Effect of Biologics on the Risk of Advanced-Stage Inflammatory Bowel Disease-Associated Intestinal Cancer: A Nationwide Study

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INTRODUCTION: **The aim of this study was to evaluate the effect of biologics on the risk of advanced-stage inflammatory bowel disease (IBD)-associated intestinal cancer from a nationwide multicenter data set.**

METHODS: **The medical records of patients with Crohn's disease (CD) and ulcerative colitis (UC) diagnosed with IBD-associated intestinal neoplasia (dysplasia or cancer) from 1983 to 2020 were included in this study. Therapeutic agents were classified into 3 types: biologics, 5-aminosalicylic acid, and immunomodulators. The pathological cancer stage was compared based on the drug used in both patients with CD and UC.**

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RESULTS: **In total, 1,042 patients (214 CD and 828 UC patients) were included. None of the drugs were significantly associated with cancer stage in the patients with CD. In the patients with UC, an advanced cancer stage was significantly associated with less use of biologics (early stage: 7.7% vs advanced stage: 2.0%, $P < 0.001$), 5-aminosalicylic acid, and immunomodulators. Biologic use was associated with a lower incidence of advanced-stage cancer in patients diagnosed by regular surveillance (biologics [−] 24.5% vs [+] 9.1%, $P = 0.043$), but this was not the case for the other drugs. Multivariate analysis showed that biologic use was significantly associated with a lower risk of advanced-stage disease (odds ratio = 0.111 [95% confidence interval, 0.034–0.356], $P < 0.001$).**

DISCUSSION: **Biologic use was associated with a lower risk of advanced IBD-associated cancer in patients with UC but not with CD. The mechanism of cancer progression between UC and CD may be different and needs to be further investigated.**

KEYWORDS: Crohn's disease, ulcerative colitis, IBD-associated intestinal neoplasia, biologics

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/C844

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INTRODUCTION

The number of new cases of inflammatory bowel disease (IBD) is increasing worldwide, especially in Asia (1–3). In Japan, the most recent report showed that the incidence of IBD increased 10-fold in 23 years (4). The risk of cancer in patients with IBD has long been known to be high, with both patients with Crohn's disease (CD) and ulcerative colitis (UC) being at an approximately 2- to 3-fold higher risk than the general population (5–7). The increase in IBD-associated cancer has been accompanied by an increase in the number of patients with IBD (8). Reducing the incidence of cancer and detecting it at an early stage are important goals, and measures to help reach these goals are being developed in many countries (9).

Since IBD-associated intestinal cancer is generally considered to be caused by chronic inflammation of the intestinal mucosa, controlling inflammation is considered to be effective in reducing the risk of this disease. In this context, there have been a number of reports on the relationship between the IBD drug use and the risk of cancer. In particular, randomized control studies and meta-analyses of 5-aminosalicylic acid (5-ASA) have shown that mesalamine but not sulfasalazine reduces the risk of cancer development by approximately 40% (10). The use of mesalamine in patients with UC is now recommended in several treatment guidelines, with an expected chemopreventive effect (11–13). As such, the risk of cancer development has been shown thus far. However, the impact of such drugs on cancer progression is still unknown.

In addition to conventional IBD drugs, great strides have been made regarding the treatment of IBD in recent years with the introduction of a range of biologic agents. Anti-tumor necrosis factor (TNF)-α agents were first developed as new biologics and are now widely used to control mucosal inflammation (14). It has become possible to maintain remission for a long period after the onset of disease, and this has contributed greatly to improving the quality of life of patients and reducing the number of surgical cases (15). The chemopreventive effect of such newer biologics in inhibiting cancer development is now in the spotlight. Currently, it is generally considered that biologics do not change the risk of cancer development, and whether they lower the risk remains unclear (16,17). On the other hand, none of the existing studies have focused on cancer progression, namely, the risk of advanced-stage cancer.

The aim of this study was to evaluate the effect of biologics, along with other drugs, on the risk of advanced-stage IBD-associated intestinal neoplasia. These findings will provide important insights into the future use of drugs for IBD.

METHODS

Study design

This was an industry-independent nationwide, retrospective study conducted by the Japanese Society for Cancer of the Colon and Rectum. Patients with UC and CD who had been diagnosed with IBD-associated intestinal neoplasia from 1983 to 2020 at a total of 43 institutions were included in the study. All patient data were retrospectively collected from the medical records at each institution.

Clinical parameters, such as demographic data, diagnostic procedure, and history of medication, along with pathological parameters, such as Union for International Cancer Control TNM stage and histological findings, were retrieved and analyzed. The diagnosis of sporadic or IBD-associated neoplasia and the grade of dysplasia were based on the pathological diagnoses at each institution. Patients with missing medication history data or an unknown cancer stage were excluded from this study.

Subjects

Information on the patients' baseline characteristics was collected as follows: age at neoplasia diagnosis, sex, duration between IBD diagnosis and neoplasia diagnosis, diagnostic procedure (diagnosed by regular surveillance, symptoms, or others), interval from the last negative endoscopy to the diagnostic endoscopy, location of neoplasia (small intestine, right-sided colon, left-sided colon, rectum, or anus), presence of anal lesion in patients with CD, and extent of disease in patients with UC (extensive, left-sided, proctitis, or others). In medication, information on the drugs received within 1 year before neoplasia diagnosis was collected. The drugs were classified into 3 types: biologics, 5-ASA, and immunomodulators (IMs). The biologics included infliximab, vedolizumab, golimumab, and

adalimumab. The number of drugs was counted as the number of these drug types. A history of steroid use within 1 year before neoplasia diagnosis was also reviewed. Information on pathological findings of detected neoplasia was collected as follows: International Cancer Control TNM stage and histological findings (dysplasia, well-differentiated adenocarcinoma, and other types of cancers).

Ethics

This study was approved by the Ethics Committee of the University of Tokyo [2019220NI-(2)], the ethics committees of each institution if necessary, and the Ethics Committee of Japanese Society for Cancer of the Colon and Rectum. The requirement for written informed consent from the patients for participation in this study was waived because of the retrospective design of the study.

Endpoints

The primary endpoint was the pathological cancer stage at the time of diagnosis. In this study, early-stage cancer was defined as either dysplasia or pathological stage 0/I cancer and advanced-stage cancer was defined as pathological stage II/III/IV cancer. This definition is based on the previous report from our group that there is almost no difference in long-term prognosis between CD and UC in dysplasia and stage 0/I cancer, but there is a significant difference in stage II/III/IV cancer, suggesting a biological difference between them in advanced stages (18). For each drug, the association between its use and stage progression was investigated. The secondary endpoints were the oncologic factors associated with the drug types used in UC-associated cancer.

Statistical analysis

All statistical analyses were performed using STATA17 (StataCorp LLC, TX), and graph drawings were generated using GraphPad Prism 9 (GraphPad Software, San Diego, CA). Continuous variables are expressed as the mean ± SD. Categorical variables are presented as numbers (percentages). The Student *t* test was performed for continuous variables, and the Pearson χ^2 test was performed for categorical variables, as appropriate. Univariate and multivariate analyses were performed using the logistic regression model. Factors that showed *P* value < 0.1 in the univariate analysis were further included in the multivariate analysis. Statistical significance was defined as *P* value < 0.05.

RESULTS

Patient characteristics

A total of 1,042 patients (214 patients with CD and 828 patients with UC) were included in the study. All baseline patient data are summarized in Table 1. Advanced-stage cancer was found in 159 patients (74.3%) with CD and 297 patients (35.9%) with UC. The patients were then divided into the early-stage and advanced-stage groups, and the clinicopathological factors were compared between the groups.

Clinicopathological factors associated with advanced cancer

Among patients with CD, advanced-stage cancer was significantly associated with a lower frequency of diagnosis by regular surveillance (early: 38.2% vs advanced: 20.1%, $P = 0.007$) and less differentiated adenocarcinoma (early: 56.4% vs advanced: 19.5%, $P < 0.001$). However, there was no significant difference in the use of biologics, 5-ASA, or IMs. Of note, the mean time interval from the last endoscopy in patients undergoing regular surveillance and patients diagnosed by other methods was 14.9 ± 15.4 months and 29.0 ± 31.7 months, respectively ($P = 0.049$).

Among patients with UC, advanced-stage cancer was significantly associated with a younger age (early: 53.4 ± 14.4 years vs advanced: 51.1 ± 13.9 years old, $P = 0.029$), a lower frequency of diagnosis by regular surveillance (early: 82.7% vs advanced: 45.8%, $P < 0.001$), a longer time interval from the last endoscopy (early: 14.6 ± 16.2 months vs advanced: 18.2 ± 17.6 months, $P = 0.002$), and less differentiated adenocarcinoma (early: 89.5% vs advanced: 66.3%, $P < 0.001$). Regarding the drug types, less use of biologics (early: 7.7% vs advanced: 2.0%, $P < 0.001$), 5-ASA (early: 87.6% vs advanced: 75.4%, $P < 0.001$), and IMs (early: 22.4% vs advanced: 11.8%, $P < 0.001$) was significantly associated with advanced-stage cancer. Regarding the number of drugs used, a lower number was associated with advanced-stage cancer ($P < 0.001$). Steroid use was also significantly lower in the advanced-stage cancer group (early: 33.3% vs advanced: 26.3%, $P = 0.035$). Of note, the mean time interval from the last endoscopy in patients undergoing regular surveillance and patients diagnosed by other methods was 13.2 ± 13.0 months and 20.4 ± 24.6 months, respectively ($P < 0.001$).

Effect of drugs on advanced cancer risk

To investigate the effect of each drug on the progression of cancer, logistic regression analysis was performed on various clinicopathological factors associated with advanced-stage cancer (see Supplementary Table, http://links.lww.com/AJG/C844). Notably, among both patients with CD and UC, regular surveillance was significantly correlated with a low frequency of advanced-stage cancer and the histological type, other than the well/moderately differentiated type, was significantly correlated with a high frequency of advanced cancer. On the other hand, an older age at cancer diagnosis and a later year of diagnosis (after 2011) were also significant factors associated with a low frequency of advanced cancer, but only in patients with UC.

Next, a multivariate analysis was performed for both diseases. By adjusting for regular surveillance and histological type, none of the drugs for CD were significantly associated with the risk of advanced-stage cancer (Table 2). On the other hand, by adjusting for age, diagnosis year, regular surveillance, and histological type in UC, biologics and 5-ASA were significantly associated with a lower risk of advanced-stage cancer: biologics (odds ratio [OR] = 0.111 [95% confidence interval [CI], 0.034–0.356], $P < 0.001$) and 5-ASA (OR = 0.628 [95% CI, 0.401–0.982], $P = 0.041$) (Table 3).

These results indicate that biologics and 5-ASA are drugs that are potentially associated with a lower risk of advanced cancer in patients with UC but not with CD (Figure 1).

Differential effect of drugs on advanced cancer risk according to regular surveillance in UC

Figures 2a,b show comparisons of the percentages of advanced-stage cancer among patients with UC who were diagnosed by regular surveillance vs other methods, respectively. Among patients who were diagnosed by regular surveillance, biologics were the only drugs associated with a significantly lower frequency of advanced-stage cancer ([−] 24.5% vs [+] 9.1%, $P = 0.043$), whereas 5-ASA and IMs did not show any significant association (Figure 2a). By contrast, among patients who were diagnosed by

Table 1. Patient characteristics

	CD				UC			
	Total (n = 214)	Early (n = 55)	Advanced (n = 159)	*P* value	Total (n = 828)	Early (n = 531)	Advanced (n = 297)	*P* value
Sex								
Male	133 (62.1%)	34 (61.8%)	99 (62.3%)	0.953	521 (62.9%)	338 (63.7%)	183 (61.6%)	0.560
Age at cancer diagnosis (y/o)	46.6 ± 11.1	48.5 ± 11.2	45.9 ± 11.1	0.131	52.6 ± 14.2	53.4 ± 14.4	51.1 ± 13.9	0.029
Duration of disease (yr)	19.4 ± 9.9	18.9 ± 10.3	19.6 ± 9.8	0.662	16.9 ± 10.2	17.0 ± 10.4	16.7 ± 10.0	0.710
Diagnosed yr				0.562				0.392
2010	65 (30.4%)	15 (27.3%)	50 (31.4%)		244 (30.9%)	147 (29.8%)	97 (32.7%)	
2011	149 (69.6%)	40 (72.7%)	109 (68.6%)		547 (69.1%)	347 (70.2%)	200 (67.3%)	
Diagnosed by regular surveillance								
Yes	53 (24.8%)	21 (38.2%)	32 (20.1%)	0.007	575 (69.4%)	439 (82.7%)	136 (45.8%)	<0.001
Time interval from last endoscopy (mo)	22.5 ± 26.2	19.1 ± 22.3	24.5 ± 28.4	0.475	14.6 ± 16.2	12.9 ± 15.2	18.2 ± 17.6	0.002
Anal lesion								
Presence	154 (72.0%)	40 (72.7%)	114 (74.0%)	0.884				
Disease extent								0.623
Extensive (E3)					648 (78.3%)	409 (77.0%)	239 (80.5%)	
Left-sided (E2)					140 (16.9%)	96 (18.1%)	44 (14.8%)	
Proctitis (E1)					25 (3.1%)	17 (3.2%)	8 (2.7%)	
Others					15 (1.8%)	9 (1.7%)	6 (2.0%)	
Cancer location				0.052				0.099
Small intestine	16 (7.5%)	7 (12.7%)	9 (5.7%)		0 (0%)	0 (0%)	0 (0%)	
Right colon	19 (8.9%)	1 (1.8%)	18 (11.3%)		143 (17.3%)	81 (15.3%)	62 (20.9%)	
Left colon	20 (9.3%)	8 (14.5%)	12 (7.5%)		373 (45.0%)	241 (45.4%)	132 (44.4%)	
Rectum	68 (31.8%)	18 (32.7%)	50 (31.4%)		312 (37.7%)	209 (39.4%)	103 (34.7%)	
Anus	91 (42.5%)	21 (38.2%)	70 (44.0%)		0 (0%)	0 (0%)	0 (0%)	
Pathological stage				<0.001				<0.001
Dysplasia	0 (0%)	0 (0%)	0		101 (12.2%)	101 (19.0%)	0	
Stage 0	19 (8.9%)	19 (34.5%)	0		211 (25.5%)	211 (39.7%)	0	
Stage 1	36 (16.8%)	36 (65.5%)	0		219 (26.4%)	219 (41.2%)	0	
Stage 2	81 (37.9%)	0	81 (50.9%)		139 (16.8%)	0	139 (46.8%)	
Stage 3	50 (23.4%)	0	50 (31.4%)		127 (15.3%)	0	127 (42.8%)	
Stage 4	28 (13.1%)	0	28 (17.6%)		31 (3.7%)	0	31 (10.4%)	
Histology in cancer[a]				<0.001[a]				<0.001[a]
Well/moderately differentiated	62 (29.0%)	31 (56.4%)	31 (19.5%)		582 (80.1%)	385 (89.5%)	197 (66.3%)	
Others	152 (71.0%)	24 (43.6%)	128 (80.5%)		145 (19.9%)	45 (10.5%)	100 (33.7%)	
Drug type	64 (29.9%)	20 (36.4%)	44 (27.7%)	0.225	47 (5.7%)	41 (7.7%)	6 (2.0%)	0.001
Biologics								
5-ASA	104 (48.6%)	30 (54.5%)	74 (46.5%)	0.306	689 (83.2%)	465 (87.6%)	224 (75.4%)	<0.001
IM	34 (15.9%)	13 (23.6%)	21 (13.2%)	0.068	154 (18.6%)	119 (22.4%)	35 (11.8%)	<0.001
No. of drugs				0.767				<0.001
None	37 (17.3%)	9 (16.4%)	28 (17.6%)		126 (15.2%)	58 (10.9%)	68 (22.9%)	
Single	77 (36.0%)	18 (32.7%)	59 (37.1%)		554 (66.9%)	356 (67.0%)	198 (66.7%)	
Multiple	100 (46.7%)	28 (50.9%)	72 (45.3%)		148 (17.9%)	117 (22.0%)	31 (10.4%)	
Steroid use	170 (79.4%)	44 (80%)	126 (79.2%)	0.905	255 (30.8%)	177 (33.3%)	78 (26.3%)	0.035

ASA, aminosalicylic acid; CD, Crohn's disease; UC, ulcerative colitis.
[a]Excluding dysplasia cases.

Table 2. Multivariate analysis on the drugs associated with advanced pathological stage in patients with Crohn's Disease

	Crude		Adjusted[a]	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Biologics	0.670 (0.350–1.283)	0.226	0.573 (0.280–1.172)	0.127
5-ASA	0.725 (0.392–1.343)	0.307	0.773 (0.397–1.508)	0.451
IM	0.492 (0.227–1.065)	0.072	0.507 (0.216–1.189)	0.118

ASA, aminosalicylic acid; CI, confidence interval; IM, immunomodulators.
[a]Adjusted for regular surveillance and histological type.

methods other than regular surveillance, all 3 types of drugs were significantly associated with a lower frequency of advanced-stage cancer (biologics [−] 66.1% vs [+] 21.4%, $P = 0.001$; 5-ASA [−] 80.0% vs [+] 57.4%, $P = 0.001$; IM [−] 67.5% vs [+] 28.0%, $P < 0.001$) (Figure 2b).

Oncologic factors associated with drug types in UC-associated cancer

The effects of each drug type on oncologic factors in patients with UC-associated cancer were then examined. As summarized in Table 4, all of the drug types tended to be associated with an early pN stage. In particular, 5-ASA was the only drug that showed a statistically significant association ($P = 0.019$). Regarding the histological type, although none of the drugs were associated with any particular type, 5-ASA use was marginally associated with well/moderately differentiated cancer, while other drugs showed an inverse association.

DISCUSSION

This study investigated how the risk of advanced neoplasia in patients with IBD varies according to the therapeutic agents used in progression at the time of diagnosis. The results showed that biologics and 5-ASA were associated with a lower risk of advanced-stage cancer in patients with UC, especially biologics, which had an equivalent impact even in patients who were diagnosed by regular surveillance. By contrast, none of the drugs in patients with CD were found to be associated with a lower risk of advanced-stage cancer.

Although much remains to be elucidated about the mechanisms underlying the development of IBD-associated intestinal neoplasia, oxidative stress caused by chronic inflammation or factors generated by the host immune response with contributions from the gut microbiome and its products are considered to be responsible for carcinogenesis (19). Assuming that this type of neoplasia arises as a consequence of chronic inflammation, anti-inflammatory drugs that sustain and control mucosal inflammation have been considered to have a suppressive effect. In particular, the chemopreventive effect of 5-ASA or IMs has been debated for many years. Evidence for 5-ASA is accumulating, as indicated by a recent meta-analysis, and its use, especially in the form of mesalamine, is recommended in several guidelines (10–13,20,21). In our study, 5-ASA use was associated with a lower risk of advanced-stage cancer. However, further information on which form of 5-ASA was used was missing in this study, which is one of the limitations. Because chronic inflammation favors the development of neoplasia in IBD, IMs are also expected to have a chemopreventive effect (22,23). Although some meta-analyses have reported positive effects, this finding is still controversial because there are also reports showing no significant effects (24–26). Our results did not show a significant association between IM use and the risk of advanced-stage cancer. Therefore, although the mechanism is unclear, IMs are considered to have a limited effect on both cancer development and progression. Regarding biologics, there are concerns that their use may result in a risk of malignancies such as lymphoma and skin cancer (27,28). Among studies on anti-TNF-α antibody, meta-analyses and large cohort observational studies have shown no significant effect on malignancy risk (16,29,30). On the other hand, the effect on the progression of IBD-associated intestinal neoplasia has not been elucidated. Our results suggest that biologic use is associated with a lower risk of advanced-stage cancer in patients with UC. However, this could not be demonstrated for patients with CD, suggesting that the mechanism of cancer progression may be different for UC and CD; this difference needs to be investigated in more detail in the future.

Needless to say, early cancer detection is as important as prevention in the management of patients with IBD. An effective surveillance program is now suggested as a major means to achieve this goal. As a number of meta-analyses suggest, regular colonoscopy screening is important (31–33). In fact, the multivariate analysis in this study showed that the diagnostic procedure was a significant independent factor associated with early-stage cancer in both patients with CD and UC, suggesting that regular surveillance

Table 3. Multivariate analysis on the drugs associated with advanced pathological stage in patients with Ulcerative Colitis

	Crude		Adjusted[a]	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Biologics	0.246 (0.103–0.588)	0.002	0.111 (0.034–0.356)	<0.001
5-ASA	0.436 (0.301–0.630)	<0.001	0.628 (0.401–0.982)	0.041
IM	0.463 (0.308–0.695)	<0.001	0.617 (0.376–1.011)	0.055

ASA, aminosalicylic acid; CI, confidence interval; IM, immunomodulators.
[a]Adjusted for age, diagnosed year, regular surveillance, and histological type.

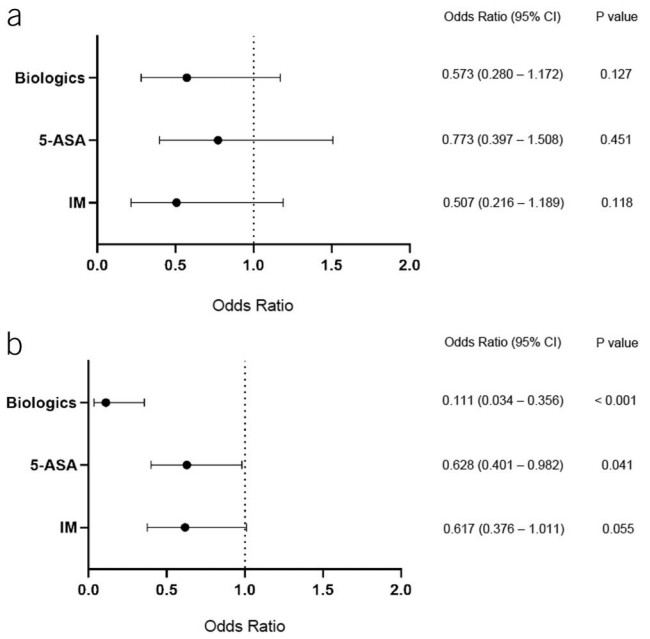

Figure 1. Forest plots of the multivariate analysis results of advanced cancer stage. (**a**) Odds ratios with 95% CI for each drug used in patients with Crohn's disease are shown. All analyses were adjusted for age, regular surveillance, histological type, and steroid use. (**b**) Odds ratios with 95% CI for each drug used in patients with ulcerative colitis are shown. All analyses were adjusted for regular surveillance and histological type. CI, confidence interval.

contributes to a favorable outcome. However, because this study involved only patients diagnosed with neoplasia, the overall number of patients who were undergoing regular surveillance is unknown. Therefore, it is not possible to know from this study whether regular surveillance was truly effective. The higher percentage of advanced cancer in patients with CD than patients with UC may suggest that regular surveillance was not effective in patients with CD or that physicians were less adherent to surveillance intervals. This is another issue that merits further elucidation; however, it has been suggested that regular surveillance in patients with CD with anorectal lesions who need inspection of the anus and transanal biopsy under anesthesia in some cases could be stressful for both the patient and the physician (18,34). According to our subgroup analysis, biologics were the only drugs that showed a significant association with a lower risk of advanced cancer, irrespective of the diagnostic procedure. This may suggest that mucosal inflammation could be better controlled by biologics themselves rather than by other drugs. In addition, because the concept of the cumulative inflammatory burden has been proposed as a determinant of cancer development, the appropriate use of biologics along with other drugs and regular surveillance may reflect better control of mucosal inflammation and result in a reduced cumulative inflammatory burden, which could be a more reliable approach (35). However, the regular use of biologics must be implemented with caution, considering the high cost, possible safety concerns, and patient inconvenience.

The use of biologics in Japan has gradually expanded since the authorization of anti-TNF-α for UC in 2010, and the results of a large national survey showed a rapid increase in its use since 2011 (36). This study showed a gradual decrease in advanced-stage cancer after 2011 in both patients with CD and UC. Particularly, in patients with UC, a diagnosis year of 2011 or later was a marginally significant factor associated with a lower risk of advanced-stage cancer according to the univariate analysis. These results could be considered to correlate with the increased use of biologics. On the other hand, it has recently been reported that the increased use of biologics has led to an increase in the frequency of cancer development owing to the longer duration of disease caused by improved control of mucosal inflammation (14). As the results of this study did not show a correlation between the duration of disease and the cancer progression, cancer development and progression might be better considered separate phenomena.

The most important limitation of this study was the lack of information on the quantity of drugs used and the duration of use. Although prospective studies taking these factors into account would be ideal in the future, it is becoming increasingly difficult from an ethical point of view to conduct prospective studies on drugs that have proven to be so effective in controlling inflammation. Therefore, it is worthwhile to use a large database of real-world data. From this point of view, this study is of great

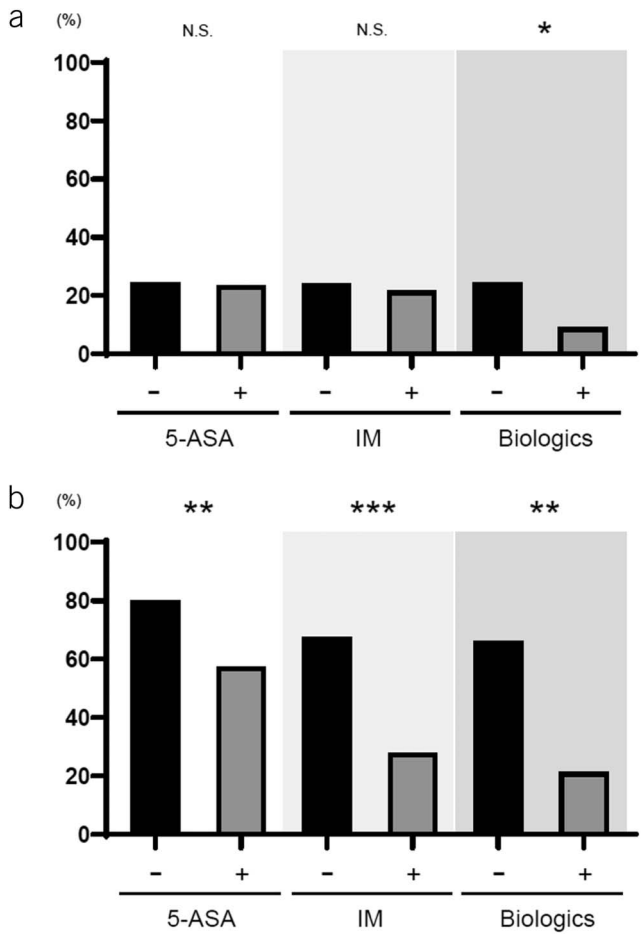

Figure 2. Comparison of the percentages of patients with advanced-stage cancer according to the type of drugs in patients with ulcerative colitis. (**a**) Patients who were diagnosed by regular surveillance and (**b**) patients who were diagnosed by other methods. $^{***}P < 0.001$; $^{**}P < 0.01$; $^{*}P < 0.05$. ASA, aminosalicylic acid; IM, immunomodulators.

Table 4. Comparison of oncologic factors in UC-associated intestinal cancers according to the drugs used

	Biologics			5-ASA			IM		
	− (n = 689)	+ (n = 38)	*P* value	− (n = 124)	+ (n = 603)	*P* value	− (n = 607)	+ (n = 120)	*P* value
pT stage			0.014[a]			0.001[a]			0.022[a]
Tis	190 (27.7%)	20 (52.6%)		22 (17.9%)	188 (31.2%)		160 (26.5%)	50 (41.7%)	
T1	143 (20.8%)	6 (15.8%)		21 (17.1%)	128 (21.3%)		126 (20.8%)	23 (19.2%)	
T2	79 (11.9%)	6 (15.8%)		13 (10.6%)	72 (12.0%)		72 (11.9%)	13 (10.8%)	
T3	188 (27.4%)	4 (10.5%)		40 (32.5%)	152 (25.3%)		166 (27.4%)	26 (21.7%)	
T4a	77 (11.9%)	2 (5.3%)		23 (18.7%)	56 (9.3%)		72 (11.9%)	7 (5.8%)	
T4b	10 (1.5%)	0 (0%)		4 (3.3%)	6 (1.0%)		9 (1.5%)	1 (0.8%)	
Unknown	2	0		1	1		2	0	
pN stage			0.324[a]			0.019[a]			0.138[a]
N0	529 (77.5%)	34 (89.5%)		83 (67.5%)	480 (80.3%)		461 (76.6%)	102 (85.7%)	
N1	88 (12.9%)	2 (5.3%)		22 (17.9%)	68 (11.4%)		81 (13.5%)	9 (7.6%)	
N2	49 (7.2%)	2 (5.3%)		13 (10.6%)	38 (6.4%)		44 (7.3%)	7 (5.9%)	
N3	17 (2.5%)	0 (0%)		5 (4.1%)	12 (2.0%)		16 (2.7%)	1 (0.8%)	
Unknown	6	0		1	5		5	1	
Histology			0.311			0.073			0.306
Well/moderately differentiated	538 (78.1%)	27 (71.1%)		89 (71.8%)	477 (79.1%)		476 (78.4%)	89 (74.2%)	
Others	151 (11.9%)	11 (28.9%)		35 (28.2%)	126 (20.9%)		131 (21.6%)	31 (25.8%)	
Duration of disease (yr)	16.9 ± 10.3	12.1 ± 7.1	0.005	16.6 ± 10.9	16.7 ± 10.1	0.946	16.8 ± 10.5	15.9 ± 8.6	0.377

ASA, aminosalicylic acid; IM, immunomodulators; UC, ulcerative colitis.
[a]Excluding unknown cases.

significance because it was a study of multiple centers from regions all over the country. Another limitation is that although the data were only from patients with pathologically proven IBD-associated intestinal cancer, the criteria may be slightly different at each institution. It is expected that a consensus will be reached on this point in the future. In addition, the regular surveillance methods may also vary among institutions. Although a recommended surveillance method has been proposed, compliance with this method seems relatively low. With the accumulation of further evidence, proposals for simple and practical surveillance methods need to be considered. Finally, the overall rate of biologic use in this study was not very high. Although a strength of the study is that it was performed using real-world data from multiple centers over a span of more than 35 years, it is expected that stronger evidence will be found because the use of biologics expands in the future.

In conclusion, biologic use was associated with a lower risk of advanced IBD-associated cancer in patients with UC, although this association was not significant in patients with CD. As the effect of drugs for IBD on cancer progression has not been widely discussed, the results of this study will lay a foundation for further investigations.

CONFLICTS OF INTEREST

Guarantor of the article: Koji Okabayashi, MD.

Specific author contributions: R.S. and KO: designed the study. R.S.: analyzed the data. R.S. and K.O.: wrote the manuscript. H.H., M.U., K.F., T.N., H.O., Y.I., K.W., M.I., K.O., Y.T., T.O., M.N., K.Y., T.W., Y.S., H.K., K.T., K.H., Y.K., F.I., J.O., K.D., F.K., H.U., T.Y., S.Y., T.H., A.M., J.A., K.K., Y.A., D.S., S.Y., K.M., K.M., T.N., R.N., S.S., J.H., E.S., Y.K., K.K., K.U., T.K., T.S., S.K., T.Y., T.G., S.I., Y.A., and K.S.: interpreted the results and critically reviewed.

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Study Highlights

WHAT IS KNOWN

- ✓ Great strides have been made regarding the treatment of inflammatory bowel disease in recent years with the introduction of a range of biologic agents.
- ✓ The chemopreventive effect of biologics on cancer development is now in the spotlight, but few studies have focused on cancer progression.

WHAT IS NEW HERE

- ✓ Biologic use was associated with a lower risk of advanced inflammatory bowel disease-associated cancer in patients with ulcerative colitis but not with Crohn's disease.
- ✓ Even in patients diagnosed by regular surveillance, biologic use was associated with a lower incidence of advanced-stage cancer in patients with ulcerative colitis.

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