cohort than in the matched cohort (SDR: 1.27, 95% CI: 1.05–1.52); women with IBD had an increased risk of CIN2+ (IRR: 1.66; 95% CI: 1.21–2.25), and persistent or recurrent CIN during follow-up (OR: 1.89; 95% CI: 1.06–3.38)
Allegretti et al. ⁷⁸ 2015 multi-national study	meta-analysis *A	77,116 IBD patients high-grade cervical dysplasia/ cancer: 995 cases	≥16 only F	the IBD diagnosis; immune-suppressive medications (including, but not restricted to, AZA, 6-MP, MTX); at least one Pap test within the defined study period	no immune-suppressive medications	IBD patients had an increased risk of cervical high-grade dysplasia/ cancer as compared to healthy controls (OR: 1.34; 95% CI: 1.23–1.46)
Mann et al. ⁷⁹ 2022 multi-national study	meta-analysis *A	74,310 IBD patients	only F	the IBD diagnosis	NA	no statistically significantly increased risk of cervical cancer in IBD patients (HR: 1.24; 95% CI: 0.94–1.63); an increased risk of low-grade cervical lesions in IBD patients (HR: 1.15; 95% CI: 1.04–1.28); no statistically significantly increased risk in CD (HR: 1.36; 95% CI: 0.83–2.23) or UC (HR: 0.95; 95% CI: 0.72–1.25)

* A – meta-analysis; D – case-controlled study; MTX – methotrexate; NA – not applicable.

Table 16. Tumor necrosis factor-alpha (TNF- α) inhibitors and the risk of extraintestinal malignancies (EMs)

Study, year, country	Study design/ quality level*	Number of participants (n)/ type of cancer	Age [years] and gender of the participants	Inclusion criteria	Exclusion criteria	Findings
Lemaitre et al. ⁷⁶ 2017 France	nationwide cohort study *C	189,289 IBD patients lymphoma (32 patients exposed to anti-TNF monotherapy)	≥ 18	the IBD diagnosis	HIV infection; organ transplant recipients; cancer before inclusion or cancer <3 months after the IBD diagnosis; an uncertain IBD diagnosis	anti-TNF monotherapy (infliximab or adalimumab) was associated with a small, but statistically significant increase in the risk of lymphoma as compared to exposure to neither medication (<i>aHR</i> : 2.41; 95% <i>CI</i> : 1.60–3.64; <i>p</i> < 0.001)
D'Haens et al. ⁸² 2017 8 EU countries and UK	prospective observational study *B	2,662 IBD patients lymphoma (9 patients) BCC 5 BC 5	≥ 18	the CD diagnosis	active and untreated latent tuberculosis; lympho-proliferative disorders; malignancies; moderate or severe heart failure NYHA class III/IV diagnosed before inclusion	anti-TNF monotherapy (infliximab) vs. conventional therapy (without infliximab) was not associated with an increased risk of lympho-proliferative disorder/ malignancy (<i>HR</i> : 1.44; 95% <i>CI</i> : 0.86–2.42; <i>p</i> = 0.163)
Chaparro et al. ⁸³ 2017 Spain	observational cohort study *C	11,011 IBD patients lymphoma (5 patients*) leukemia (4 patients*) NMSC 4* MSC 3* * exposed to both anti- TNF drug and immune- suppressants (mainly thiopurines)	NA	the IBD diagnosis	cancer development before the IBD diagnosis; receiving an immune-suppressant other than thiopurines, MTX or an anti-TNF agent (such as cyclosporine or tacrolimus)	TNF- α inhibitors (vs. no treatment) did not increase the risk of EMs (<i>HR</i> : 0.72; 95% <i>CI</i> : 0.52–1.00)
Kopylov et al. ⁸⁴ 2015 Canada	nested case-control cohort study *D	19,582 IBD	NA	the IBD diagnosis	<1 year of follow-up; never exposed to IBD- related medications; the cancer diagnosis predating the inclusion in the database or within the first year	no association was found between the risk of the evaluated malignancies and anti-TNF- α medications

* B – randomized-controlled study; C – cohort study; D – case-controlled study; NYHA – New York Heart Association classification; NA – not applicable.

Table 17. Anti-integrin drugs (vedolizumab) and the risk of extraintestinal malignancies (EMs)

Study, year, country	Study design/quality level*	Number of participants (n)/type of cancer	Age [years] and gender of the participants	Inclusion criteria	Exclusion criteria	Findings
Colombel et al. ⁸⁵ 2017	meta-analysis based on 6 studies *A	2,830 patients HCC KC NMSC B cell lymphoma	NA	the IBD diagnosis; phase 2 and phase 3 clinical studies; -patients who received at least one dose of vedolizumab	data from a phase 1 clinical study	18 vedolizumab-exposed patients (<1%) were diagnosed with a malignancy; the incidence of NMSC in vedolizumab-exposed patients was not greater than in patients who received placebo
Card et al. ⁸⁶ 2020	meta-analysis based on the GEMINI long-term safety (LTS) study and post-marketing (PM) setting *A	1,785 patients TC respiratory tract cancer UBC KC	NA	the IBD diagnosis	patients with a history of malignancy prior to starting treatment with vedolizumab or with a diagnosis of malignancy within 1 year following the initiation of vedolizumab	the total number of the observed malignancies was similar to that expected after standardizing against patients with IBD in the databases
Singh et al. ⁸⁷ 2022 USA	retrospective cohort study *C	4,807 patients solid organs cancer hematological cancer skin cancer	18–89	the IBD diagnosis	patients with HIV infection, congenital immune-deficiency or organ transplantation; a diagnosis of any malignancy within the baseline 12 months prior to index biologic initiation date; a concomitant diagnosis of rheumatoid arthritis, ankylosing spondylitis, psoriasis, or psoriatic arthritis within the baseline 12 months prior to index biologic initiation date	no difference was observed in time to incident malignancy between the vedolizumab and TNF- α antagonists groups (<i>HR</i> : 1.15; 95% <i>CI</i> : 0.61–2.19)
Cohen et al. ⁸⁸ 2020	meta-analysis of cohort studies *A	32,752 patients respiratory tract cancer UBC KC lymphoma skin cancer	NA	the IBD diagnosis	NA	in patients with CD, UBC and KC (18 events), skin cancer – unspecified and other (12 events); in patients with UC, respiratory tract cancer (11 events) and lymphoma (14 events)

* A – meta-analysis; C – cohort study; HCC – hepatocellular carcinoma; NA – not applicable.

Table 18. Anti-interleukin drugs and the risk of extraintestinal malignancies (EMs)

Study, year, country	Study design/quality level*	Number of participants (n)/type of cancer	Age [years] and gender of the participants	Inclusion criteria	Exclusion criteria	Findings
Hong et al. ⁹⁰ 2022 USA	retrospective cohort study *C	390 patients hematological cancer dermatological cancer	adults M and F	the IBD diagnosis	patients with exposure to multiple agents were excluded from the primary analysis	no increase in the risk of subsequent cancer with ustekinumab (aHR: 0.96; 95% CI: 0.17–5.41)
Sandborn et al. ⁹¹ 2021 USA	meta-analysis *A	2,574 patients papillary RCC PCa testis cancer plasma cell myeloma (multiple myeloma)	NA	the IBD diagnosis; data from phase 2 and phase 3 clinical trials	NMSC	the risk of malignancy was similar in placebo and ustekinumab; placebo – 0.17 (95% CI: 0.00–0.93) vs. ustekinumab – 0.40 (95% CI: 0.16–0.83)

* A – meta-analysis; C – cohort study; NA – not applicable.

drugs, observed that in patients with a previous history of malignancy there was no recurrence of cancer.⁹⁴ The results of the discussed studies are presented in Table 19.^{93,94}

Molecular and immunological mechanisms of extraintestinal malignancies in inflammatory bowel diseases

One of the leading factors contributing to an increased risk of cancer in IBD is the chronic inflammatory process.⁹⁵ The available studies indicate that this factor plays a key role not only in the development of CRC or small bowel adenocarcinoma, but also EMs. Other factors, such as an older age, smoking, HPV infection, and the coexisting PSC, may independently increase the risk of developing EMs in IBD.⁹⁶ Chronic inflammation in IBD leads to the release of pro-inflammatory mediators, like TNF- α , IL-6 and IL-17, which drive cancer development by activating key signaling pathways, such as NF- κ B, JAK/STAT, Wnt/ β -catenin, and PI3K/AKT. Inflammation leads to oxidative stress by overproducing reactive oxygen species, which can damage DNA and contribute to cancer-related genetic changes.⁹⁷ Gut microbiota is the key to maintaining intestinal balance and immune regulation. Dysbiosis is strongly associated with IBD, colitis-associated cancer, and could also contribute to the formation of EMs. Harmful bacteria, like *E. nucleatum* and certain *E. coli* strains, can disrupt the mucosal barrier, trigger inflammation and promote carcinogenesis through mechanisms such as toxin production and DNA damage.⁹⁸

Limitations

Our review has several limitations. Our literature search was limited to the papers published after January 1, 2015, to review the most recent studies. Due to the changing incidence of cancer and dynamic changes in IBD therapy, we decided to limit our search to the last 10 years. Studies of EMs in IBD were characterized by high heterogeneity. Several studies were of retrospective nature and referred to a small sample of IBD patients. The results of these studies do not provide strong evidence and must be interpreted with extreme caution.

Conclusions

An increased risk of oral, pancreatic and hepatobiliary malignancies is observed among EMs in IBD patients (Fig. 2). As for other types of EMs, the results of the presented research are inconsistent and require verification in large population studies.

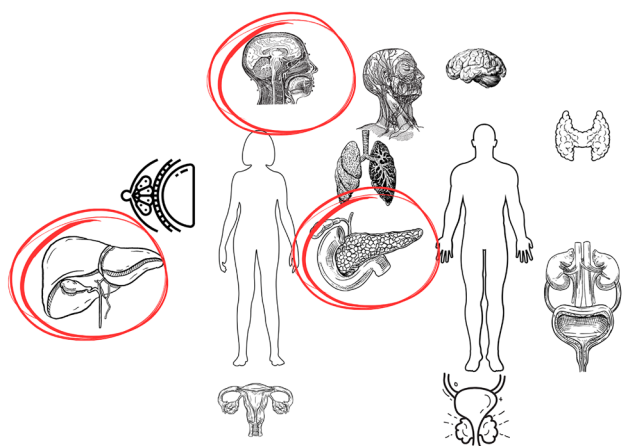


Fig. 2. Extraintestinal cancers in inflammatory bowel disease (IBD)

The dynamic epidemiological situation, combined with the methodological limitations of many existing studies, underscores the need for further research to better understand the relationship between IBD and cancer. In this group of patients, special oncological vigilance, the employment of the available prevention methods (e.g., vaccination), patient education, and, when recommended, screening tests are required. A clinical challenge involving a multidisciplinary approach is the treatment of IBD in cancer patients, especially during disease exacerbation, as well as cancer therapy in IBD patients.

It should be emphasized that the overall risk of EMs in IBD patients remains low, and even if the therapies used are associated with an increase in this risk, it should not influence the decision on the optimal available therapy.

Ethics approval and consent to participate

Not applicable.

Data availability

Not applicable.

Consent for publication

The datasets supporting the findings of the current study are available from the corresponding author on reasonable request.

Use of AI and AI-assisted technologies

The graphical abstract and the figures were created using Canva.

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Table 19. Small-molecule drugs and the risk of extraintestinal malignancies (EMs)

Study, year, country	Study design/quality level*	Number of participants (n)/type of cancer	Age [years] and gender of the participants	Inclusion criteria	Exclusion criteria	Findings
Chen et al. ⁹³ 2024 multi-national study	meta-analysis of randomized controlled trials (RCT) *A	10,623 different types of cancer (including NMSC and other EMs)	adults M and F	patients diagnosed with IBD, receiving the administered SMDs	pediatric patients with IBD	in general, no malignancies were linked to SMDs; using SMDs was not significantly associated with the risk of developing malignant tumors, excluding NMSC (RR: 1.20; 95% CI: 0.55–2.59); using SMDs was not associated with an increased risk of developing NMSC (RR: 1.14; 95% CI: 0.41–3.23)
Goessens et al. ⁹⁴ 2021 multi-national study	retrospective observational study *C	98	adults M and F	IBD patients with the concomitant use of 2 biologics or 1 biologic with SMDs	pediatric patients with IBD	4% of the study population had a previous history of cancer before undergoing combination therapy, with no recurrence noted after a median follow-up of 14.5 months

* A – meta-analysis; C – cohort study; SMDs – small-molecule drugs; NA – not applicable.

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