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Original Article

Inflammatory Bowel Disease Phenotype as Risk Factor for Cancer in a Prospective Multicentre Nested Case-Control IG-IBD Study

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Abstract

Background and Aims: Cancer risk in inflammatory bowel disease [IBD] is still debated. In a prospective, multicentre, nested case-control study, we aimed to characterise incident cases of cancer in IBD. The role of immunomodulators vs clinical characteristics of IBD as risk factors for cancer was also investigated.
Materials and Methods: From January 2012 to December 2014, each IBD patient with incident cancer was matched with two IBD patients without cancer for: IBD type, gender, and age. Risk factors were assessed by multivariate regression analysis.
Results: IBD patients considered numbered 44 619: 21 953 Crohn's disease [CD], 22 666 ulcerative colitis [UC]. Cancer occurred in 174 patients: 99 CD [CD-K], 75 UC [UC-K]. Controls included 198 CD

[CD-C], 150 UC [UC-C]. Cancer incidence in IBD was 3.9/1000, higher in CD (4.5/1000 [99/21,953]) than in UC (3.3/1000 [75/22,666]; p = 0.042). Cancers involved: digestive system [36.8%], skin [13.2%], urinary tract [12.1%], lung [8.6%], breast [8%], genital tract [6.9%], thyroid [4.6%], lymphoma [3.5%], others [6.3%]. In CD, penetrating behaviour and combined thiopurines and tumour necrosis factor alpha [TNFα] antagonists were risk factors for cancer overall: odds ratio [OR] (95% confidence interval [CI] 2.33 [1.01–5.47]); 1.97 [1.1–3.5]; and for extracolonic cancers 3.9 [1.56–10.1]; 2.15 [1.17–4.1], respectively. In UC, risk factors were pancolitis and disease-related surgery for cancer overall (OR: 2.52 [1.26–5.1]; 5.09 [1.73–17.1]); disease-related surgery for colorectal cancer [CRC] (OR 3.6 [1.0–12]); and extensive and left-sided vs distal UC for extracolonic cancers (OR: 2.55 [1.15–5.9]; 2.6 [1.04–6.6]), respectively.

Conclusions: In a multicentre study, penetrating CD and extensive UC were risk factors for cancer overall. Cancer incidence was higher in CD than in UC.

Keywords: Inflammatory bowel disease; cancer risk; phenotype

1. Introduction

Risk factors for cancer in inflammatory bowel disease [IBD] are still debated.[1] Thiopurines [IS] have been reported to increase the risk of lymphoma[1,2] and of non-melanoma skin cancers [NMSC], particularly in Crohn's disease [CD].[3,4] The cancer risk associated with tumour necrosis factor-α [TNFα] antagonists is undefined, due to the relatively short follow-up [first trial published in 1995] and to the frequently combined treatment with IS.[5,6] Nevertheless, TNFα antagonists currently appear not to increase the risk of cancer overall, as supported by a multicentre case-control study in 2006.[7,8] and by several independent studies.[1,9,10,11,12] An increased risk of melanoma has been reported using TNFα antagonists in IBD.[13,14] Hepatosplenic T-cell lymphoma [HSTCL] has been associated with thiopurine use, particularly in young male patients with CD, treated with combined TNFα antagonists.[15,16] However, the absolute risk of these cancers appears to be low.

Recently, research has been focused on the cancer risk associated with IS and/or anti-TNFα treatments. Conversely, the role of clinical characteristics of IBD in determining the cancer risk when using any immunomodulator [IMM] has been less extensively investigated. In 2012, in a single-centre study we indicated penetrating CD and pancolitis in ulcerative colitis [UC] as significant risk factors for cancer overall.[17] In 2013, a Danish study indicated CD phenotype as a risk factor for cancer.[18] To the best of our knowledge, the role of clinical characteristics and phenotype of IBD in determining the cancer risk in relation to IMM treatments is currently undefined. This issue may assume relevance due to the frequent use of IMM in IBD, particularly in young patients with severe and chronically active disease.

In order to address these issues, we aimed to prospectively assess, in a multicentre nested case-control study, the incidence and characteristics of cancer in a cohort of IBD patients followed up for 3 years. The role of clinical characteristics of IBD vs the use of thiopurines and/or TNFα antagonists in determining the incidence of cancer was also investigated.

2. Materials and Methods

2.1. Study design

In a prospective multicentre, nested case-control study, all incident cases of cancer diagnosed in 16 IBD referral centres from January 1, 2012 to December 31, 2014 were recorded. All the units referred to the Italian Group for the study of Inflammatory Bowel Disease [IG-IBD]. In each of the 16 centres, each IBD patient with incident cancer/ neoplasia [IBD-K] was retrospectively matched with two IBD controls with no cancer [IBD-C] referring to the same IBD centre, for: IBD type [CD vs UC], gender, and age [± 5 years].

2.2. Study population

Inclusion criteria shared by IBD-K and IBD-C were: 1] diagnosis of CD or UC, defined according to current guidelines[5,6]; 2] diagnosis of IBD ≥ 6 months; 3] regular follow-up [≥ two visits/year]; 4] age > 15 years; 5] no history of cancer; 6] clinical records including characteristics of IBD and of cancer; and 7] informed consent. All incident cases of neoplasia and characteristics of patients were recorded in a shared database including: date of birth, age at time of last visit and at diagnosis of IBD and of cancer, IBD type [CD/UC], CD extent [L1-L4],[5,19] CD behaviour [B1-B3],[5,19] perianal disease (yes/no [Y/N]), family history of IBD [Y/N], smoking [Y/N], extraintestinal manifestations [EIM][Y/N], disease-related surgery, current or past use of thiopurines [IS; azathioprine, AZA], TNFα antagonists, other IMM, date at first and last use of any IMM, and cancer subtype. For each patient enrolled, the use of TNFα antagonists [≥ one administration] and/or IMM at any time during the disease course, and not only during the 3 years' follow-up, was reported and updated.

In this study, we aimed to confirm in a larger population findings from our single-centre study,[17] suggesting the role of IBD phenotype in determining the cancer risk. In our previous study, as in other studies[17,20], UC extent was subgrouped into distal [rectum and sigmoid colon], left-sided [or subtotal: up to the left flexure], and pancolitis [or extensive].[17,20] In order to confirm our findings and to calculate the sample size on the basis of our preliminary study,[17] UC was subgrouped into distal, left-sided [subtotal], and extensive [pancolitis].[17,20] In a separate analysis, UC was also subgrouped into proctitis, left-sided, and extensive.[6,19] The accuracy of cancer incidence was provided by the written histological analysis of cancers [including date at diagnosis].

IBD phenotypes were defined only at enrolment, as described.[5,6,17,20] In order to estimate with good accuracy cancer incidence in CD vs UC, the study involved only tertiary IBD centres and patients were assessed by experienced, senior, IBD-dedicated gastroenterologists, routinely following clinical practice guidelines and procedures in order to accurately assess: diagnosis of IBD, IBD phenotype, and malignancy diagnosis and classification.[5,6,32] In

particular, the diagnosis of CD vs UC was defined on the basis of clinical, haematochemical, endoscopic, histological and radiological assessments, including colonoscopy with biopsies and small-bowel imaging (ie entero-magnetic resonance imaging [MRI], entero-computed tomography [CT] and/or small intestine contrast ultrasonography).[5,6] The diagnosis and phenotype of IBD were assessed and eventually discussed before entry, and patients with unclassified or indeterminate IBD were not included in the study.

2.3. Statistical analysis

Calculation of the sample size should require the knowledge of the expected incidence of cancer not only in the general IBD population, but also in patients with different CD phenotypes and UC extent, with and without IS and/or anti-TNFα use. The risk of incident cancer when considering IBD phenotype, CD pattern, UC extent, and IMM use is undefined. Sample size calculation was therefore based on our study[17] assessing the cancer risk in CD vs UC patients treated or not treated with IMM, subgrouped according to CD phenotype, and UC extent subgrouped as described.[17] In our single-centre study, the incidence of cancer in UC and CD was 2.8% and 5.5%, respectively.[17] On the basis of this observation, we estimated that a minimum of 2001 person-years of follow-up would be needed to have a statistical power of 80% and type I error probability of 0.05 not to reject the hypothesis that CD-UC type relative risk is equal to 1.96. The frequency of incident cancer was therefore assessed in 44619 IBD patients, including 21953 CD and 22666 UC, with or without IS and anti-TNFα use.

Association between risks factors and cancer was investigated in a multivariate logistic regression analysis in IBD and, separately, in UC and CD. ORs [95% CI] were calculated. Risk factors for cancer in IBD included: IBD phenotype, CD pattern [B1, B2 vs B3],[5,19] IBD extent, and perianal disease [Y/N] in CD. Adjusted factors in CD and, separately, UC patients included: smoking [Y/N], disease-related surgery [Y/N], age [≥ 40 vs < 40 years], IBD duration [≥10 *vs* < 10 years], and IS and/or anti-TNFα [Y/N] used as mono- or combotherapy. A crude cumulative incidence of cancer in UC and CD was estimated in terms of rate per 1000 patients, during the 3-year follow-up. All incident cancers/neoplasia were reported and defined. Results were expressed as median [range]. Among UC and CD patients, differences between cases and controls were assessed by the Wilcoxon test [non-parametric test for continuous variables], chi-square or Fisher's test [categorical variables], as appropriate.

3. Results

3.1. Incidence of cancer

The analysis included 44619 IBD [21953 CD and 22666 UC] patients. Incident cancer was observed in 174 IBD patients [IBD-K], including 99 CD [CD-K], and 75 UC [UC-K]. In IBD, the overall cumulative incidence of cancer was 3.9/1000 [174/44, 619 patients]. The cumulative incidence of cancer overall was significantly higher in CD at 4.5/1000 [99/21, 953 patients] than in UC at 3.3/1000 [75/22, 666 patients]; *p* = 0.042 [Figure 1]. As each of the 174 IBD-K patients was matched with two IBD patients without cancer, controls included 348 IBD patients [IBD-C]: 198 CD-C and 150 UC-C, without cancer. All the 522 IBD patients completed the 3 years' follow up. None of the 348 IBD-C showed cancer at entry according to the study protocol, and none of them developed cancer during the 3 years' follow-up.

3.2. Clinical characteristics

The IBD group [*n* = 522] included 174 patients with incident cancer (CD-K: *n* = 99, 57%; UC-K: *n* = 75, 43%; age 57 [17–85] years); and 348 matched IBD controls with no cancer (CD-C: *n* = 198, 57%; UC-C: *n* = 150, 43%; age 57 [15–87] years). Matched clinical characteristics were comparable between CD and UC patients and controls [Table 1]. When considering unmatched characteristics, only the frequency of surgery was higher in UC-K than in UC-C [*p* = 0.0007]. The other variables, including CD and UC duration, were comparable between IBD patients with or without cancer [Table 1]. A comparable proportion of CD-K and CD-C showed perianal disease [*n* = 25 [25.3%] vs 42 [21.2%], respectively, p = 0.43]. CD localisation was comparable between CD-K and CD-C (L1: 38 [38%] vs 117 [40%]; L2: 16 [16%] vs 54 [18%]; L3: 39 [39%] vs 115 [39%]; no recurrence: 1 [1%] vs 2 [2%]; others: 5 [5%] vs 7 [2%]), respectively. At diagnosis of IBD, patients were younger in CD-K vs UC-K [*p* = 0.025], but not in CD-C vs UC-C [Table 1]. No differences were observed in terms of age at diagnosis of IBD, in CD and UC patients with or without cancer [CD-K vs CD-C and UC-K vs UC-C] [Table 1]. The frequency of smokers was higher in CD-C than in UC-C [*p* < 0.0001] and comparable between CD-K vs UC-K. At diagnosis of cancer, the age was lower in CD patients with a B1 vs a B2 phenotype (47 [17–77] vs 59.5 [25–80]; *p* = 0.005, respectively), whereas no differences were observed between CD patients with a B1 vs B3 (50 [20–84]; *p* = 0.29) or with a B3 vs B2 [*p* = 0.16])
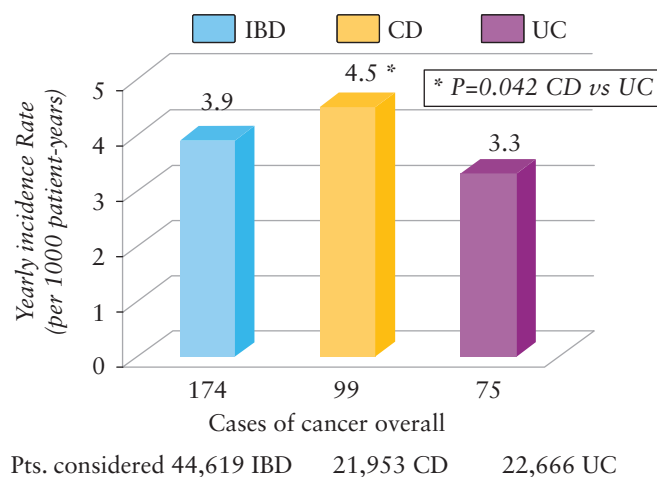

Figure 1. Incidence rates of cancer overall in patients with inflammatory bowel disease [IBD]: Crohn's disease [CD], ulcerative colitis [UC]. The incidence rate of cancer in general was significantly higher in CD than in UC [*p* = 0.042].

Table 1. Clinical characteristics of CD and UC patients with incident cancer [CD-K, UC-K], and of their matched CD and UC controls with no cancer [CD-C, UC-C], including matched* and unmatched variables [patients *n* = 150].

	CD-K	CD-C	UC-K	UC-C
Patients [*n*]	99	198	75	150
Age [years]*	55 [16–84]	54 [15–79]	61 [32–85]	60 [29–87]
Gender*				
Females [%]	47 [47%]	94 [47%]	32 [43%]	64 [43%]
Males [%]	52 [53%]	104 [53%]	43 [57%]	86 [57%]
IBD duration [years]	13 [1–50]	12 [1–45]	12 [1–37]	13.5 [1–54]
Age at diagnosis of IBD	37 [6–80][a]	39 [5–79]	42 [15–79]	42 [7–81]
Smoking habits [Y]	35 [35.4%]	78 [39.4%][b]	17 [22.7%]	20 [13.3%]
Previous surgery [Y]	59 [59.6%][d]	107 [54%][e]	12 [16%][c]	5 [3.3%]
Appendectomy [Y]	20 [20.2%][f]	48 [24.2%][g]	6 [8.0%]	13 [8.7%]
EIM [Y]	20 [27%]	49 [31%][h]	10 [13.3%]	13 [8.7%]
IS [with no anti-TNFα]	20 [20.2%]	36 [18.2%]	15 [20%]	25 [16.7%]
Anti-TNFα [with no IS]	12 [12.1%]	23 [11.6%][i]	4 [5.3%]	6 [4%]
IS with anti-TNFα	28 [28.3%][l]	76 [38.4%][m]	10 [13.3%]	21 [14.0%]
No IS, no anti-TNFα	39 [39.4%]	63 [31.8%]	46 [61.3%][n]	98 [65.3%][o]

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; CD-K and UC-K, CD and UC patients with cancer, CD-C and UC-C, CD and UC patients with no cancer,;Y, yes; IS, thiopurines; EIM, extra-intestinal manifestations; TNF, tumour necrosis factor.

*Matched variables [not including matched phenotype].

[a]*p* = 0.025 CD-K vs UC-K; [b]*p* < 0.0001 CD-C vs UC-C; [c]*p* < 0.0007 UC-K vs UC-C; [d,e]*p* < 0.0001 CD-K vs UC-K and CD-C vs UC-C; [f]*p* = 0.025 CD-K vs UC-K; [g]*p* < 0.0001 CD-C vs UC-C; [h]*p* < 0.0001 CD-C vs UC-C; [i]*p* < 0.001 CD-C vs UC-C; [l]*p* = 0.018 CD-K vs UC-K; [m]*p* < 0.0001 CD-C vs UC-C; [n]*p* = 0.004 CD-K vs UC-K; [o]*p* < 0.001 CD-C vs UC-C.

phenotype. Age at diagnosis of cancer was comparable between patients with distal, left-sided, or extensive UC (64 [35–83] vs 65 [33–80] vs 59 [35–85]).

3.3. Use of immunomodulators

Current or past use of IS monotherapy was comparable between CD and UC patients with or without cancer [Table 1]. IS and/or TNFα antagonists were used in a higher proportion of CD vs UC patients [CD-K vs UC-K: *p* = 0.004; CD-C vs UC-C: *p* < 0.0001 [Table 1]. Anti-TNFα monotherapy was more frequent in CD-C than in UC-C [*p* < 0.001] and comparable between CD-K and UC-K. Combined IS and anti-TNFα treatment was also more frequent in CD than in UC [CD-K vs UC-K; *p* = 0.018; CD-C vs UC-C; *p* < 0.0001]. In CD patients, the median duration of IS treatment [months] at the end of the study was (27 [1–180]), showing no significant differences between patients with vs without cancer (CD-K vs CD-C: 36 [1–168] vs 24 [1–180], *p* = 0.4). In the UC group, the median duration of IS treatments was 24 [1–132] months, being comparable between cases and controls (UC-K vs UC-C: 30 [1–132] vs 24 [1–120]; *p* = 0.61). In the CD group, the median months of any anti-TNFα treatment during the disease course was 27 [1–312], being comparable between patients with vs without cancer (CD-K vs CD-C: 21 [1–123] vs 32 [3–312]; *p* = 0.15). In UC patients also the median months of any anti-TNFα treatment was comparable between cases and controls (UC-K vs UC-C: 11 [3–57] vs 7 [1–43]; *p* = 0.23; all UC patients: 8 [1–57]). Further analysis regarding cancer and dose/duration of IMM will be investigated in a longer follow-up.

The median age at diagnosis of cancer did not differ between CD and UC patients with or without history of IS and/or anti-TNFα use (IS: 57 [31–73] vs 52 [17–84] in CD; 53 [33–71] vs 60 [35–85] in UC; anti-TNFα: 46 [24–74] vs 54 [17–84] in CD; 59 [43–78] vs 59 [33–85] in UC; combined IS and anti-TNFα: 48 [17-70] vs 55 [24–84] in CD; 56 [36–80] vs 59 [33–85] in UC; no IS, no anti-TNFα: 56 [25–84] vs 51[17–74] in CD; 61 [36–80] vs 55 [33–80] in UC).

3.4. Characterization of incident cases of cancer

Cancer in the 174 IBD patients involved [Figure 2]: digestive system [*n* = 64; 36.8%], skin [*n* = 23; 13.2%], urinary tract [*n* = 21;12.1%], lung [*n* = 15; 8.6%], breast [*n* = 14; 8.0%], genital tract [*n* = 12;6.9%], thyroid [*n* = 8;4.6%], lymphoma [*n* = 6; 3.5%], and others [≤ 2 cases] [*n* = 11; 6.3%] [Table 2]. The 64 cancers of the digestive system in IBD included [Figure 2]: colorectal cancer [CRC] [*n* = 43; 67.2%], small-bowel carcinoma [SBC][*n* = 8;12.5%], carcinoid [*n* = 3; 4.7%], cholangiocarcinoma [*n* = 3; 4.7%], anal carcinoma [*n* = 2; 3.1%], and others [*n* = 5; 7.8%]. Skin cancers in IBD [*n* = 23] included 9 NMSC [all basal cell carcinomas, BSC] [Table 3].

Lymphoma [four nonHodgkin, NHL, two Hodgkin, HL] occurred in six patients after the diagnosis of CD (six males, age at diagnosis of CD 38 [16–50]). In these six patients, the median age at diagnosis of lymphoma was 46 [28–62] and CD duration at diagnosis of lymphoma was 9 years [5–30]. Current or past use of both AZA and TNFα antagonists was reported in two of the six patients (Patient [Pt 1]: NHL, AZA monotherapy for 1 year, combined adalimumab for 2 years, CD diagnosed at 16 years, lymphoma at 28 years; Pt 2: NHL, AZA for 21 months, combined adalimumab for 3 months, CD diagnosed at 18 years, lymphoma at 48 years). History of AZA monotherapy [5 years] was reported in one of the six patients [Pt 3: NHL, CD diagnosed at 38, lymphoma at 62 years]. Any IMM was used by three patients [Pt 4: HL, stage IV, CD diagnosed at 38, lymphoma at 43 years; Pt 5: HL, CD diagnosed at 45, lymphoma at 50 years; Pt. 6: NHL, CD diagnosed at 48, lymphoma at 54 years].

All eight SBC occurred in patients with stricturing CD (eight males, age 56 [40–68]), with current IMM [AZA] use in one patient. The median CD duration in these eight patients was 1 year [1–38][≤ 1 year in five patients; ≥ 13 years in three patients]. Cholangiocarcinoma occurred in three patients [one CD, two UC]: 1.72% [3/174] of overall cancers and 4.7% [3/64] of cancers of the digestive system. Primary sclerosing cholangitis [PSC] was present in one of these three patients [UC, female, age 32, UC duration 9 years, AZA for 26 months, no anti-TNFα]. PSC was also diagnosed in two CD patients with CRC and no cholangiocarcinoma.
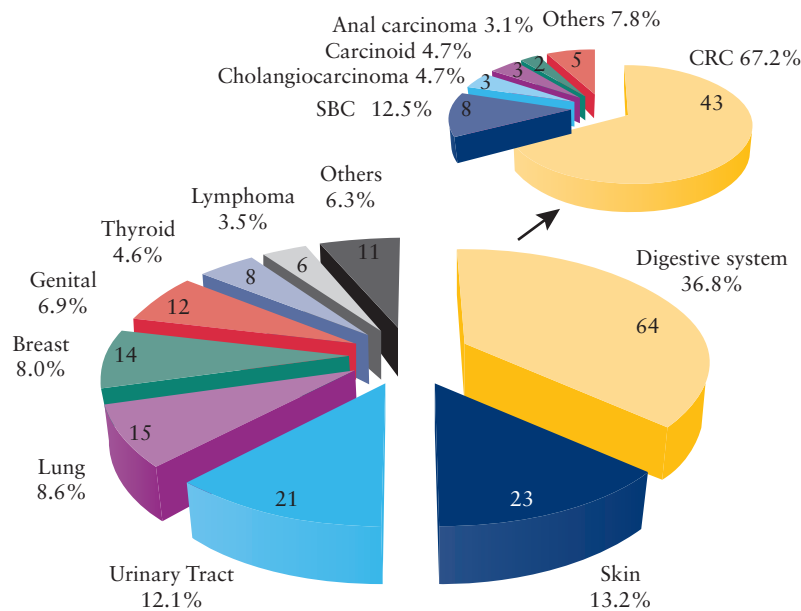
Figure 2. Characteristics of the 174 incident cases of cancer in patients with inflammatory bowel disease [IBD].

3.5. Incident cancer in CD vs UC

The frequency of cancer subtypes did not differ between CD [*n* = 99] and UC [*n* = 75] and involved: digestive system [35.3% vs 38.6%], urinary tract [9.1% vs 16%], skin [14.1% vs 12%], lung [17% vs 7%], breast [9% vs 6%], lymphoma [6 vs 0%], respectively [Table 2]. Among the 64 cancers involving the digestive system, 43 [67.1%] were CRC [Figure 2]. The higher frequency of CRC in UC vs CD was at the limit of statistical significance (CRC/extracolonic cancers: 24/75 [32%] vs 19/99 [19.2%]; *p* = 0.052, respectively).

Lymphoma [*n* = 6] and SBC [*n* = 8] occurred only in CD. The frequency of cancer involving the digestive system or the genitourinary tract vs other cancers did not differ between UC and CD [38.7% vs 35.4%; 21.3% vs 17.2%, respectively; *p* = non-significant].

3.6. Risk factors for cancer

When considering CD phenotypes, among patients with penetrating disease there was a significantly higher proportion of patients with vs without cancer [B3 vs B1 and B2 in CD-K vs CD-C: 26/99 [26%] vs 30/198 [15%]; *p* = 0.02][Figure 3a]. Conversely, a comparable proportion of patients with vs without cancer was observed within patients with a non-penetrating non-stricturing or with stricturing CD [Figure 3a].

In patients with extensive UC there was a significantly higher proportion of patients with vs without cancer (extensive UC vs others: UC-K vs UC-C: 41/75 [55%] vs 51/149 [34%]) [Figure 3b]. The frequency of distal and left-sided UC was comparable between patients with vs without cancer [Figure 3b]. Comparable findings were observed when UC extent was subgrouped into proctitis, left-sided, and extensive disease.

In CD, multivariate analysis adjusted for the reported variables [age at the latest visit, smoking, current or past treatments with IS and TNFα antagonists, disease-related surgery, CD duration] identified a penetrating vs non-penetrating non-stricturing CD as a significant risk factor for cancer overall (OR 2.33 [1.01–5.4]) [Figure 4a]. Current or past treatment with IS and anti-TNFα, considered as an adjustment factor, slightly increased the cancer risk (OR 1.95 [1.10–3.50]). Conversely, in a separate analysis, IS

or anti-TNFα monotherapies were not identified as risk factors for cancer in CD (IS: OR 0.84 [0.45–1.59]; anti-TNFα: OR 0.95 [0.44–2.12]). Multivariate analysis did not include CD location, as univariate analysis did not identify this variable as a risk factor for cancer.

In UC, multivariate analysis adjusted for the above reported variables identified extensive vs distal UC as a significant risk factor for any cancer (OR 2.52 [1.26–5.14]) [Figure 4b]. Comparable findings were observed when UC extent was subgrouped into proctitis, left-sided, or extensive UC,[19] as only extensive UC vs proctitis was a risk factor for cancer overall (OR 3.60 [1.13–14.6]). Disease-related surgery, considered as an adjustment factor, increased the cancer risk (OR 5.10 [1.73–17.15]) [Figure 4b]. Conversely, current or past treatment with IS and anti-TNFα did not increase the cancer risk in UC (combined IS and anti-TNFα: OR 1.10 [0.47–2.72]; IS: OR 0.68 [0.32–1.48]; anti-TNFα: OR 0.99 [0.25–4.46]). In IBD, current or past treatment with IS and TNFα antagonists (OR 1.57 [1.00–2.49]) and disease-related surgery (OR 1.54 [1.02–2.33]) were identified as risk factors for any cancer. The same finding was not observed for IS or anti-TNFα monotherapy (OR 0.85 [0.53–1.36]; OR 0.96 [0.50–1.89], respectively).

3.7. Risk factors for colorectal vs extracolonic cancers

As CRC represented almost one-fourth of cancers in IBD [24.7%], risk factors were also assessed for CRC and, separately, for extracolonic cancers. Although the relatively small number of CRCs limited this analysis [CD *n* = 19; UC *n* = 24], perianal disease was identified as the only significant risk factor for CRC in CD (OR 3.86 [1.87–12.5]) [Figure 4c].

Among the 19 CD patients with CRC, 8 also showed perianal disease. In these eight patients, CRC [all adenocarcinomas] involved the rectum in four [CRC adjacent to the fistula in one patient]. In CD, penetrating vs non-penetrating, non-stricturing behaviour and use of IS and TNFα antagonists were identified as risk factors for any cancer, but not for CRC (OR 0.37 [0.07–1.66]; OR 1.06 [0.36–3.39]). Conversely, both variables increased the risk of extracolonic cancers [*n* = 80] (OR 3.9 [1.56–10.1]; OR 2.15 [1.16–4.1],

Table 2. Characterization of incident cancers in inflammatory bowel disease patients.

Cancer	Crohn's disease n = 99	Ulcerative colitis n = 75
Digestive system [n = 64]		
CRC	19	24
SBC	7	1 [pouch]
Anal carcinoma	2	0
Cholangiocarcinoma	1	2
GIST	1	0
Carcinoid	3	0
Gastric	1	0
Pancreatic	1	0
HCC	0	1
Oesophageal	0	1
Skin [n = 23]		
NMSC	7	2
Melanoma	6	5
Kaposi	0	2
Keratoacanthoma	1	0
Urinary tract [n = 21]		
Renal	4	4
Prostatic	5	6
Bladder	0	2
Lung [n = 15]	7	8
Breast [n = 14]	7	7
Genital [n = 12]		
Ovary	1	1
Uterine	5	2
Testis	2	1
Thyroid [n = 8]	6	2
Lymphoma [n = 6]	6	0
Leukaemia [n = 1]	1	0
Multiple myeloma [n = 1]	0	1
Larynx [n = 1]	1	0
Tongue [n = 2]	0	2
Medulloblastoma [n = 1]	1	0
Suprarenal gland [n = 1]	1	0
Undifferentiated carcinoma metastatic [n = 1]	0	1
Carotid paraganglioma [n = 1]	1	0
Hibernoma [n = 1]	1	0
Pituitary adenoma [n = 1]	1	0

CRC, colorectal cancer, SBC, small-bowel cancer; NMSC, non-melanoma skin cancer; HCC, hepatocellular carcinoma; GIST, gastrointestinal stromal tumour.

respectively) [Figure 4c]. In CD, disease-related surgery was at the limit of the statistical significance as risk factor for extracolonic cancers (OR 1.54 [0.77–3.10]) [Figure 4c].

In UC, disease-related surgery was the only significant risk factor for CRC (OR 3.6 [1.0–12.0]) [Figure 4d]. Extensive vs distal UC and current or past treatment with combined IS and anti-TNFα were not identified as risk factors for CRC (OR 1.41 [0.54–3.86]; OR 0.68 [0.20–2.8], respectively). Conversely, risk factors for extracolonic cancers in UC [n = 51] included extensive vs distal (OR 2.55 [1.15–5.9]) and left-sided vs distal disease (OR 2.6 [1.04–6.6]), surgery being at the limit of the statistical significance (OR 2.59 [0.84–7.58]) [Figure 4d]. Comparable findings were observed when UC extent was subgrouped into proctitis, left-sided, and extensive disease, as disease-related surgery was identified as the only significant risk

factor for CRC [OR 3.93 [1.12–12.47]]. Accordingly, risk factors for extracolonic cancers included extensive UC vs proctitis (OR 5.07 [1.25–35.12]), whereas disease-related surgery was at the limit of the statistical significance (OR 2.59 [0.84–7.58]). In IBD, disease duration was a significant risk factor for CRC [n = 43] (OR 2.3 [1.06–5.4]). Risk factors for extracolonic cancers in IBD [n = 131] included disease-related surgery (OR 2.09 [1.34–3.27]) and current or past treatment with combined IS and anti-TNFα (OR 1.65 [1.01–2.76]), but not with IS or anti-TNFα monotherapy (OR 1.21 [0.80–1.84]; OR 1.35 [0.86–2.14]).

In IBD, maintenance treatment with oral 5-aminosalicylic acid [5-ASA] was observed in 91.2% [476/522] of patients. The percentage of patients treated with 5-ASA was comparable between patients with vs without cancer ([IBD-K: 90.2% [157/174] vs IBD-C 91.6% [319/348]; CD-K vs CD-C: 83.8% [83/99] vs 86.8% [172/198]; UC-K vs UC-C: 98.6% [74/75] vs 98% [147/ 150]; p = non-significant [n.s.]). No use of 5-ASA was observed in only 46/522 [8.81%] IBD patients: 17 patients with cancer [16 CD-K, 1 UC-K], 29 controls [26 CD-C, 3 UC-C]. No CRC or SBC occurred in any of the patients never treated with 5-ASA.

3.8. Cancers involving the gastrointestinal system, the skin, and the urinary tract

Risk factors were also searched for incident cancers involving the digestive system [n = 64], the skin [n = 23], or the urinary tract [n = 21]. Although the few observed cases limited this analysis, no risk factors were detected for cancer of the digestive system (combined IS and TNFα antagonists use: OR 1.40 [0.63–3.28]), urinary tract (combined IS and anti-TNFα use: OR 2.0 [0.64–8.8]; smoking: 0.72 [0.22–1.95]), and skin (combined IS and anti-TNFα use: OR 1.58 [0.46–6.3]).

Current and/or past history of IS and/or TNFα antagonists was observed in seven of the nine IBD patients with NMSC [IS in six], in five of the 11 patients with melanoma [anti-TNFα in four], in three of the six CD patients with lymphoma [IS in 1], in one of the eight CD patients with SBC, and in 11 of the 21 IBD patients with urinary tract cancer [Table 3].

3.9. Second and third incident cancer

During the 3 years' follow-up, a second incident cancer occurred in 11 of the 174 [6.32%] IBD patients: 6/99 [6.06%] with CD, 6/75 [8%] with UC [Table 4]. Current or past use of IS and/or TNFα antagonists was reported in 5/11 IBD patients developing a second cancer. Among these 11 IBD patients with two incident cancers, two [18.1%] also developed a third cancer [2/174; 1.14%] [Table 4]. Both patients had a history of IS [n = 1] or anti-TNFα [n = 1] use. None of these 11 patients were treated with any IMM after the first cancer.
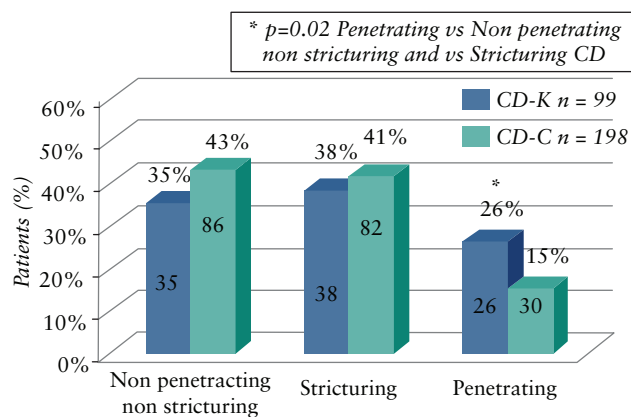
4. Discussion

The benefits when using immunomodulators in IBD currently appear to outweigh the cancer risk.[1,2,5,6] Thiopurines and anti-TNFα treatments may increase the cancer risk by interfering with the immune response towards tumour cells.[1,5,6,21] In 1975, TNFα was described as an endotoxin causing necrosis of tumours, thus suggesting that blocking this cytokine may reduce the suppression of cancer cells.[22] TNFα antagonists have been reported to increase melanoma risk.[13,14] Thiopurines increase the risk of Epstein-Barr virus-related lymphoma, B-cell lymphoma, HSTCL,[1,23,24,25,26] and NMSC.[1,3,4,27,28]

Table 3. Immunomodulators use in the 174 inflammatory bowel disease patients with incident cancer.

Cancer	IS monotherapy [n =]	Anti-TNFα monotherapy [n =]	IS and anti-TNFα [n =]	No IS, no anti-TNFα [n =]
CRC	7	2	10	24
SBC	1	0	0	7
Anal carcinoma	0	0	2	0
Carcinoid	0	0	0	3
Cholangiocarcinoma	1	0	1	1
Oesophagus	0	0	0	1
GIST	0	0	0	1
Hepatocarcinoma	0	1	0	0
Pancreas	0	0	0	1
Breast	3	2	3	6
Lymphoma	1	0	2	3
Uterus	0	2	3	2
Ovary	1	0	0	1
Testis	1	0	1	1
Prostate	4	1	1	5
Kidney	2	1	2	3
Urinary bladder	1	0	0	1
Melanoma	1	2	2	6
NMSC	3	1	3	2
Kaposi	1	0	0	1
Keratoacantoma	0	0	1	0
Lung	7	0	1	7
Thyroid	1	1	3	3
Pituitary adenoma	0	1	0	0
Hibernoma	0	1	0	0
Larynx	0	0	0	1
Leukaemia	0	0	0	1
Tongue	0	0	0	2
Undifferentiated carcinoma metastatic	0	0	0	1
Medulloblastoma	0	0	1	0
Multiple myeloma	0	0	0	1
Carotid paraganglioma	0	0	1	0
Suprarenal gland	0	1	0	0

CRC, colorectal cancer; SBC, small-bowel cancer; NMSC, non-melanoma skin cancer; HCC, hepatocellular carcinoma; GIST:=, gastrointestinal stromal tumour; IS, thiopurines; TNF, tumour necrosis factor.
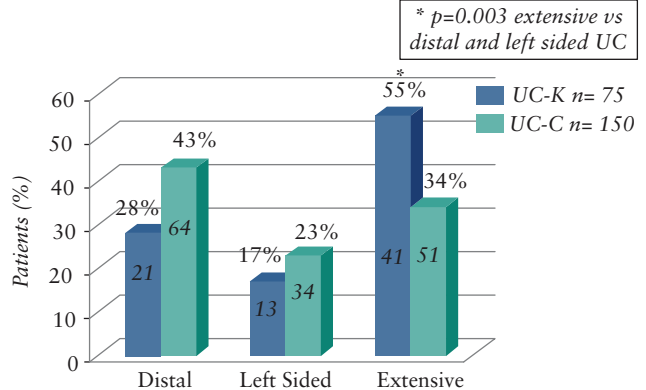

Figure 3. Panel a. Crohn's disease [CD], behaviour in patients with [CD-K: n = 99] or without [CD-C: n = 198] incident cancer. A higher proportion of CD patients with vs without cancer was observed in patients with penetrating disease [p = 0.02]. The frequency of patients with or without cancer did not significantly differ between patients with non-penetrating non-stricturing vs stricturing CD. Panel b. Ulcerative colitis [UC] extent in patients with distal, left-sided, and extensive disease in patients with [UC-K: n = 75] or without [UC-C: n = 150] incident cancer. A higher proportion of patients with vs without cancer was observed in patients with extensive UC [p = 0.003]. The frequencies of distal and left-sided UC were comparable between patients with vs without cancer. Comparable findings were observed when UC extent was subgrouped into extensive, left-sided, and proctitis.
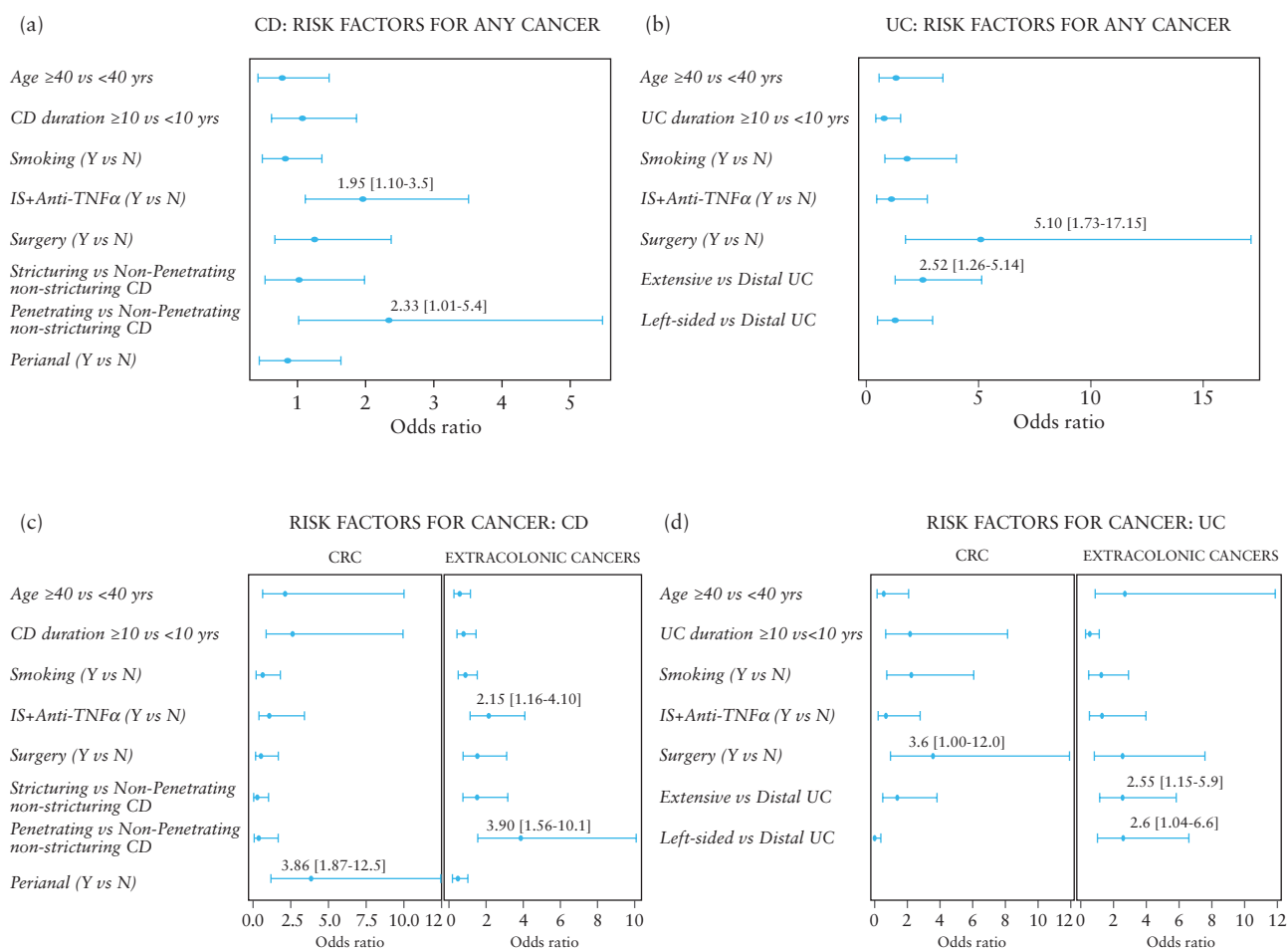
Figure 4. Multivariate analysis assessing risk factors for cancer overall, for colorectal cancer [CRC] and for extracolonic cancers in patients with Crohn's disease [CD] and ulcerative colitis [UC]. The following risk factors for cancer were identified. Panel a. In CD, penetrating vs non-penetrating non-stricturing CD for cancer overall: current or past treatment with thiopurines [IS] and tumour necrosis factor alpha [TNFα] antagonists slightly increased the risk for any cancer. Panel b. In UC, disease-related surgery and extensive vs distal disease increased the overall cancer risk. Comparable findings were observed when UC extent was subgrouped into proctitis, left-sided, or extensive UC. Panel c. In CD, perianal disease was the only risk factor for colorectal cancer [CRC], whereas a penetrating vs non-penetrating non-stricturing behaviour and current or past treatment with thiopurines [IS] and TNFα antagonists were identified as risk factors for extracolonic cancers. Panel d. In UC, disease-related surgery was the only significant risk factor for CRC, whereas extensive vs distal and left-sided vs distal UC were identified as risk factors for extracolonic cancers. Comparable findings were observed when UC extent was subgrouped into proctitis, left-sided, and extensive disease.

Table 4. Second and third incident cancer occurring in the cohort of 174 IBD patients during the 3 years' follow-up: characterisation and immunomodulators use before cancer.

Immunomodulator use before the first cancer	IS monotherapy [*n* =]	Anti-TNFα monotherapy [*n* =]	IS and anti-TNFα [*n* =]	No IS, no anti-TNFα [*n* =]
Second cancer				
CRC [*n* = 2]	0	1	0	1
Testis [*n* = 1]	0	0	0	1
Prostate [*n* = 1]	1	0	0	0
Urinary bladder [*n* = 1]	0	1	0	0
Kidney [*n* = 1]	0	1	0	0
Breast [*n* = 1]	0	0	0	1
Melanoma [*n* = 1]	0	0	0	1
Thyroid [*n* = 1]	1	0	0	0
Leukaemia [*n* = 1]	1	0	0	0
Lung [*n* = 1]	0	0	0	1
Third cancer				
Pancreas [*n* = 1]	1	0	0	0
Carcinoid [*n* = 1]	0	1	0	0

IBD, inflammatory bowel disease; CRC, colorectal cancer; IS, thiopurines; anti-TNFα, anti-tumour necrosis factor-α.

However, the absolute risk of these cancers is low,[1,2,23,24,25,26,28] and a lower risk of CRC has been reported in patients with severe IBD treated with IMM.[29,30,31] The overall cancer risk associated with IMM use in IBD has been extensively investigated.[1,2,7,8,9,10,11,12,13,14,15,16,23,24,25,26,27,28] Conversely, evidence regarding the cancer risk associated with clinical characteristics of IBD vs the use of IMM treatments is lacking.[17,18] We therefore investigated this issue in a prospective, multicentre, nested case-control study.

In our IBD population, the incidence of overall cancer was higher in CD than in UC, thus representing one of the main messages of the study. The low proportion of UC patients treated with IMM may be involved in this finding. A single-centre study reported an overall excess risk of cancer in CD, but not in UC,[18] in agreement with our retrospective study including a different IBD population.[17] Differences in terms of study design and populations may account for discrepant findings in this regard.[1,32,33] Moreover, to the best of our knowledge, data from prospective, multicentre, nested case-control studies including incident cancers are currently lacking.[1,32,33] To find whether IBD phenotype [CD vs UC] is a risk factor for cancer represented one of the aims of this study. Therefore, only patients with a definite diagnosis of UC or CD, according to current guidelines[5,6] as judged by experienced, IBD-dedicated gastroenterologists referring to tertiary IBD centres, were enrolled. For proper assessment, cases requiring revisions in order to confirm the diagnosis [CD vs UC] were excluded before entry. Although any diagnosis, including of IBD [CD vs UC], may change over time, the methods applied provide evidence for an accurate diagnosis of CD vs UC in the tested population.

Multivariate analysis identified penetrating CD and extensive UC as risk factors for overall cancer and for extracolonic cancers, and this represented one of the main findings of the study. A higher frequency of penetrating CD and of extensive UC was observed in patients with vs without cancer, further supporting that severe inflammation may increase the cancer risk, as suggested by our retrospective study.[17] Extensive UC is a known risk factor for CRC.[1,29,32,33] However, to the best of our knowledge, whether extensive UC and perforating CD may increase the risk of overall cancer and of extracolonic cancers is currently undefined.[1,29,32,33] Comparable findings were observed when UC extent was subgrouped according to studies from our group[17] and others[20] or to current guidelines.[6,19] Although IBD phenotype may have changed during the study period, IBD phenotypes were defined only at enrolment. Indeed, we aimed to assess the role of IBD phenotype vs IMM in determining the cancer risk, and at entry all cases [IBD-K] had an incident cancer according to the inclusion criteria. The present study therefore evaluated risk factors for cancer in IBD, when considering IBD phenotype defined at time of the diagnosis of cancer. In particular, IBD phenotype was defined at enrolment when considering the entire disease history,[5,6,17,20] and the median IBD duration of the tested population was quite long [≥ 12 years in both CD and UC groups]. However, IBD phenotype may have changed in subgroups of patients during the few additional 3 years of follow-up. This is not the case for patients with a perforating phenotype in CD or with pancolitis in UC [identified as the two IBD subgroups at higher cancer risk in the present study] at enrolment. Although a large population [> 46 000 patients] was considered, whether these findings may be extended to the general IBD population is being evaluated in a longer follow-up.

A comparable proportion of IBD patients with or without cancer showed a current or past treatment with IS and/or TNFα antagonists. However, TNFα antagonists were used in a higher proportion of CD vs UC patients without cancer. Although almost half of UC patients showed extensive disease, IMM were used in a low proportion of patients.

Current or past combined treatment with IS and TNFα antagonists, considered as an adjustment variable, was identified as a risk factor for overall cancer in CD, although less significant than perforating CD. This observation, representing one of the main findings of the study, is in agreement with a recent study,[34] although conflicting data are reported.[1,32,33] As for IBD behaviour, differences in terms of study design and populations may account for the observed discrepancies. In the present study, treatment with anti-TNFα and/or IMM at any time during the study period was considered, and treatments reported at time of enrolment were updated during the 3 years' follow-up. These observations suggest the reliability of the reported findings. Combined IS and anti-TNFα treatment was also identified as a risk factor for overall cancer when data from CD and UC patients were grouped into one IBD group. Conversely, IS and/or anti-TNFα treatments did not appear to increase the cancer risk in UC, possibly due to the low proportion of treated patients. Whether IS monotherapy may increase the overall cancer risk is debated.[1,32,33,35] Several studies report no excess risk using IS,[36] although the CESAME study, including NMSC, reported a higher risk.[11] On the other hand, anti-TNFα monotherapy currently appears not to increase the overall cancer risk.[1,5,6,7,8,9,10,11,12,32,33,34] IMM are indicated in severe IBD, including perforating CD and extensive UC.[5,6] As present findings identified these characteristics as risk factors for cancer, the possible relationship between IBD phenotypes and IMM in determining the cancer risk is being further defined in a longer follow-up.

In CD, perianal disease was identified as a risk factor for CRC, but not for overall cancer or for extracolonic cancers. Anal adenocarcinomas arising from perianal fistulas have been reported in CD,[1,32] but data regarding perianal CD as a risk factor for CRC are lacking. In our CD population, almost half of CRC occurred in perianal CD [8 out of 19 CRC, all adenocarcinomas], showing rectal involvement in half of cases [4 out of 8]. The limited number of cases did not allow the assessment of the role of the severity of inflammation vs the use of IMM in the occurrence of CRC in perianal CD. Whether perianal CD is a risk factor for CRC requires further investigations for proper surveillance.

IMM have been reported to reduce the risk of CRC in severe and extensive IBD colitis.[1,29,32] In CD and in the whole group of IBD patients, treatment with IS and anti-TNFα was identified as a risk factor for overall cancer and for extracolonic cancers, but not for CRC. This finding further supports that controlling inflammation by using IMM may reduce the risk of colitis-associated CRC in IBD. A high proportion of IBD patients [91.2%] was on maintenance treatment with 5-ASA, thus not allowing a proper assessment of the role of 5-ASA for preventing CRC and SBC. However, the observed incidence of these cancers was comparable to the general IBD population.[32]

Further supporting that the severity of IBD may increase the cancer risk, in UC not only extensive colitis, but also disease-related surgery were identified as risk factors for overall cancer and for CRC. Accordingly, disease-related surgery was observed in a higher proportion of UC patients with cancer [*p* = 0.0007], whereas the same finding was not observed in CD, due to the high frequency of surgery in CD [> 50%]. In UC, disease-related surgery was associated with a 5-fold increased risk of overall cancer. This observation appeared mainly related to patients requiring colectomy for CRC, although disease-related surgery was at the limit of statistical significance as risk factor for extracolonic cancers. Disease-related surgery was indeed a risk factor for extracolonic cancers in the whole group

of IBD patients, but not in CD and in UC groups separately considered. An explanation for this apparent discrepancy is that in both CD and UC, disease-related surgery as risk factor for extracolonic cancers was at the limit of the statistical significance. When data from CD and UC patients were grouped into one IBD group, both disease-related surgery and combined IS and anti-TNFα treatment were therefore identified as risk factors for extracolonic cancers. These findings further support a role for severe IBD often requiring surgery and IMM, in determining the cancer risk.

Age at the latest visit was not a significant risk factor, as cases and controls were matched for this variable of adjustment. IBD duration increased the CRC risk, as expected.[1,6,29,32] The same finding was not observed when UC and CD were separately considered, due to the relatively limited number of cases [*n* = 19; *n* = 24, respectively].

Clinical characteristics and the cumulative incidence of cancer in IBD were comparable to the general IBD population,[1,18,32,33] thus supporting the reliability of our findings. This is further suggested by the observation that IBD duration [not matched variable] was comparable between cases and controls. Patients and controls were not matched for smoking nor for family history of cancer, although these may possibly be relevant for some types of malignancies. As data were prospectively recorded, these risk factors invariably changed several times during the 3 years' follow-up. Therefore, an accurate and updated match for smoking and for family history of cancer appeared not to be guaranteed for each patient and control recruited from the 16 centres. This is particularly true for incident cancers occurring in each family member of each patient and control during the 3 years' follow-up. Supporting these considerations, to the best of our knowledge, data from prospective multicentre studies assessing risk factors for incident cancer in IBD patients and controls matched for all these variables are lacking.[1,2,7,8,9,10,11,12,13,14,15,16,17,18,23,24,25,26,27,28,29,30,32,33,34] However, the observed percentage of smokers did not differ between CD and UC cases and controls, matched for gender and age. The expected higher frequency of smokers in CD vs UC[5,6] was significant only for patients without cancer [CD-C vs UC-C; *p* < 0.0001]. This may suggest a role for smoking in determining the cancer risk in UC, although this risk factor was not statistically significant. The low proportion of both smokers and smoking-related cancers observed in our population may account for this finding. Although no scheduled surveillance protocols were planned at enrolment, routine clinical practice guidelines/consensus were followed by the referral IBD-dedicated, experienced gastroenterologist in each centre. However, as not scheduled at entry, a minority of patients may have not followed the surveillance programme [particularly for extra-colonic cancers]. Nevertheless, the observation that all patients concluded the follow-up at 3 years and that detailed information of characteristics of cancer were timely available for all patients, suggests good compliance of the study population and reliability of the reported findings. A high frequency of recurrent cancer was observed, in agreement with recent observations.[37,38] thus representing one of the new messages of our study.

Although a large IBD population was considered, the number of incident cancers [*n* = 174] allowed only the assessment of risk factors for cancer overall, for CRC, and for extracolonic cancers. Some of the observed associations for the overall population in contrast to the individual subtypes of IBD [CD or UC] may indeed be related to the small number of incident cases of cancer in the subtypes and to the relatively short period of both observation and IBD duration. However, in both CD and UC groups, the median IBD duration appeared not short [from 12 to 13.5 years], although

showing wide inter-individual variations [from 1 to 54 years]. Risk factors for specific cancer subtypes, excluded from the aims of the study, are being assessed in a longer follow-up. Nevertheless, the more frequent cancers involved the digestive system, the skin, and the urinary tract, supporting recent studies.[35] IS were used by almost half [11 out of 21] of IBD patients with urinary tract cancer, recently associated with IS use.[35] SBC and lymphoma were observed only in CD, and CRC was the most frequent cancer of the digestive system, as expected.[1,6,29,30,31,32,33] CRC and SBC represented more than two-thirds of cancers, supporting the role of chronic inflammation in these cancers. SBC developed only in small-bowel CD, showing a high frequency [7.07%], thus supporting a role for the sequence 'uncontrolled inflammation-dysplasia-cancer' not only in CRC, but also in SBC.[28,39] This is also suggested by the finding that, despite the small sample, seven out of eight CD patients with SBC never received IS or TNFα antagonists. Conversely, although the incidence of SBC was at least equivalent to that of lymphoma, half of lymphomas were treated with IS or anti-TNFα [and still more in some extracolonic cancers, principally NMSC]. SBC was diagnosed either at CD onset or after a long history of stricturing CD. Despite the small sample, these preliminary findings suggest that both refractory/recurrent obstructions at CD onset and a long history of stricturing small-bowel CD may represent risk factors for SBC even in patients never treated with IMM.

The present prospective, multicentre, nested case-control study supports that penetrating CD and extensive UC represent significant risk factors for cancer in general. In the tested IBD population, the cumulative incidence of cancer was higher in CD than in UC, whereas present or past treatments with IS and anti-TNFα, considered as an adjustment factor, slightly increased the risk of overall cancer and of extracolonic cancers in CD. On the other hand, the risk of CRC in CD was not increased by IS and TNFα antagonists, thus supporting that controlling severe inflammation by using IMM may reduce the risk of CRC in IBD.[1,29,30,31,32,33] These findings suggest that IBD patients showing an aggressive course associated with severe and diffuse lesions, as observed in perforating CD and in extensive UC, may bear an increased overall cancer risk. Clinical characteristics of IBD should be considered among risk factors for cancer in general, particularly in young patients with perforating CD or extensive UC, most often requiring immunomodulators.

Funding

Conflicts of Interest

References

1. Beaugerie L, Itzkowitz SH. Cancers complicating inflammatory bowel disease. *N Engl J Med* 2015;**372**:1441–52.

2. Lewis JD, Schwartz S, Lichtenstein GR. Azathioprine for maintenance of remission in Crohn's disease: benefits outweigh the risk of lymphoma. *Gastroenterology* 2000;**118**:1018–124.

3. Peyrin-Biroulet L, Khosrotehrani K, Carrat F, *et al*. Increased risk for non-melanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. *Gastroenterology* 2011;**141**:1621–8.

4. Singh H, Nugent Z, Demers AA, *et al*. Increased risk of non-melanoma skin cancers among individuals with inflammatory bowel disease. *Gastroenterology* 2011;**41**:1612–20.

5. Dignass A, Van Assche G, Lindsay JO, *et al*. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. *J Crohns Colitis* 2010;**4**:28–62.

6. Dignass A, Eliakim R, Magro F, *et al*. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 1: Definitions and diagnosis. *J Crohns Colitis* 2012;**6**:965–90.

7. Biancone L, Orlando A, Kohn A, *et al*. Infliximab and newly diagnosed neoplasia in Crohn's disease: a multicentre matched pair study. *Gut* 2006;**55**:228–33.

8. Biancone L, Petruzziello C, Orlando A, *et al*. Cancer in Crohn's Disease patients treated with infliximab: a long-term multicentre matched pair study. *Inflamm Bowel Dis* 2011;**17**:758–66.

9. Peyrin-Biroulet L, Deltenre P, de Suray N, *et al*. Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials. *Clin Gastroenterol Hepatol* 2008;**6**:644–53.

10. Lichtenstein GR, Feagan BG, Cohen RD, *et al*. Drug therapies and the risk of malignancy in Crohn's disease: results from the TREAT™ Registry. *Am J Gastroenterol* 2014;**109**:212–23.

11. Williams CJM, Peyrin-Biroulet L, Ford AC. Systematic review with meta-analysis: malignancies with anti-tumour necrosis factor-α therapy in inflammatory bowel disease. *Aliment Pharmacol Ther* 2014;**39**:447–58.

12. Andersen NN, Pasternak B, Basit S, *et al*. Association between tumor necrosis factor-α antagonists and risk of cancer in patients with inflammatory bowel diseases. *JAMA* 2014;**311** :2406–13.

13. Long MD, Herfarth HH, Pipkin C, *et al*. increased risk for non-melanoma skin cancer in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2010;**8**:268–74.

14. Singh S, Nagpal SJ, Murad MH, *et al*. Inflammatory bowel disease is associated with an increased risk of melanoma: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2014;**12**:210–8.

15. Thai A, Prindiville T. Hepatosplenic T-cell lymphoma and inflammatory bowel disease. *J Crohns Colitis* 2010;**4**:511–22.

16. Kotlyar DS, Osterman MT, Diamond RH, *et al*. A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2011;**9**:36–41.

17. Biancone L, Zuzzi S, Ranieri M, *et al*. Fistulizing pattern in Crohn's disease and pancolitis in ulcerative colitis are independent risk factors for cancer: a single-centre cohort study. *J Crohns Colitis* 2012;**6**:578–87.

18. Jess T, Horváth-Puhó E, Fallingborg J, *et al*. Cancer risk in inflammatory bowel disease according to patient phenotype and treatment: a Danish population-based cohort study. *Am J Gastroenterol* 2013;**108**:1869–76.

19. Silverberg MS, Satsangi J, Ahmad T, *et al*. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005;Suppl A:5–36.

20. Fiorino G, Gilardi D, Naccarato P, *et al*. Safety and efficacy of sodium hyaluronate [IBD98E] in the induction of clinical and endoscopic remission in subjects with distal ulcerative colitis. *Dig Liv Dis* 2014;**46**:330–4

21. Harwood CA, Attard NR, O'Donovan P, *et al*. PTCH mutations in basal cell carcinomas from azathioprine-treated organ transplant recipients. *Br J Cancer* 2008;**99**:1276–84.

22. Carswell EA, Old LJ, Kassel RL, *et al*. An endotoxin-induced serum factor that causes necrosis of tumors. *Proc Nat Acad Sci U S A* 1975;**72**:3666–70.

23. Kandiel A, Fraser AG, Korelitz BI, *et al*. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut* 2005;**54**:1121–5.

24. Siegel CA, Marden SM, Persing SM, *et al*. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. *Clin Gastroenterol Hepatol* 2009;**7**:874–81.

25. Beaugerie L, Brousse N, Bouvier AM, *et al*. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet* 2009;**374**:1617–25.

26. Herrinton LJ, Liu L,Weng X, *et al*. Role of thiopurine and anti-TNF therapy in lymphoma in inflammatory bowel disease. *Am J Gastroenterol* 2011;**106**:2146–53.

27. Masunaga Y, Ohno K, Ogawa R, *et al*. Meta-analysis of risk of malignancy with immunosuppressive drugs in inflammatory bowel disease. *Ann Pharmacother* 2007;**41**:21–8.

28. Siegel CA, Finlayson SR, Sands BE, *et al*. Adverse events do not outweigh benefits of combination therapy for Crohn's disease in a decision analytic model. *Clin Gastroenterol Hepatol* 2012;**10**:46–51.

29. Rutter M, Saunders B, Wilkinson, *et al*. Severity of inflammation is a key factor for colorectal neoplasia in ulcerative colitis. *Gastroenterology* 2004;**126**:451–9.

30. van Shaik FDM, van Oijen GHM, Smeets HM, *et al*. Thiopurines prevent advances in colorectal neoplasia in patients with inflammatory bowel disease. *Gut* 2012;**61**:235–40.

31. Popivanova BK, Kitamura K, Wu Y, *et al*. Blocking TNF-α in mice reduces colorectal carcinogenesis associated with chronic colitis. *J Clin Invest* 2008;**118**:560–70.

32. Annese V, Beaugerie L, Egan L, *et al*. European evidence-based consensus: inflammatory bowel disease and malignancies. *J Crohns Colitis* 2015;**9**:945–65.

33. Biancone L, Onali S, Petruzziello C, *et al*. Cancer and immunomodulators in inflammatory bowel diseases. *Inflamm Bowel Dis* 2015;**21**:674–98.

34. Osterman MT, Sandborn WJ, Colombel JF, *et al*. Increased risk of malignancy with adalimumab combination therapy, compared with monotherapy, for Crohn's disease. *Gastroenterology* 2014;**146**:941–9.

35. Pasternak B, Svanström H, Schmiegelow K, *et al*. Use of azathioprine and the risk of cancer in inflammatory bowel disease. *Am J Epidemiol* 2013;**177**:1296–305.

36. Armstrong RG, West J, Card TR. Risk of cancer in inflammatory bowel disease treated with azathioprine: a UK population-based case-control study. *Am J Gastroenterol* 2010;**105**:1604–9.

37. Beaugerie L, Carrat F, Colombel JF, *et al*. Risk of new or recurrent cancer under immunosuppressive therapy in patients with IBD and previous cancer. *Gut* 2014;**63**:1416–23.

38. Axelrad J, Bernheim O, Colombel JF, *et al*. Risk of new or recurrent cancer in patients with inflammatory bowel disease and previous cancer exposed to immunosuppressive and anti-tumor necrosis factor agents. *Clin Gastroenterol Hepatol* 2016;**14**:58–64.

39. Elriz K, Carrat F, Carbonnel F, *et al*. Incidence, presentation, and prognosis of small bowel adenocarcinoma in patients with small bowel Crohn's disease: a prospective observational study. *Inflamm Bowel Dis* 2013;**19**:1823–6.