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Age of onset of inflammatory bowel disease is the strongest risk factor for the development of malignancy

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Abstract

Background Inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis, is a multifactorial inflammatory disorder of the gastrointestinal system that impairs the patient's quality of life. Its presentation includes a spectrum of symptoms that may also be secondary to IBD complications, such as malignancy. On the other hand, immunosuppressive treatment to maintain remission also carries a risk of malignancy, which can cause patients distress due to the risk/benefit balance of IBD control and malignancy.

Methods In this nationwide retrospective study, we aimed to elucidate which patient and treatment factors have the greatest impact on the development of malignancy in IBD patients. Statistical analysis was performed on patient factors, including treatment types, and nominal regression analysis was carried out to assess the effects of multiple risk factors on the incidence of malignancy in patients with IBD.

Results Age at diagnosis of IBD correlated significantly with malignancy development, as did the diagnosis of ulcerative colitis. IBD patients diagnosed with malignancy had an older age of onset of IBD than those who did not develop malignancy. Sex, treatment type, treatment duration, and extent or location of disease did not correlate significantly with malignancy development.

Conclusion We conclude that age of onset of IBD plays the greatest role in malignancy development, whilst immunosuppressive treatment is not a significant risk factor.

Keywords Malignancy, inflammatory bowel disease, risk factors

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Introduction

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a multifactorial inflammatory disorder of the gastrointestinal system that impairs the patient's quality of life. Chronic gastrointestinal inflammation may present with a multitude of symptoms, as well as extraintestinal manifestations or complications such as intestinal obstruction or perforation. Other sequelae of prolonged or untreated inflammation include the development of malignancy.

The malignancy risk associated with IBD has been a topic of interest for several decades, with research initially focusing on colonic malignancy risk in IBD patients [1,2]. Over the years, interest shifted to extracolonic malignancies associated with IBD, whose spectrum includes dermatological, hepatobiliary, hematological and respiratory types [3]. Eventually, research was directed at identifying risk factors for malignancy in IBD patients, and several conclusions emerged. In CD, a penetrating (Montreal B3) subtype confers greater malignancy risk than Montreal B1 (non-stricturing, non-penetrating) and B2 (stricturing) subtypes, whereas in UC, extent of disease (pancolitis) and abdominal surgery for UC present a greater malignancy risk [4]. Furthermore, skin and urinary tract malignancy risk increase with IBD duration [4]. Another documented risk factor for malignancy in IBD patients is

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treatment-associated. Whilst thiopurine therapy is linked to lymphoproliferative disorders and non-melanoma skin malignancy [5,6], biological agents such as anti-tumor necrosis factor (TNF) therapy are associated with melanoma skin malignancy [7]. Other potential risk factors for malignancy in IBD patients include sex [8] and duration of therapy [9]. The aim of this nationwide retrospective multivariate analysis was to elicit statistically significant variables conferring a risk for malignancy development in IBD patients locally.

Patients and methods

Population studied

Following ethical approval from the local regulatory body, data were collected from the local IBD registry in an anonymized manner. All Maltese patients with IBD under active treatment between 2008 and 2022 were included. Our study excluded foreign patients residing in Malta to eliminate genetic bias and environmental differences. Data were collected from patient records, and included sex, IBD phenotype histologically, extent of disease at diagnosis, disease behaviour at diagnosis, age at diagnosis, current age, treatment at diagnosis, current treatment, duration of treatment/s, age at malignancy diagnosis (if any) and histology of malignancy.

Statistical analysis

The statistical analysis was carried out using SPSS Statistics v29 (IBM Corp. Released 2015. IBM SPSS Statistics for Mac, Version 29.0. Armonk, NY: IBM Corp.). We evaluated descriptive statistics, including sex, mean and median age at diagnosis, the percentages of patients on different treatment types and the percentages of IBD patients diagnosed with malignancy. The Mann-Whitney test was used to assess statistical significance across individual continuous variables. Fisher's exact test was used to assess statistical significance across individual non-continuous variables. Results were considered statistically significant if the P-value was <0.05. Nominal regression analysis was carried out to assess the effects of multiple risk factors on the incidence of malignancy in patients with IBD.

Results

Demographic data

One thousand five hundred sixty-six patients were included in the study, of whom 713 (45.5%) were female. The predominant type of IBD was UC (65.2%), followed by CD (33.4%), and 1.3% had unclassified IBD (IBD-U). Mean age at diagnosis was 42.4±18.47 years (range 4-88 years), and the median age was 41 years.

One hundred thirty-five patients (8.6%) had a malignancy diagnosis during their lifetime; 2.7% (n=42) of patients had a malignancy diagnosis preceding the diagnosis of IBD, whereas 5.9% (n=93) developed malignancy following the IBD diagnosis. In the latter group, the mean time between IBD diagnosis and malignancy diagnosis was 6.4±5.1 years. Ten patients developed 2 or more malignancies following IBD diagnosis, with an average time to diagnosis of first malignancy of 10.6±6.83 years. The commonest malignancy types were dermatological (n=39, 2.49%), prostate (n=17, 1.09%) and breast (n=14, 0.89% of the whole population). These findings are summarized in Supplementary Table 1.

Correlation of variables with incidence of malignancy

Sex was not a significant risk factor for malignancy in our population: 8.2% (59 of 713) of females and 8.9% (76 of 853) male IBD patients were diagnosed with malignancy during their lifetime (P=0.718). Malignancy prevailed in a statistically significant manner in patients with UC, as 10.5% (n=107) of UC patients were diagnosed with malignancy, compared with 5.3% (n=28) of CD patients (P=0.001). None of the IBD-U patients developed malignancy.

There was no statistical association between occurrence of malignancy and extent of disease in UC patients (P=0.571), and location of disease according to the Montreal classification in the Crohn's population (P=0.209). Among the latter group, ileal location (L1) carried the highest risk of malignancy (10/155 patients), followed closely by colonic (L2) (9/146 patients).

Age at diagnosis was also a significant risk factor for malignancy in our population (range 4-88 years, mean 42.4±18.5 years; P<0.001). In patients who never developed malignancy, median age at IBD diagnosis was 39±17.9 years, whereas in those who developed malignancy it was 60±15.6 years.

With respect to treatment, age at start of treatment correlated with age at diagnosis (median age 41 years). A statistically significant difference for age at treatment initiation was noted: patients without malignancy had a lower median age at start of treatment (41±19.7 years) compared to those who developed malignancy (52±18.6). Duration of treatment was not a risk factor for malignancy in this population, as the median duration of treatment was 5±2.7 years in both those with and without malignancy (P=0.959).

As regards treatment, 45.8% (n=717) of the population were solely on mesalazine treatment since diagnosis, that is, there was no exposure to immunosuppressive treatment during their lifetime; 27.7% (n=434) of patients were on immunomodulatory treatment alone, 2.8% (n=44) were on biological agents alone and 23.6% (n=371) were on combined therapy. Patients who were on combined therapy and downgraded to monotherapy were included in the combined therapy group for exposure purposes. Treatment type did not affect malignancy development in our patients (P=0.943).

Comparing the different types of immunomodulatory treatment, namely azathioprine (n=724, 46.2%), 6-mercaptopurine (n=51, 3.3%) and methotrexate (n=30, 1.9%), no significant risk for malignancy was identified, including in patients exposed to more than 1 immunomodulatory agent (P=0.203). The biological agents used locally are infliximab, adalimumab, vedolizumab and ustekinumab. Comparison of the biological agents showed that infliximab (n=328, 20.9%) carried the highest risk of malignancy, although patients on infliximab were mostly on concomitant immunomodulatory therapy (P=0.012). Fifty-seven patients (3.6%) required switching of biological agents, and this did not significantly increase malignancy risk (n=5, 0.3% vs. n=52, 3.3%; P=0.967).

Nominal regression analysis to determine risk of malignancy

In addition to the above results, we performed likelihood ratio tests to further elicit the significance of risks. Age at diagnosis was a persistently significant risk (P<0.001), whilst type of IBD was not (P=0.060). Combined treatment retained a similar risk profile to that calculated using Fisher's exact test (P=0.011; Table 1).

Table 1 Variables analyzed for malignancy risk in IBD patients

Variable	% who developed malignancy	P-value
Sex	8.2% females 8.9% males	0.718
Type of IBD	10.5% UC 5.3% CD 0.0% IBD-U	0.001
Treatment Classes	9.5% immunomodulator therapy 9.3% biological therapy 2.3% combined therapy 7.3% mesalazine monotherapy	0.297
Age at Diagnosis	Median age at diagnosis in those without malignancy: 39.00 (SD +/- 18.0) Median age at diagnosis in those who developed malignancy: 60.00 (SD +/- 15.57)	<0.001

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; IBD-U, inflammatory bowel disease-unclassified

Discussion

Our study assessed the risks for malignancy development in IBD patients whilst taking into consideration several risk factors. Keeping in mind the available data on risk factors for malignancy in IBD patients, we aimed to establish a correlation between sex, type and extent of IBD, age at diagnosis, treatment exposure and its duration.

Whilst the type of IBD and age at diagnosis emerged as statistically significant risk factors for malignancy development in IBD patients in this study, age at diagnosis was the predominant risk factor locally. Recently, interest in elderly-onset IBD has peaked, with studies aiming to determine disease course, treatment strategies and surgical requirements. However, data on malignancy risk remain scarce, and the few available studies have shown conflicting results concerning the impact of age of IBD onset and malignancy development [3,10,11].

Literature on malignancy risk in IBD tends to focus on intestinal malignancies, whereas our study took into account any type of malignancy. Our study agrees with international data that UC is associated with a higher risk of colorectal malignancy [12]. However, our study fails to correlate with international data suggesting that pancolitis confers the greatest risk of malignancy in patients with UC [12]. This study recorded the extent of disease at diagnosis; thus, there may have been cases of progression of extent over time. CD also increases the risk of small and large bowel malignancy, yet there is no precise quantification of this risk—possibly because the Crohn's phenotype is extremely variable and hence it is difficult to assess the effect of disease extent on risk of malignancy [13]. On the other hand, a recent Dutch study counters the emphasis placed on increased risk of colorectal malignancy amongst IBD patients, claiming this risk is lower in Dutch patients than previously mentioned [14].

Our study did not reveal any significant increase in risk of malignancy related to treatment. The inclusion of a cohort of patients receiving only mesalazine therapy (oral and/or topical) reduced the possibility of bias in our results. Initiation of treatment at an older age was associated with a higher incidence of malignancy in our study. This indicated that the likely risk factor for malignancy was age at diagnosis and not duration of exposure to treatment. Contrary to common concerns, patients on combined therapy had lower malignancy rates in our study than patients on immunomodulator monotherapy or biological monotherapy. Immunomodulator therapy has been linked to hematological and dermatological malignancies, as described in the CESAME study [5,15]. Hepatosplenic T-cell lymphoma remains a rare entity associated with thiopurine use, and none of the lymphoma patients in our cohort were diagnosed with this subtype [16]. Whilst a single study stated thiopurines may have a protective role in IBD with respect to colorectal neoplasia [17], other studies counter this claim, stating that it is in fact mesalazine that has a protective effect [18]. Our study did not identify any statistically significant difference in the risk of malignancy amongst different immunomodulators, including in patients who switched between immunomodulators.

Exposure to anti-TNF treatment over a short term (median duration used in quoted study 3.5 years) does not appear to increase malignancy risk [19]. A retrospective study revealed a risk of melanoma skin malignancy with biological agents [20]. Lymphoma risk was found to be greater under either anti-TNF or immunomodulator monotherapy, and even more in combination therapy [21]. As previously mentioned, the results obtained from our study are not concordant with these studies. Malignancy risk with other biological agents and small molecules is still being investigated [22].

To aid physicians in balancing the risks and benefits of IBD treatment, Beaugerie *et al* advise that in uncontrolled

inflammation prompt treatment is advisable, as the risks of severe inflammation outweigh the risks of adverse effects, whereas in patients with sustained deep remission, consideration of long-term treatment side-effects should be taken into account [23].

When treating patients who have a history of malignancy or have ongoing malignancy, one may refer to the European Crohn's and Colitis Organisation (ECCO) guidelines. Developed in 2015 and recently updated, these guidelines consolidate the knowledge that patients with IBD are at increased risk of specific malignancies. Those with a history of malignancy have a 2-fold greater risk of new or recurrent malignancy, regardless of immunosuppressive treatment. In those diagnosed with malignancy, ECCO advises temporary cessation of thiopurines, calcineurin inhibitors and anti-TNF therapy, at least until cancer therapy is completed [24]. There should always be a discussion with the caring oncologist, and at a multidisciplinary team level, about the treatment of IBD during and following cancer treatment.

Our study had certain limitations that could not be avoided. Firstly, it did not take into account patients diagnosed and treated privately for IBD, who never made contact with the public hospital service, as our population consisted of patients with entitlement to treatment under the national health system. Furthermore, patients may have sought private care in certain instances, such as treatment of dermatological malignancies, which may have led to lower documented malignancy rates. As previously mentioned, we recorded the extent of disease at diagnosis; thus, there may have been cases of progression of extent over time. Our study also assumed that patients were compliant with the treatment prescribed, as duration of treatment exposure relies heavily on compliance.

Despite these limitations, our study had several strengths, namely the strict utilization of the local population with a formal histological IBD diagnosis, a significant number of patients, and a control group of IBD patients who were never exposed to immunosuppressive treatment. Several risk factors for malignancy were recorded and statistically analyzed over a long follow-up period. A comparison of malignancy incidence per 100,000 individuals to the local population is delineated in Table 2, to give an overview of the malignancy incidence in the IBD population and in the general population.

Table 2 Malignancy in inflammatory bowel disease (IBD) versus general population per year

Malignancy type	Expected rate per 100,000 IBD population per year	Observed % per 100,000 general local population per year
Melanoma	18	21
Prostate adenocarcinoma	56.7	111
Breast adenocarcinoma	56.7	153
Lymphoma	24.7	25.26
Colonic adenocarcinoma	46	55

Summary Box

What is already known:

- Patients with inflammatory bowel disease (IBD) are at risk of malignancy from the inflammatory processes in the gastrointestinal tract, as well as from the treatment required to control this inflammatory process
- The type of IBD, as well as its extent and phenotype, play a role in malignancy development in IBD patients
- The side-effects and malignancy risk of different types of immunosuppression, such as immunomodulators and biological agents, have been well documented

What the new findings are:

- Age of onset of IBD was the greatest risk factor for malignancy in IBD patients, with patients being diagnosed at an older age running a higher risk of malignancy than those diagnosed younger
- Exposure to immunosuppression plays less of a role than previously predicted, as older age at diagnosis correlated inversely with duration of exposure to immunosuppressive treatment
- The type of immunosuppressive medication, including whether given as monotherapy or combination therapy, showed no statistically significant correlation with the development of malignancy in IBD patients

Our study concludes that previously described risk factors for malignancy in IBD patients may not be as significant as previously thought, especially with regard to treatment, and this may help alleviate physician and patient anxiety when considering these therapies. This is particularly significant with the rising incidence of IBD in the elderly population. Whilst the topic of elderly-onset IBD is gaining momentum, formal guidance is required on the follow up, treatment and malignancy surveillance of this IBD population subtype.

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Supplementary Table 1A Summary of extraintestinal malignancies in our IBD patient cohort

Sex	Date of diagnosis of IBD	Age at diagnosis of IBD	Type of IBD CD/ UC	Extent at diagnosis	Date of diagnosis of malignancy	Diagnosis (CT, MRI, PET)	Immunomodulator exposure?	Duration of Treatment/ years
Before IBD Diagnosis								
M	2016	57	UC	E3	2011	Malignant melanoma *in situ*, prostate adenocarcinoma Grade III	0	0
M	2013	21	CD	L3	2001	Hodgkin's lymphoma	Azathioprine	5
M	2018	20	CD	L2	2000	Left Wilm's tumor	Azathioprine	5
M	2021	50	UC	E3	2006	Ulcerated basal cell carcinoma	Azathioprine	1
F	2019	58	CD	L3	2011	Grade III invasive ductal breast carcinoma	Azathioprine	4
F	2019	39	UC	E2	2014	2014: invasive ductal carcinoma grade II, 2017: cervical squamous cell carcinoma	Azathioprine	4
F	2015	69	UC	E2	2012	Grade III *in situ* ductal breast carcinoma with minor component of invasive carcinoma	Azathioprine	4
F	2014	53	UC	E2	2012	Grade II invasive ductal breast carcinoma	Methotrexate	1
F	2015	70	UC	E3	2013	Grade III invasive ductal breast carcinoma	0	0
F	2018	70	UC	E3	2011	Breast lobular carcinoma	0	0
F	2021	70	UC	E2	2011	Grade II invasive ductal breast carcinoma	0	0
M	2018	55	UC	E3	2016	Renal cell carcinoma	0	0
M	2014	70	UC	E1	2008	Grade 3 muscle invasive urothelial carcinoma	0	0
M	2013	73	UC	E3	1979	Prostate acinar carcinoma Gleason 7	0	0
M	2019	68	UC	E1	2012	Prostate adenocarcinoma grade IV + V	0	0
M	2018	69	UC	E2	2016	Prostate adenocarcinoma Gleason 4	0	0
F	2021	63	UC	E3	2011	B cell lymphoma	0	0
F	2016	60	UC	E1	2015	Bilateral high-grade poorly differentiated ovarian serous carcinoma, pT1c (FIGO 1C)	0	0
F	2020	66	UC	E1	2013	Right High grade *in situ* ductal breast carcinoma with microcalcifications. B5a	0	0
M	2018	55	UC	L2	2010, 2019	Basal cell carcinoma	0	0
F	2021	45	UC	E3	2008	Invasive squamous cell cervical carcinoma	0	0
F	2019	83	UC	E1	2007	Cutaneous large T cell lymphoma	0	0
M	2018	74	UC	E1	2015	Prostate adenocarcinoma, Gleason score 6	0	0
M	2020	72	UC	E2	2018	Sarcomatoid carcinoma	0	0

(*Contd...*)

Supplementary Table 1A *(Continued)*

Sex	Date of diagnosis of IBD	Age at diagnosis of IBD	Type of IBD CD/ UC	Extent at diagnosis	Date of diagnosis of malignancy	Diagnosis (CT, MRI, PET)	Immunomodulator exposure?	Duration of Treatment/ years
				Before IBD Diagnosis				
F	2017	53	UC	E1	2008	Poorly differentiated ovarian teratoma	0	0
M	2022	79	UC	E2	2009	Basal cell carcinoma	0	0
M	2016	68	UC	E1	2010	Basal cell carcinoma	0	0
F	2021	83	UC	E3	2012	Basal cell carcinoma	0	0
M	2016	78	UC	E3	2008	Squamous cell carcinoma	0	0
F	2017	79	UC	E1	2007	Grade 2 adenocarcinoma left breast	0	0
F	2018	60	UC	E3	2012	Urinary bladder: Grade I papillary urothelial carcinoma, Stage pTa.	0	0
F	2017	77	UC	E3	2008	Superficial basal cell carcinoma	0	0
M	2019	77	UC	E1	2017	Bowen's disease	0	0
M	2020	69	UC	E1	2017, 2021	Basal cell carcinoma (2017). Low grade clear cell renal cell carcinoma; Adenoid basal cell carcinoma, Chronic lymphocytic leukemia	0	0
				After IBD Diagnosis				
F	2016	31	CD	L3	2016	Mycosis Fungoides	Methotrexate	2
M	2014	56	UC	E3	2014	Squamous cell carcinoma	Methotrexate	7
F	2013	35	CD	L4	2021	Lung high grade neuroendocrine carcinoma	Azathioprine	10
F	2009	37	UC	E3	2014, 2019	2014- Mature cystic ovarian teratoma 2019- microadenoma	Azathioprine	9
F	2004	40	UC	E3	2022	Focal well differentiated (G1) endometrioid endometrial adenocarcinoma	Azathioprine	5
F	2012	14	CD	L3	2021	Classical Hodgkin lymphoma (mixed cellularity type)	Azathioprine	9
M	2010	54	UC	E2	2021	Nodular basal cell carcinoma with infiltrative features.	Methotrexate	13
M	2008	62	UC	L2	2015, 2018	Prostate cancer, renal cell carcinoma	Azathioprine	2
M	2015	54	CD	TI	2017	Cerebral lymphoplasmacytic lymphoma	Azathioprine	2
M	2008	56	UC	E3	2013	Urothelial carcinoma *in situ*	Azathioprine	7
F	1989	34	CD	L1	2023	Renal cell carcinoma	Methotrexate	21

(*Contd...*)

Supplementary Table 1A *(Continued)*

Sex	Date of diagnosis of IBD	Age at diagnosis of IBD	Type of IBD CD/ UC	Extent at diagnosis	Date of diagnosis of malignancy	Diagnosis (CT, MRI, PET)	Immunomodulator exposure?	Duration of Treatment/ years
After IBD Diagnosis								
M	2014	45	CD	TI	2020	Basal cell carcinoma	Azathioprine	6
M	2012	66	CD	L1	2017	Metastatic follicular thyroid carcinoma	Azathioprine	5
M	2011	59	UC	E2	2018	Prostate adenocarcinoma	Azathioprine	2
M	2017	25	CD	L2	2020	Melanoma *in situ*	Azathioprine	6
F	2014	55	UC	E3	2017	Clear cell renal cell carcinoma, Fuhrman grade I stage pT1a	Methotrexate	5
F	2013	49	UC	E3	2022	Focal well differentiated (G1) endometrioid endometrial adenocarcinoma	Azathioprine	5
M	2015	71	CD	L3	2021	Thumb squamous cell carcinoma, axilla squamous cell carcinoma	Azathioprine	13
M	2018	71	CD	TI	2019	Prostate acinar carcinoma	Azathioprine	1
M	2009	26	UC	E3	2012	Myeloid leukemia	Azathioprine	1
M	2014	48	CD	ICV	2016	Poorly differentiated (G3) invasive lung adenocarcinoma	Azathioprine	4
M	2009	51	UC	E3	2023	Melanoma	Azathioprine	7
M	2008	51	UC	E3	2020, 2022	Basal cell carcinoma	Azathioprine	7
F	2001	57	CD	L3	2019	Breast ductal carcinoma *in situ*	Azathioprine	22
F	2016	72	UC	E3	2021	Basal cell carcinoma	Azathioprine	5
M	2002	45	CD	TI	2021	Grade 1 clear cell renal cell carcinoma	Azathioprine	4
M	2004	7	CD	L1	2018	Classical Hodgkin lymphoma - EBV associated	Azathioprine	2
F	2016	50	UC	E3	2017	Breast ductal invasive carcinoma grade I	Azathioprine	7
F	2015	70	CD	TI	2022 (both)	Well differentiated (G1) invasive squamous cell carcinoma skin and high grade urothelial carcinoma	Azathioprine	7
M	2008	67	UC	E1	2014; 2016; 2019	2014-Squamous cell carcinoma; basal cell carcinoma; 2016-squamous cell carcinoma; 2019-invasive prostate adenocarcinoma	Azathioprine	13
F	2001	46	UC	E3	2018	Superficial basal cell carcinoma	Azathioprine	1
F	2015	44	CD	L2	2017	Multiple myeloma	Azathioprine	1

(*Contd...*)

Supplementary Table 1A *(Continued)*

Sex	Date of diagnosis of IBD	Age at diagnosis of IBD	Type of IBD CD/ UC	Extent at diagnosis	Date of diagnosis of malignancy	Diagnosis (CT, MRI, PET)	Immunomodulator exposure?	Duration of Treatment/ years
After IBD Diagnosis								
F	2012	47	CD	L2	2014	Well differentiated endometrioid endometrial carcinoma, pT1a, FIGO1a	Azathioprine	9
M	2008	67	UC	E1	2021	Squamous cell carcinoma, basal cell carcinoma	Azathioprine	5
F	1999	41	UC	E2	2016	Basal cell carcinoma	Azathioprine	7
F	2015	63	UC	E2	2020	Well differentiated (G1) invasive ductal carcinoma	Azathioprine	4
F	2015	64	UC	E2	2020	Ovarian cancer	Azathioprine	4
F	2010	67	CD	L3	2020	Infiltrative and micronodular basal cell carcinoma	Azathioprine	3
M	1988	27	UC	E2	2022	Tenosynovial giant cell tumor	Azathioprine	1
F	2019	58	CD	TI	2020	Papillary thyroid carcinoma	Azathioprine	3
M	2015	59	UC	E3	2016	High grade (G3) papillary urothelial carcinoma	Azathioprine	4
F	2020	73	UC	E2	2020	Basal cell carcinoma	Azathioprine	1
M	2010	64	UC	E3	2013	Adenocarcinoma prostate	Azathioprine	3
F	2012	45	UC	E1	2021	Focal cervical intraepithelial neoplasia	Methotrexate	4
M	2008	27	UC	E3	2014	Basal cell carcinoma	Azathioprine	1
M	2016	69	UC	E1	2018	Urothelial cancer	6mercaptopurine	5
F	2017	73	UC	E1	2021	Basal Cell Carcinoma	6mercaptopurine	5
F	2022	58	UC	E2	2019	Nodular basal cell carcinoma	6mercaptopurine	0
M	2016	64	UC	E2	2018	Prostate cancer	6mercaptopurine	1
M	2010	77	UC	E3	2018	Basal cell carcinoma	0	0
F	2010	58	UC	E3	2009	Basal cell carcinoma	0	0
M	2005	45	UC	E3	2015	Basal cell carcinoma	0	0
F	2011	64	UC	E3	2018	Moderately differentiated (G2) invasive lobular carcinoma of the right breast	0	0
F	2014	74	UC	E1	2021	Lobular invasive breast cancer	0	0
M	2015	71	CD	E3	2021	Chronic lymphocytic leukemia	0	0
M	2021	76	UC	E1	2016	Prostate adenocarcinoma right base	0	0
M	2014	50	UC	E3	2022	Prostate acinar adenocarcinoma, Gleason score VII+VIII	0	0

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Supplementary Table 1A *(Continued)*

Sex	Date of diagnosis of IBD	Age at diagnosis of IBD	Type of IBD CD/ UC	Extent at diagnosis	Date of diagnosis of malignancy	Diagnosis (CT, MRI, PET)	Immunomodulator exposure?	Duration of Treatment/ years
After IBD Diagnosis								
F	2019	70	UC	E3	2022	Basal cell carcinoma	0	0
M	2013	77	UC	E1	2016	Prostate adenocarcinoma, Gleason grades III+IV	0	0
M	2019	59	UC	E2	2021	Low grade papillary urothelial cell carcinoma	0	0
F	2013	75	UC	E3	2019	Basal cell carcinoma	0	0
M	2016	57	UC	E1	2020	Papillary renal cell carcinoma, type 1	0	0
M	2014	71	UC	E3	2017	Basal cell carcinoma	0	0
M	2018	54	UC	E3	2021	Papillary renal cell carcinoma, type 1	0	0
F	2018	47	UC	E3	2021	Breast invasive ductal carcinoma grade 1	0	0
M	2016	26	UC	E3	2017	Minimally invasive thyroid follicular carcinoma, leukemia	0	0
F	2017	23	UC	E3	2021	Cervical intraepithelial neoplasia	0	0
M	2017	64	UC	E1	2021	Acinar prostate adenocarcinoma with perineural invasion, Gleason score VII	0	0
M	2019	82	UC	E3	2019	Prostate acinar adenocarcinoma, Gleason score 9, with perineural invasion	0	0
18	2016	54	UC	E1	2017	Mantle cell lymphoma	0	0
M	2016	60	UC	E3	2021	Morphoeic basal cell carcinoma	0	0
M	2018	82	UC	E3	2021	Non-small cell lung carcinoma	0	0
F	2012	68	UC	E3	2021	Basal cell carcinoma	0	0
M	2013	71	UC	E2	2021	Infiltrative basal cell carcinoma	0	0
M	2016	72	UC	E1	2016	Clear-cell type renal cell carcinoma	0	0
F	2018	58	CD	L2	2019	Breast adenocarcinoma	0	0
M	2010	66	UC	E1	2014	Malignant solitary fibrous tumor lung	0	0
F	2015	58	CD	L2	2018	Papillary thyroid carcinoma	0	0
M	2016	75	UC	E1	2016	Prostate adenocarcinoma Gleason 8	0	0
M	2012	48	UC	E2	2020	Superficial spreading melanoma	0	0
M	2013	61	UC	E2	2012	pT2bN0M0 undifferentiated nasopharyngeal cancer	0	0

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Supplementary Table 1A *(Continued)*

Sex	Date of diagnosis of IBD	Age at diagnosis of IBD	Biological exposure?	Duration of Treatment/ years	Switch to other biologics	Malignancy on immunomodulator or biologic?	Time between RX and CA/months
				Before IBD Diagnosis			
M	2016	57	0	0	0	0	0
M	2013	21	Infliximab	4	0	0	0
M	2018	20	Infliximab	4	0	0	0
M	2021	50	Infliximab	1	0	0	0
F	2019	58	0	0	0	0	0
F	2019	39	0	0	0	0	0
F	2015	69	0	0	0	0	0
F	2014	53	0	0	0	0	0
F	2015	70	0	0	0	0	0
F	2018	70	0	0	0	0	0
F	2021	70	0	0	0	0	0
M	2018	55	0	0	0	0	0
M	2014	70	0	0	0	0	0
M	2013	73	0	0	0	0	0
M	2019	68	0	0	0	0	0
M	2018	69	0	0	0	0	0
F	2021	63	0	0	0	0	0
F	2016	60	0	0	0	0	0
F	2020	66	0	0	0	0	0
M	2018	55	0	0	0	0	0
F	2021	45	0	0	0	0	0
F	2019	83	0	0	0	0	0
M	2018	74	0	0	0	0	0
M	2020	72	0	0	0	0	0
F	2017	53	0	0	0	0	0
M	2022	79	0	0	0	0	0
M	2016	68	0	0	0	0	0

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Supplementary Table 1A *(Continued)*

Sex	Date of diagnosis of IBD	Age at diagnosis of IBD	Biological exposure?	Duration of Treatment/ years	Switch to other biologics	Malignancy on immunomodulator or biologic?	Time between RX and CA/months
				Before IBD Diagnosis			
F	2021	83	0	0	0	0	0
M	2016	78	0	0	0	0	0
F	2017	79	0	0	0	0	0
F	2018	60	0	0	0	0	0
F	2017	77	0	0	0	0	0
M	2019	77	0	0	0	0	0
M	2020	69	0	0	0	0	0
				After IBD Diagnosis			
F	2016	31	Infliximab	2	Vedolizumab 2018, Ustekinumab 2023	0	0
M	2014	56	0	0	0	0	0
F	2013	35	Infliximab	2	0	1	58
F	2009	37	Infliximab	3	0	0	0
F	2004	40	Infliximab	7	0	1	60
F	2012	14	Infliximab	6	Vedolizumab 2022 Ustekinumab 2023	1	108
M	2010	54	Infliximab	7	0	1	132
M	2008	62	Infliximab	6	0	1	12
M	2015	54	Infliximab	8	0	1	24
M	2008	56	Infliximab	5	0	0	0
F	1989	34	adalimumab	20	0	1	240
M	2014	45	adalimumab	1	0	1	72
M	2012	66	Vedolizumab	0	0	1	60
M	2011	59	Vedolizumab	0	0	1	18

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Supplementary Table 1A *(Continued)*

Sex	Date of diagnosis of IBD	Age at diagnosis of IBD	Biological exposure?	Duration of Treatment/ years	Switch to other biologics	Malignancy on immunomodulator or biologic?	Time between RX and CA/months
				After IBD Diagnosis			
M	2017	25	Infliximab	3	Vedolizumab 2020	1	12
F	2014	55	Infliximab	4	Vedolizumab 2023	0	0
F	2013	49	Vedolizumab	1	0	0	0
M	2015	71	Vedolizumab	1	0	1	150
M	2018	71	Usetkinumab	3	0	1	40
M	2009	26	Vedolizumab	2	Ustekinumab 2022	0	0
M	2014	48	0	0	0	1	24
M	2009	51	0	0	0	1	80
M	2008	51	0	0	0	1	48
F	2001	57	0	0	0	1	18
F	2016	72	0	0	0	1	60
M	2002	45	0	0	0	1	48
M	2004	7	0	0	0	1	24
F	2016	50	0	0	0	1	12
F	2015	70	0	0	0	1	72
M	2008	67	0	0	0	1	96
F	2001	46	0	0	0	1	195
F	2015	44	0	0	0	1	12
F	2012	47	0	0	0	1	20
M	2008	67	0	0	0	1	45
F	1999	41	0	0	0	1	40
F	2015	63	0	0	0	1	20
F	2015	64	0	0	0	1	35
F	2010	67	0	0	0	1	12
M	1988	27	0	0	0	1	11

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Supplementary Table 1A *(Continued)*

Sex	Date of diagnosis of IBD	Age at diagnosis of IBD	Biological exposure?	Duration of Treatment/ years	Switch to other biologics	Malignancy on immunomodulator or biologic?	Time between RX and CA/months
				After IBD Diagnosis			
F	2019	58	0	0	0	0	0
M	2015	59	0	0	0	0	0
F	2020	73	0	0	0	0	0
M	2010	64	0	0	0	1	35
F	2012	45	0	0	0	1	45
M	2008	27	0	0	0	1	12
M	2016	69	0	0	0	0	0
F	2017	73	0	0	0	0	0
F	2022	58	0	0	0	0	0
M	2016	64	0	0	0	0	0
M	2010	77	0	0	0	0	0
F	2010	58	0	0	0	0	0
M	2005	45	0	0	0	0	0
F	2011	64	0	0	0	0	0
F	2014	74	0	0	0	0	0
M	2015	71	0	0	0	0	0
M	2021	76	0	0	0	0	0
M	2014	50	0	0	0	0	0
F	2019	70	0	0	0	0	0
M	2013	77	0	0	0	0	0
M	2019	59	0	0	0	0	0
F	2013	75	0	0	0	0	0
M	2016	57	0	0	0	0	0
M	2014	71	0	0	0	0	0
M	2018	54	0	0	0	0	0
F	2018	47	0	0	0	0	0
M	2016	26	0	0	0	0	0

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Supplementary Table 1A *(Continued)*

Sex	Date of diagnosis of IBD	Age at diagnosis of IBD	Biological exposure?	Duration of Treatment/ years	Switch to other biologics	Malignancy on immunomodulator or biologic?	Time between RX and CA/months
				After IBD Diagnosis			
F	2017	23	0	0	0	0	0
M	2017	64	0	0	0	0	0
M	2019	82	0	0	0	0	0
M	2016	54	0	0	0	0	0
M	2016	60	0	0	0	0	0
M	2018	82	0	0	0	0	0
F	2012	68	0	0	0	0	0
M	2013	71	0	0	0	0	0
M	2016	72	0	0	0	0	0
F	2018	58	0	0	0	0	0
M	2010	66	0	0	0	0	0
F	2015	58	0	0	0	0	0
M	2016	75	0	0	0	0	0
M	2012	48	0	0	0	0	0
M	2013	61	0	0	0	0	0

Supplementary Table 1B Summary of intestinal malignancies in our IBD patient cohort

Sex	Date of diagnosis of IBD	Age at diagnosis of IBD	Type of IBD CD/ UC	Extent at diagnosis	Date of diagnosis of malignancy	Diagnosis (CT, MRI, PET)	Immunomodulator exposure?	Duration of Treatment/ years	Biological exposure?	Duration of Treatment/ years	Switch to other biologics	Malignancy on immunomodulator or biologic?	Time between RX and CA/ months
Before IBD Diagnosis													
M	2020	63	CD	L2	2019	Well differentiated (G1) intestinal adenocarcinoma in cecum	0	0	Vedolizumab	3	0	0	0
F	2014	78	UC	E3	2004	Colorectal adenocarcinoma	0	0	0	0	0	0	0
F	2019	59	UC	E3	2014	Colonic adenocarcinoma	Azathioprine	2	0	0	0	0	0
F	2004	56	CD	E1	2003, 2019	2003: Duke A colonic carcinoma, 2019: Giant cell tumor of tendon sheath	Azathioprine	6	0	0	0	0	0
M	2011	71	UC	E3	2009, 2010	2009: colonic adenocarcinoma, 2010: basal cell carcinoma	6-Mercaptopurine	6	0	0	0	0	0
M	2015	71	UC	E3	2014	Grade II colonic adenocarcinoma	0	0	0	0	0	0	0
F	2020	68	UC	E3	2017	Low-grade appendiceal mucinous neoplasm with low-grade mucinous carcinoma peritonei.	0	0	0	0	0	0	0
F	2020	74	UC	E3	2008	Colonic adenocarcinoma	0	0	0	0	0	0	0
After IBD Diagnosis													
M	2011	62	CD	L3	2021	Moderately differentiated keratinizing squamous cell carcinoma esophagus	Azathioprine	12	Infliximab	1	0	1	25

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Supplementary Table 1B *(Continued)*

Sex	Date of diagnosis of IBD	Age at diagnosis of IBD	Type of IBD CD/ UC	Extent at diagnosis	Date of diagnosis of malignancy	Diagnosis (CT, MRI, PET)	Immunomodulator exposure?	Duration of Treatment/ years	Biological exposure?	Duration of Treatment/ years	Switch to other biologics	Malignancy on immunomodulator or biologic?	Time between RX and CA/ months
After IBD Diagnosis													
M	2018	55	UC	E3	2020	Well-differentiated (Grade 1) intestinal-type adenocarcinoma	Azathioprine	1	Vedolizumab	1	0	1	12
M	2019	56	UC	E3	2020	Well-differentiated intestinal-type adenocarcinoma	Azathioprine	4	Vedolizumab	1	0	1	12
M	2019	73	UC	E2	2022	Metastatic adenocarcinoma likely gastrointestinal origin (ascitic fluid cytology)	Azathioprine	4	0	0	0	1	36
M	2016	57	CD	L1	2022	Stomach: Moderate to poorly differentiated intestinal-type adenocarcinoma with metastatic disease	Azathioprine	7	0	0	0	1	62
M	2011	65	UC	E2	2021	Mucinous rectal adenocarcinoma	Azathioprine	5	0	0	0	1	60
F	2015	68	UC	E1	2016	Anal adenocarcinoma and endometrial carcinoma	0	0	0	0	0	0	0
M	2017	51	UC	E1	2021	Esophageal adenocarcinoma	0	0	0	0	0	0	0
M	2014	45	UC	E3	2017	Neuroendocrine colonic tumor	0	0	0	0	0	0	0
M	2015	51	UC	E1	2022	Appendiceal intestinal-type adenocarcinoma	0	0	0	0	0	0	0
F	2000	50	UC	E2	2016, 2022	2016: Morphoeic basal cell carcinoma, 2022: Mucinous adenocarcinoma	0	0	0	0	0	0	0
F	2011	30	UC	E3	2018	Rectal squamous carcinoma	Azathioprine	4	0	0	0	1	47

IBD, inflammatory bowel disease; M, male; F, female; CD, Crohn's disease; UC, ulcerative colitis; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; RX, diagnosis; CA, malignancy